Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Glecaprevir / pibrentasvir

Proprietary Product Name: Maviret

Sponsor: AbbVie Pty Ltd

November 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADME	Absorption, distribution, metabolism and excretion
2-DAA	Two component DAA therapy
AE	Adverse event
AFP	Alpha fetoprotein
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ART	Anti-retroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{inf}	Area under the plasma concentration-time curve from time zero to infinity
AUC_t	Area under the plasma concentration-time curve from time zero to time of last measurable concentration
B/P	Blood to plasma ratio
BCRP	breast cancer resistance protein
BID	Twice daily
BMI	body mass index
BSA	body surface area
CBZE	carbamazepine-10, 11-epoxide
CI	confidence interval
CKD	chronic kidney disease
CL/F	apparent oral clearance
Cmax	maximum observed plasma concentration

Abbreviation	Meaning
COC	Combined oral contraceptive
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450 enzymes
DAA	Direct-acting antiviral agent
DCV	Daclatasvir
DDI	Drug-drug interaction
DDQ	Desire for Drugs Questionnaire
DF	Disoproxil fumarate
DNA	Deoxyribonucleic acid
DSV	Dasabuvir
ECG	Electrocardiogram
EE	Ethinyl estradiol
eGFR	Estimated glomerular filtration rate
EOTR	End of treatment response
ESRD	End-stage renal disease
F	Bioavailability
FDC	Fixed-dose combination
FIH	First-in-human
FMO	Flavin monooxygenase
f_u	Unbound fraction
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLE	Glecaprevir/ABT-493/A-1282576
GLE/PIB	Glecaprevir (GLE) 100 mg/pibrentasvir (PIB) 40 mg as a fixed-dose combination (FDC) tablet
GT1	Genotype 1

Abbreviation	Meaning
GT1a	Genotype 1a
GT1b	Genotype 1b
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLM	Human liver microsomes
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL28B	Interleukin 28B
IRT	Interactive response technology
ISEF	Inter-system extrapolation factor
ITT	Intent to treat
IU	International units
KA/Ka	Absorption rate constant
LCB	Lower bound of the 95% confidence interval
LC-MS/MS	Liquid chromatography with tandem mass spectrometric detection
LDV	Ledipasvir
LFT	Liver function test
LLN	Lower limit of normal
LLOD	Lower limit of detection

Abbreviation	Meaning
LLOQ	Lower limit of quantitation
LNG	Levonorgestrel
MAD	Multiple-ascending dose
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger RNA
NET	Norethindrone
NG	Norgestrel
NGM	Norgestimate
NGMN	Norelgestromin
NS3	Non-structural protein 3
NS4A	Non-structural protein 4A
NS5A	Non-structural 5A inhibitor
NS5B	Non-structural protein 5B
OATP1B1	Organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
OBV	Ombitasvir
OCT	Organic cation transporter
PCS	Potentially clinically significant
PD	Pharmacodynamic
pegIFN	Pegylated interferon
P-gp	P-glycoprotein
PI	Product Information
PI	Protease inhibitor
PIB	Pibrentasvir/ABT-530/A-1325912
PK	Pharmacokinetic

Abbreviation	Meaning
POP	Progestin only pill
PP	Per protocol
PR	Pegylated interferon (pegIFN) + ribavirin (RBV)
PT	Preferred term
PT	Post-treatment
PTV	Paritaprevir
PVF	Primary virologic failure
QD	Once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's correction formula
R	Ritonavir
RBV	Ribavirin
RNA	Ribonucleic acid
RVR	Rapid virologic response
SAD	Single-ascending dose
SAE	Serious adverse event
SAF	Safety population
SmPC	Summary of Product Characteristics
SMV	Simeprevir
SOC	System Organ Class
SOF	Sofosbuvir
SOWS	Short Opiate Withdrawal Scale
StD	Standard deviation
SVR	Sustained virologic response
SVR12	Percentage of subjects achieving sustained virologic response 12 weeks following treatment, defined as HCV RNA < LLOQ

Abbreviation	Meaning
SVR24	Sustained virologic response 24 weeks post-dosing
SVR4	Sustained virologic response 4 weeks post-dosing
$T_{1/2}$	Terminal phase elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum observed plasma concentration
UGT	UDP-glucuronosyltransferases
ULN	Upper limit of normal
USP	US Pharmacopeia Convention
V2 or Vc	Volume of distribution of the central compartment
V2/F or Vc/F	Apparent volume of distribution of the central compartment
V3 or Vp	Volume of distribution of the peripheral compartment
V3/F or Vp/F	Apparent volume of distribution of the peripheral compartment
VAS	Visual analogue scale
WBC	White blood cell
β	Apparent terminal phase elimination rate-constant
ΔΔQTcF	Time-matched drug-placebo difference in QTcF interval, baseline-adjusted

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	21 December 2017
Date of entry onto ARTG	2 January 2018
ARTG number:	284948
Active ingredients:	Glecaprevir / pibrentasvir
Product name:	Maviret
Sponsor's name and address:	AbbVie Pty Ltd 241 O'Riordan Street Mascot NSW 2020
Dose form:	Film coated tablet
Strength:	Fixed-dose combination of glecaprevir 100 mg and pibrentasvir 40 mg
Container:	Blister pack
Pack size:	84 tablets representing four-week supply
Approved therapeutic use:	*Maviret is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of an NS5A inhibitor or with an NS3/4A protease inhibitor but not both classes of inhibitors (see 4.2 DOSE AND METHOD OF ADMINISTRATION and CLINICAL TRIALS).*
Route of administration:	Oral
Dosage:	Three tablets taken once daily with food. The tablets should be swallowed whole and not chewed, crushed, or broken.

Product background

This AusPAR describes the application by the sponsor to register a pangenotypic indication for two new chemical entities, glecaprevir/pibrentasvir, as a fixed dose combination (FDC) tablet with the tradename 'Maviret' for the treatment of chronic hepatitis C virus (HCV) infection. Glecaprevir is an inhibitor of HCV NS3/4A protease and pibrentasvir is an inhibitor of HCV NS5A. As a fixed dose combination tablet, Maviret

shows potent activity against HCV genotypes (GT) 1 to 6 in vitro, with minimal cross-resistance with earlier direct acting antivirals, and minimal renal elimination.

It is suggested by the sponsor that glecaprevir/pibrentasvir will fulfil the following treatment gaps:

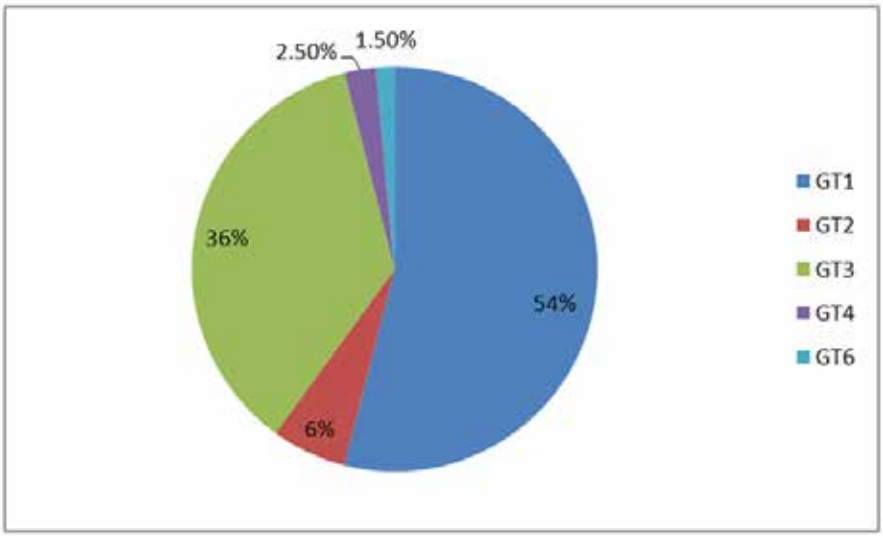
- Patients with renal failure, stages 4 and 5, including dialysis and GT2, 3, 5, 6 infection.
- Patients who previously failed direct-acting antiviral (DAA) containing regimens.
- Patients with cirrhosis and GT3 HCV infection.

Treatment for hepatitis C has evolved rapidly in recent years, with the development and approval of DAA therapies superseding interferon based therapies. These therapies have the potential to cure and achieve a sustained virological response in affected patients, with associated benefits including loss of infectivity, regression of liver fibrosis and cirrhosis, reduction in the risk of liver failure and hepatocellular carcinoma, and reduction in mortality.[1] DAAs were made available via the Pharmaceutical Benefits Scheme (PBS) on 1 March 2016.

Direct-acting antivirals initially approved had variable potency across genotypes and subpopulations;[2] with newer, second generation therapies now being considered for broader, pangenotypic indications.

In Australia, HCV Genotype 1 (54%) and 3 (36%) are the most common genotypes, compared with GT2 (6%), GT4 (2.5%) and GT6 (1.5%) as shown in Figure 1, below.

Figure 1: Prevalence of HCV genotypes in Australia



The sponsor proposes a broad indication for Australia, as for the European Union (EU), as shown in Table 1, below.

Table 1: Maviret indications

Country	Indication
Australia	**Proposed**: Maviret is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults (see DOSAGE AND ADMINISTRATION, PRECAUTIONS and CLINICAL TRIALS).

[1] Australian recommendations for the management of hepatitis C virus infection: a consensus statement (August 2017)
[2] European Medicines Agency. Assessment Report. Maviret. 22 June 2017.

Country	Indication
EU centralised procedure	**Approved**: Maviret is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults (see sections 4.2, 4.4. and 5.1).
USA	**Approved**: MAVYRET is a fixed-dose combination of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor, and is indicated for the treatment of patients with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis and with compensated cirrhosis (Child-Pugh A). MAVYRET is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.
Canada	**Approved**: Maviret is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor but not both classes of inhibitors (see DOSAGE AND ADMINISTRATION and CLINICAL TRIALS).

Regulatory status

The regulatory status of Maviret at the time of this submission to TGA is shown above.

- In the EU, it was granted an Accelerated Assessment status on 15 December 2016 and approved 26 July 2017.
- In the USA, it was granted Breakthrough Therapy Designation on 21 April 2016, Priority review on 12 February 2017, and approved 3 August 2017.
- In Canada, it was granted Priority Review on 22 December 2016 and approved 16 August 2017.
- In Switzerland, it was granted Fast-Track Status on 26 October 2016 and approved on 22 September 2017 for the following:
  - *Maviret is indicated for the treatment of adult patients with chronic hepatitis C.*

Product Information

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

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Registration timeline

Description	Date
Submission dossier accepted and first round evaluation commenced	28 February 2017
First round evaluation completed	31 August 2017
Sponsor provides responses on questions raised in first round evaluation	28 September 2017
Second round evaluation completed	23 October 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	31 October 2017
Sponsor's pre-Advisory Committee response	9 November 2017
Advisory Committee meeting	30 November 2017
Registration decision (Outcome)	21 December 2017
Completion of administrative activities and registration on ARTG	2 January 2018
Number of working days from submission dossier acceptance to registration decision*	181

* Legislative timeframe is 255 working days (see *Therapeutic Goods Regulations 1990*).

III. Quality findings

Introduction

The proposed product is a bilayer, film-coated, fixed dose combination tablet containing two new DAA used for the treatment of patients with chronic HCV infection of any genotype (genotypes 1 to 6). Glecaprevir is a nonstructural (NS) 3/4A protease inhibitor and pibrentasvir is a NS5A inhibitor, which together target multiple steps in the HCV lifecycle.

The recommended dosage of the proposed tablet is three 100 mg/40 mg tablets to be taken orally once daily with food, irrespective of fat or calorie content; that is, 300 mg/day of glecaprevir and 120 mg/day of pibrentasvir.

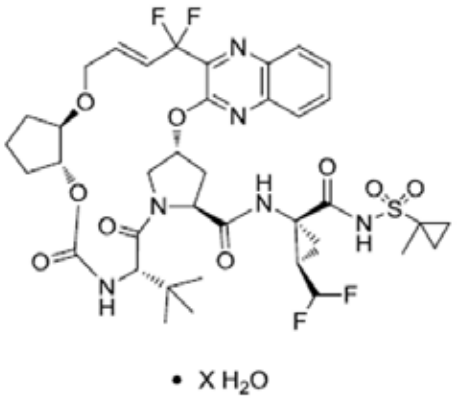
The proposed tablets have the appearance '*pink-coloured, film-coated, oblong biconvex shaped and debossed with 'NXT' on one side*' and will be packaged in PVC /PE/PC TFE (Aclar)/Al blister packs of 84 tablets, representing a four-week supply. Four 'weekly' cartons of 21 tablets (each containing 7 'daily' blister packs of 3 tablets) will be packaged inside the 'monthly' carton.

Drug substance (active ingredient)

Glecaprevir

The API code ABT-493, Glecaprevir, IUPAC 3a*R*,7*S*,10*S*,12*R*,21*E*,24a*R*)-7-*tert*-butyl-*N*-{(1*R*,2*R*)-2-(difluoromethyl)-1-[(1-methylcyclopropane-1-sulfonyl)carbamoyl]cyclopropyl}-20,20-difluoro-5,8-dioxo-2,3,3a,5,6,7,8,11,12,20,23,24a-dodecahydro-1*H*,10*H*-9,12-methanocyclopenta[18,19][1,10,17,3,6]trioxadiazacyclononadecino[11,12-*b*]quinoxaline-10-carboxamide hydrate, is a white to off-white crystalline powder.

Figure 2: Chemical structure of glecaprevir



- Molecular formula: $C_{38}H_{46}F_4N_6O_9S$ (anhydrate); $C_{38}H_{46}F_4N_6O_9S \bullet x\ H_2O$ (hydrate; non-stoichiometric).
- Molecular weight: 838.87 g/mol (anhydrate).
- pKa: 4.0 and 11.7.
- Partition coefficient: log D (*n*-octanol/pH 7.4) is 2.5.

Glecaprevir is practically insoluble in water and exhibits poor solubility across a pH range of 2-7, and is sparingly soluble in ethanol. It has low to moderate passive permeability (Paap 1.4 x 10^{-6} cm/sec). The low solubility/low permeability of the drug substance places the drug substance in Class IV under BCS.

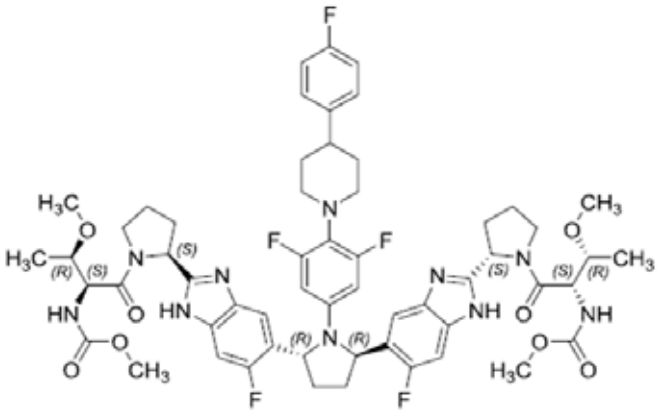
Glecaprevir drug substance is produced by chemical synthesis. A number of crystalline forms of glecaprevir have been identified but it has been demonstrated that the manufacturing process consistently produces the same crystalline form, which has been shown that it does not change during the proposed re-test period.

The drug substance specifications are sufficient to ensure the quality and consistency of the API.

Pibrentasvir

The API code ABT-530, Pibrentasvir, IUPAC {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate, is a white to off-white to light yellow crystalline powder.

Figure 3: Chemical structure of pibrentasvir



- Molecular formula: $C_{57}H_{65}F_5N_{10}O_8$.
- Molecular weight: 1113.18 g/mol.
- pKa: 4.0 (basic), 4.1 (basic) and 11.6 (acidic).
- Partition coefficient: log D (*n*-octanol/pH 7.4) is 7.5.

Pibrentasvir is practically insoluble in water and exhibits poor solubility across a pH range of 1-7 (<0.1 mg/mL), and is freely soluble in ethanol. It has low passive permeability (Paap <1 x 10^{-6} cm/sec). The low solubility/low permeability of the drug substance places the drug substance under BCS Class IV.

Pibrentasvir drug substance is produced by chemical synthesis. A number of crystalline forms of pibrentasvir have been identified as solvates but it has been demonstrated that the manufacturing process consistently produces the same crystalline form. There are 8 chiral centres and a single isomer is produced.

The drug substance specifications are sufficient to ensure the quality and consistency of the API.

Drug product

The proposed tablet product is immediate release, bilayer, film-coated, fixed dose combination containing glecaprevir 100 mg and pibrentasvir 40 mg. The tablets are unscored, pink, oblong, and biconvex with 'NXT' debossed on one side, plain on the other. They will be packed in PVC/PE/PCTFE/Al blisters.

Both glecaprevir and pibrentasvir are poorly water-soluble compounds and accordingly they are each formulated individually as amorphous solid dispersions (ASD) in a matrix, in order to enable adequate in vivo absorption.

Amorphous solid dispersions are an effective method to improve the oral absorption of poorly soluble drugs. This improvement is based on the ability to form and sustain supersaturated solutions of the amorphous drug compared to the crystalline counterpart.

Glecaprevir and pibrentasvir drug substances are separately processed into amorphous solid dispersions (ASDs). The drug substances are formulated using some or all of the following excipients:

- copovidone (Type K 28),
- Vitamin E polyethylene glycol succinate,
- Propylene glycol monocaprylate (Type II), and

- Colloidal anhydrous silica.

The amorphous solid dispersions of each drug substance are milled, blended together, combined with tabletting aids, compressed into 2-layer tablets and film-coated.

The finished product specifications include tests for description, identification, assay, uniformity of dosage, control of impurity levels, dissolution (at two points), water content, and microbiological quality. The finished product specifications are sufficient to ensure the quality of the finished product at release and throughout the shelf-life. A shelf life of 30 months is supported by the stability data.

Chemistry and quality control aspects are acceptable.

Biopharmaceutics

Clinical Study M14-714 was considered the most pertinent as it is performed with pivotal bioavailability test batch of glecaprevir / pibrentasvir 100/40 mg film-coated bilayer tablets that has the same formulation as proposed for registration. The study is a single dose, open label, four-period, randomised, crossover, conducted under fasting and non-fasting (moderate fat meal or a high–fat meal) conditions. The study compares the bioavailability and food effect of the proposed FDC test tablet (3 x 100/40 mg) relative to Phase IIb single agent reference formulations i.e. single dose of glecaprevir tablets (3 x 100 mg) and single dose of pibrentasvir tablets (3 x 40 mg). The oral dosing of the test formulation is consistent with dosage in the PI, that is, three tablets once daily.

Other remaining clinical studies involve comparison of the bioavailability of early and late development dosage forms. A justification for the absence of an absolute biostudy was provided and this is further discussed below.

The reported PK parameters for the pivotal clinical Study M14-714 are below.

Table 3: Geometric mean (mean, % CV) PK parameters of ABT-493 and ABT-530

Pharmacokinetic Parameters (units)	Regimen A: Fasting N = 23	Regimen B: Moderate-Fat Breakfast N = 23	Regimen C: High-Fat Breakfast N = 23	Regimen D: Fasting N = 23
	ABT-493			
C_{max} (ng/mL)	294 (384, 78)	937 (1190, 84)	633 (723, 54)	803 (973, 72)
T_{max}[a] (h)	3.0 (1.5, 5.0)	4.0 (3.0, 5.0)	5.0 (4.0, 6.0)	2.0 (1.0, 3.0)
$t_{1/2}$[b] (h)	6.0 (23.7)	6.0 (16.1)	6.3 (17.9)	5.7 (16.1)
AUC_t (ng•h/mL)	1150 (1430, 70)	3030 (3460, 60)	2110 (2390, 54)	2620 (2970, 53)
AUC_∞ (ng•h/mL)	1150 (1440, 69)	3040 (3470, 60)	2110 (2390, 54)	2620 (2980, 53)
	ABT-530			
C_{max} (ng/mL)	116 (140, 60)	221 (239, 44)	237 (262, 45)	175 (192, 38)
T_{max}[a] (h)	4.0 (2.0, 5.0)	5.0 (3.0, 5.0)	5.0 (4.0, 6.0)	4.0 (2.0, 5.0)
$t_{1/2}$[b] (h)	13.3 (8.9)	13.0 (9.6)	13.5 (8.8)	12.5 (8.3)
AUC_t (ng•h/mL)	910 (1100, 64)	1280 (1400, 49)	1390 (1560, 49)	1420 (1570, 40)
AUC_∞ (ng•h/mL)	960 (1160, 64)	1346 (1470, 49)	1460 (1650, 50)	1490 (1650, 40)

Regimen A: Single 300 mg/120 mg dose of ABT-493/ABT-530 (3 × 100 mg/40 mg film-coated bilayer tablets) under fasting conditions (Test).

Regimen B: Single 300 mg/120 mg dose of ABT-493/ABT-530 (3 × 100 mg/40 mg film-coated bilayer tablets) following a moderate fat breakfast (Test).

Regimen C: Single 300 mg/120 mg dose of ABT-493/ABT-530 (3 × 100 mg/40 mg film-coated bilayer tablets) following a high fat breakfast (Test).

Regimen D: Single dose of 300 mg ABT-493 (3 × 100 mg tablets) and 120 mg ABT-530 (3 × 40 mg tablets) under fasting conditions (Reference).

a. Median (minimum through maximum).

b. Harmonic mean (pseudo-CV%).

The exposures of glecaprevir (ABT-493) in the film-coated bilayer tablet administered under non-fasting conditions were higher (3.2-fold C_{max} and 2.6-fold AUC with moderate fat; 2.1-fold C_{max} and 1.8-fold AUC with high fat breakfast) than under fasted conditions. Similarly, the exposures of pibrentasvir (ABT-530) in the film-coated bilayer tablet administered under non-fasting conditions were higher (1.9-fold C_{max} and 1.4-fold AUC with moderate fat; 2.1-fold C_{max} and 1.5-fold AUC with high fat breakfast) than under fasted conditions.

These results support the recommendation in the PI to take the tablets with food.

The PK properties in the PI, aT_{max} 5.0 h for both glecaprevir and pibrentasvir, and $T_{1/2}$ of 6 h for glecaprevir and $T_{1/2}$ of 13 h for pibrentasvir are also consistent with the above PK data.

A *Justification for waiving the requirement of Absolute Bioavailability Studies* has been submitted. The sponsor's bases for not conducting an absolute bioavailability study, and conclusion, are:

- *Difficult to produce a formulation for intravenous (IV) administration*
- *Sufficient evidence showing that factors impacting absorption of glecaprevir (GLE) / pibrentasvir (PIB) have been well characterized in clinical studies*
- *The selected Phase III/proposed commercial tablet formulation achieved therapeutic and supra-therapeutic exposures for glecaprevir and pibrentasvir*
- *Based on the physiochemical characteristics of GLE and PIB, it is very difficult to formulate an IV solution of GLE/PIB. AbbVie has conducted over 42 Phase I studies that characterized the pharmacokinetics of GLE and PIB alone and in combination following oral administration and believes the factors that impact absorption of GLE/PIB have been well characterized. Furthermore, the pharmacokinetics of the Phase III/proposed commercial formulation was also evaluated extensively in Phase I studies and Phase III studies. With various techniques considered and explored in formulation development, the FIH tablets and Phase IIa/b tablets still showed the highest bioavailability of GLE and PIB. In addition, the inhibition of P-gp and BCRP in GI tract was saturated at 300 mg GLE dose. Therefore, no further increase in absorption can be achieved through the DDI route. Based upon the available data, one factor that improves GLE and PIB exposures is food. As the FIH tablets and Phase II tablets were adequate to achieve therapeutic and supra-therapeutic exposures, and the selected Phase III/proposed commercial formulation under non-fasting conditions was able to provide similar GLE and PIB exposures to the Phase IIa/b tablets, absolute bioavailability studies for GLE and PIB are not needed to understand the absorption characteristics of GLE and PIB and aid formulation or clinical development. The GLE/PIB 300 mg/120 mg Phase III/proposed commercial regimen was well tolerated in HCV subjects in Phase II and Phase III studies with a large margin (> 48-fold) for potential ALT elevation. [The sponsor] hence requests the TGA to waive the requirement for absolute bioavailability data for GLE and PIB.*

As noted under '*Drug Substance*' in this summary, the low solubility/low permeability of each of the drug substance classifies them as Class IV under BCS. The poor solubilities of the drug substances in aqueous media would prove difficult to have a fully-dissolved solution of the APIs suitable for IV administration.

A level A 'In Vitro-In Vivo correlation' (IVIVC) study was conducted. As per the FDA guidelines, the IVIVC criteria was not met for the formulations suggesting that the IVIVC correlation is not adequate to predict plasma concentration time profiles from in vitro dissolution data. In addition, different slopes of fraction absorbed in vivo (observed) versus fraction released in vitro (observed) for each formulation suggested no single correlation between in vitro release rates and in vivo absorption for all formulations. A predictive Level A correlation could not be established.

Quality summary and conclusions

A valid Good Manufacturing Practice (GMP) clearance is not in place for the manufacturer. This site performs the manufacturing step testing chemical and physical for the finished product. It is anticipated that this will be resolved prior to the decision phase.

Approval is recommended from a chemistry and quality perspective.

IV. Nonclinical findings glecaprevir

Introduction

This evaluation report concerns nonclinical studies and investigations on GLE, an inhibitor of the HCV NS3/4A protease. Glecaprevir thus belongs to the same pharmacological class as boceprevir (Victrelis) and telaprevir (Incivo), simeprevir (Olysio), paritaprevir (Viekira pak, Viekira pak-rbv), asunaprevir (Sunvepra) and grazoprevir (Zepatier).

The nonclinical dossier was of high quality, and clearly identified the rationale behind the submitted studies. Pivotal core safety pharmacology, toxicokinetic and repeat dose toxicity studies were performed in accordance with Good Laboratory Practice (GLP) and the studies were generally in agreement with International Conference on Harmonisation (ICH) guidelines. One notable exception is absence of adequate combination studies with pibrentasvir, as stipulated in the relevant TGA-adopted EMA guideline on fixed dose combination products.[3] However, the sponsor cited a more recent draft FDA guidance document;[4] which concludes that combination toxicology studies may not be required for direct-acting antivirals combinations that are expected to be a substantial improvement over approved therapies, do not raise significant safety concerns regarding off-target or overlapping toxicities or unmanageable drug interactions, and for which toxicology studies have substantial safety margins for the intended clinical exposure or exposures. A 4 week safety study with a low dose of the combination (one dose level only) was submitted.

Pharmacology

Primary pharmacology

Glecaprevir is a pangenotypic inhibitor of HCV NS3/4A protease, which is essential for proteolytic cleavage of the HCV encoded polyprotein, and hence for viral replication. In biochemical assays GLE inhibited protease purified from HCV GT1a, GT1b, GT2a, GT2b, GT3a, GT5a and GT6a, with half-maximal inhibitory concentration (IC_{50}) values between 3.5 and 11 nM. Glecaprevir selectivity for HCV proteases compared with a panel of seven human proteases was > 20,000-fold. The EC_{50} for GLE inhibition of replication of subgenomic stable replicons in cell culture assays ranged from 0.85 to 4.6 nM (using laboratory strains GT1a-H77, GT1b-Con1, GT2a-JFH1 and chimeric replicons containing the NS3/4A gene from GT2b, GT3a, GT4a and GT6a, but excluding GT5a). In the presence of 40% human plasma the EC_{50} values for GT1a-H77 and GT1b-Con1 were 5.3 and 10 nM, compared with 0.85 nM and 0.94 nM without plasma respectively, indicating that the potency of GLE was reduced by 6 to 11-fold. Similar activity was seen against a panel of 40

[3] Guideline on the nonclinical development of fixed combinations of medicinal products. EMEA/CHMP/SWP/258498/2005

[4] FDA Draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing direct-acting antiviral drugs for treatment. October 2013, Revision 1.

clinical samples of HCV GT1a, 1b, 2a, 2b, 3a, 4a, 4d and 5a in transient replicon assays, with a median EC_{50} value of 0.3 nM (range 0.05 to 3.8 nM), compared with the unbound plasma C_{max} and C_{min} of 17.8 nM and 0.4 nM, respectively in non-cirrhotic patients;[5] and likely much higher hepatic concentrations (liver exposures to GLE based on AUC were more than 25 fold higher than plasma exposure in rodents, and 10-fold higher in dogs; see also '*Pharmacokinetics* below').

Amino acid substitutions at positions 155 (R155K), 156, 168 (D168V) and 80 (Q80K) are signature mutations for NS3/4A protease inhibitors.[6] Resistance variants at position 156 were the predominant substitution arising in resistance selection studies with GLE in GT1a-H77, GT1b-Con1, GT2a-JFH-1, GT2b and GT4a replicon cell lines (A156T and A156V). In GT3a replicons the reported substitutions were A156G or Y56H+Q168R, while variants selected in GT6a replicons were D168H and D168V. The susceptibility of common resistance variants was investigated. Glecaprevir retained activity against common R155 variants (including double substitutions), in particular R155K in GT1a (levels of resistance for R155 variants were up to 2.6 fold for variant R155C in GT4a and 1.9 fold for variant R155T in GT1a). Changes at position 156 were often associated with marked resistance to GLE, with A156M/T/V/G associated with 148 to 3106-fold resistance in 1a, 1b, 2a, 2b, 3a or 4a replicons. Substitutions at position 168 in GT 1a, 1b, 3a or 4a reduced susceptibility to GLE by up to 55-fold, and by 38- to 191-fold in GT6a, but had no or minimal impact in GT 2a and 2b (up to 5.6-fold increases in EC_{50}). Q168R in GT3a showed 54-fold resistance and Y56H+Q168R showed 1387-fold resistance to GLE. Substitutions at position 80 did not reduce susceptibility to GLE except in GT3a, where a Q80R substitution led to a 21 fold increase in EC_{50}.

With respect to other single amino acid substitutions, activity was retained (less than 5 fold resistance) in GT 1a, 1b, 2a, 2b, 3a, 4a, 4d and 6a transient replicons containing substitutions at positions 15, 36, 41, 43, 54, 55, 56, 67, 71, 79, 89, 146, 150, 154, 160, 166, 170, 173, 176, 178, or 179, or in the helicase domain at 334, 342, 357, 406, 449, or NS4A position 23. Antiviral efficacy was also examined against HCV replicons containing GT1a or 1b variants resistant to NS5A or NS5B polymerase inhibitors in transient transfection cell culture assays. All NS5A/B variants tested were sensitive to GLE (< 5 fold resistance). However, based on the resistance selection studies, cross-resistance with other NS3/4A protease inhibitors may occur.

Glecaprevir and PIB showed additive to synergistic antiviral activity in a three day HCV replicon cell culture assay. In a colony survival assay, only very small numbers of colonies containing the HCV GT1a-H77 or 1b-Con1 replicons were able to survive in the presence of either GLE or PIB at 10 fold above their respective EC_{50} values. Colony survival was reduced to zero with both GLE and PIB present at 10-fold above their respective EC50 values. Glecaprevir was also shown to display additive to synergistic antiviral activity when tested in combination with either sofosbuvir or with ribavirin in HCV replicon assays.

Glecaprevir does not have activity against HIV-1 or HBV. Two representative HIV-1 protease inhibitors (lopinavir (LPV) and darunavir (DRV)) had no effect on the antiviral efficacy of GLE in an HCV 1b-Con1 replicon assay. Similarly, GLE did not affect the antiviral efficacy of LPV or DRV in the HIV-1 pNL4-3 assay.

Secondary pharmacodynamics and safety pharmacology

The only potential off-target binding of GLE detected in an extensive battery of *in vitro* screening assays was at the GABA-activated chloride channel, where the GLE IC_{50} for

[5] In non-cirrhotic patients: total C_{max} 597 ng/mL (712 nM), C_{min} = 13 ng/mL (15.5 nM), unbound fraction 2.5%.
[6] Götte, M. and Feld, J.J. (2016). *Nature Reviews (Gastroenterology & Hepatology)* **13:** 338-351.

inhibition of radioligand binding was 11 µM. This is more than 300 fold higher than the plasma C_{max} for unbound GLE in HCV patients, which in turn is likely to be higher than CNS concentrations of GLE, based on the results of tissue distribution studies in rats. There were no effects observed in CNS or neurobehavioural studies in rats dosed orally at up to 100 mg/kg (3 x the proposed clinical dose per unit of BSA), nor in repeat dose toxicity studies in which rats were dosed at up to 600 mg/kg PO (associated with a mean plasma C_{max} approximately 82 x the clinical C_{max}). Similarly, no notable secondary pharmacodynamic activity was observed in a battery of safety pharmacology studies that encompassed the CNS, cardiovascular and respiratory systems. The only effect reported was a slight increase in respiratory rate and concomitant reduction in tidal volume following oral administration of GLE to rats at 60 mg/kg (approximately 2 x the proposed clinical dose per unit of BSA), but no adverse respiratory effects were noted in the repeat dose toxicity studies.

Pharmacokinetics

Glecaprevir is a lipophilic compound with low passive cellular permeability. The pharmacokinetic profile was characterised by rapid absorption following oral administration of GLE in lipid formulation to mouse, rat and dog (T_{max} approximately 1 h), with slower absorption in the monkey (T_{max} 2.8 h). Oral bioavailability was very high (> 90%) in the mouse and rat, only moderate (44%) in the dog and low (26%) in the monkey. Plasma clearance was moderate in mice, dogs and monkeys, and low in rats. Plasma concentrations measured after oral administration of a solution formulation were higher in fasted compared with fed dogs.

There were no apparent sex differences in mice, rats and dogs, and no accumulation with repeated dosing.

Glecaprevir was highly bound to proteins in plasma in all species, being approximately 97.5% bound to proteins in mouse, dog and human plasma and approximately 99.5% bound in rat plasma at 0.1 to 30 µM, independent of concentration. The mean blood to plasma ratio was similar across species (0.55 to 0.75) which indicates no preferential partitioning into blood cells. Comparison of the steady state volume of distribution with total body water indicated that tissue distribution would be expected to be limited in the rat (possibly owing to the more extensive binding to plasma proteins), moderate in the dog, and extensive in mice and humans. High levels of liver exposure (based on plasma concentrations or AUC) were demonstrated in mice, rats and dogs, with liver exposures (AUC) more than 100 fold higher than plasma exposure in mice, and 34 and 10 fold higher in rats and dogs, respectively. In extra-hepatic tissues, the ratio of tissue: plasma radioactivity exceeded unity only in the large and small intestine at 24 h post-dose, indicating that there was limited distribution in tissues other than liver. The rate of elimination of radioactivity from tissues mirrored that of plasma, indicating no tissue accumulation or retention of GLE or its metabolites, and there was no preferential distribution into melanin-containing tissues (skin: plasma ratio 0.1).

The metabolism of GLE was very limited in all species, and unchanged GLE was the predominant component circulating in plasma (≥ 98% of total radioactivity in mouse and rat, and 95% in dog plasma) following oral administration of single or multiple doses of GLE. There were no major metabolites in plasma, with minor metabolites formed through oxidation of the *tert*-butyl, cyclopentyl, difluorobutenyl or quinoxaline groups, conversion of difluoromethyne in the macrocycle to the ketone, amide hydrolysis at the methylcyclopropane-sulfonamide group and dehydrogenation. Glutathione and/or cysteine conjugation of quinoxaline or difluorobutenyl groups was observed only in dogs, and accounted for less than 1% of total drug related material. Unchanged GLE accounted for 97.2% of drug related material in the plasma of eight healthy subjects given GLE doses

of 800 mg/day for ten days (clinical Study M13-356), with nine minor metabolites detected (each comprising less than 1% of drug-related material). The dihydroxylation product M12, present at <0.1% of drug related material, was not detected in any of the nonclinical species.

Glecaprevir and its metabolites were predominantly eliminated via faeces in rats (98.5%), dogs (76.4%) and humans (92.1%). In rats, 99.7% of a radioactive dose was eliminated in the bile following IV administration, with only 0.3% excreted in urine, and 62.4% in the bile following PO dosing. The most significant human (and rat) faecal metabolite was the sulphonamide hydrolysis product M6, which is likely formed through the activity of intestinal microflora. In humans, unchanged GLE and M6 together accounted for over 64% of faecal radioactivity, with oxidative metabolites and their hydrolysis products accounting for 26% of the dose, indicating that metabolism plays a secondary role in the elimination of GLE. The nonclinical species were qualitatively very similar in this regard.

In conclusion, the pharmacokinetic profile of GLE in animals is comparable to that in humans, supporting their use in the toxicity studies.

Pharmacokinetic drug interactions[7]

Glecaprevir undergoes minimal metabolism and thus its clearance is unlikely to be affected by CYP450 inhibitors or inducers. An in vitro study showed no induction of CYP1A2 or 2B6 at 50 μM, and weak induction (mRNA expression by 2-fold) of CYP3A4 only in hepatocytes of one out of 3 donors. Glecaprevir is not an inhibitor of CYP1A2, 2B6, 2C19 or 2D6, or UGT1A6, 1A9 or 2B7, and is a weak inhibitor of CYP2C8, 2C9 and 3A4 (IC_{50} 31.7, 175 and 28.3 μM, respectively) and UGT1A1 and 1A4 (IC_{50} 17.2 and 14.6 μM, respectively). Glecaprevir is not predicted to have clinically relevant inhibition of hepatic CYP450 or UGTs, but has the potential to inhibit intestinal CYP3A4.

In vitro assays showed that GLE is both a substrate and an inhibitor of P-gp and BCRP (IC_{50} 0.33 and 2.3 μM, respectively in assays using membrane vesicles) and the hepatic uptake transporters OATP1B1 and OATP1B3 (IC_{50} 0.017 and 0.064 μM, respectively), and potential drug-drug interactions (DDIs) mediated by these transporters are predicted. GLE as a substrate of these transporters was also demonstrated in MDR1a/b-BCRP knockout mice and OATP1a/1b cluster knockout mice. A study in MDR1 and BCRP knockout FVB mice revealed a 2-fold increase in systemic exposure and a slight increase in liver exposure to GLE, compared to wild type mice. Mice lacking the OATP1a/1b cluster had a 20 fold increase in AUC compared with wild type, although liver exposure was similar to that seen in wild type mice.

Inhibition of BSEP was also observed, which is an additional possible source of DDI. Glecaprevir is not an inhibitor of OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K and is not a substrate of OCT1.

[7] The following assumptions were made:
• molecular weight 838.87; dose 300 mg; $C_{max,}$ 1.32 μM (total; cirrhotic patients); free fraction 2.5 %; intestinal volume, 0.25 L; absorption rate constant, 0.4 min^{-1}, k_{deg} for CYP3A 0.0005 min^{-1}
• for intestinal CYP (CYP3A) and intestinal transporters (P-glycoprotein and BCRP): if the IC_{50} is ≤0.1-fold the intestinal concentration, an *in vivo* interaction is considered possible
• for systemic CYP, renal uptake and efflux transporters, and hepatic efflux transporters (OAT1, OAT3, OCT2, MRP2, BCRP, P-glycoprotein, MATE1 and MATE2K): if the IC_{50} is ≤50-fold the unbound clinical C_{max}, an *in vivo* interaction is considered possible
• for hepatic uptake transporters (OCT1, OATP1B1 and OATP1B3): if the IC_{50} is ≤25-fold the unbound hepatic inlet concentration, an *in vivo* interaction is considered possible.

Toxicology

Acute toxicity

No single dose toxicity studies were conducted. GLE is lipophilic and has minimal aqueous solubility, so the effect of formulation and dose defined the maximum feasible exposures in the nonclinical species, which were used in the repeat-dose toxicity studies. There were no mortalities or notable toxicities at single doses up to 400 mg/kg in mice, 300 mg/kg in rats or 200 mg/kg in dogs with C_{max} up to around 180 µg/mL in mice and around 100 µg/mL in rats and dogs (compared with a clinical C_{max} of 1.1 µg/mL), indicating that GLE has a low order of oral toxicity.

Repeat dose toxicity

Studies of up to 4 weeks duration were conducted in mice, 26 weeks in rats, and 9 months in dogs. Glecaprevir was dosed orally, as this is the intended route of administration, but unlike the intended clinical single daily dose, rats and dogs were dosed BID. The design and conduct of the pivotal studies were consistent with ICH guidelines;[8] with respect to GLP compliance, species used, group sizes, duration of treatment and extent of monitoring.

As already noted, combination toxicity studies with pibrentasvir were not submitted, other than a 4 week safety study with low doses of the combination as required by Russian regulatory authorities. The acceptability of this approach will be discussed elsewhere.[9]

Relative exposure

Exposure ratios have been calculated based on animal: human plasma $AUC_{0-24\,h}$. Human reference values are from Population PK model-estimated steady state exposures, Phase II/III Study RD160234. The AUC data used for animals is the mean of male and female values on the last sampling occasion, and refers to total (not unbound) GLE. As discussed above, GLE binds more extensively to proteins in rat plasma compared with plasma from humans or the other nonclinical species, by a factor of 7. However, it is not considered to be appropriate to use a lower f_u than 1% in any calculations due to the uncertainty in the determination.[10] Thus, assuming a value of 1% for f_u in rats (compared with 2.5% in humans) then the relative exposure estimates for unbound GLE from the rat toxicokinetic studies in the table below will be reduced by approximately one half.

The maximum achieved relative exposures in the repeat dose toxicity studies in all 3 species were high when based on total GLE concentrations (and even taking into consideration the very high plasma protein binding in rats). In rats and dogs, the maximum exposures were achieved at 120 and 200 mg/kg/day, respectively, which were the highest dose levels administered in the pivotal studies.

[8] ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. EMA/CPMP/ICH/286/1995; Guideline on repeated dose toxicity. CPMP/SWP/1042/99/Rev 1.
[9] Glecaprevir + Pibrentasvir (Maviret) new fixed dose combination Nonclinical Evaluation Report
[10] Guideline on the investigation of drug interactions. CPMP/EWP/560/95/Rev.1

Table 4: Relative exposure in repeat-dose toxicity studies

Species	Study duration [Study no.]	Dose mg/kg/day	$AUC_{0-24\,h}$^ µg·h/mL	Exposure ratio#	
				HCV infected, no cirrhosis	HCV infected with cirrhosis
Mouse (TgHras wild type)	7 days RD13348	100	95	20	9
		200	250	52	24
		300	357	74	34
	4 weeks RD13682	40	39.2	8	4
		125	399	83	38
		300	737	154	70
Rat (SD)	13 weeks RD11930	10†	46	10	4
		40†	253	53	24
		120†	580	121	55
	26 weeks Pivotal: RD140001	10†	37.9	8	4
		40†	274	57	26
		120†	735	153	70
Dog (Beagle)	2 weeks RD11535	40†	102	21	10
		100†	787	164	75
		200†	1629	339	155
	13 weeks RD11925	20†	16.1	3	1.5
		60†	368	77	35
		200†	765	159	73
	9 months Pivotal; RD140002	20†	50.5	11	5
		50†	237	49	23
		200†	1440	300	137

Species	Study duration [Study no.]	Dose mg/kg/day	$AUC_{0-24\,h}$^ µg·h/mL	Exposure ratio#	
				HCV infected, no cirrhosis	HCV infected with cirrhosis
Human (HCV infected without cirrhosis)	Population PK model-estimated steady state exposures, Phase II/III Study RD160234	300 mg	4.8	-	
HCV infected with cirrhosis			10.5		

= animal: human plasma $AUC_{0-24\,h}$; ^ = data are for the sexes combined at the last sampling occasion;
†administered in 2 divided doses

Major toxicities

Glecaprevir showed generally low toxicity in all species, with clinical signs limited to salivation in rats in the 13 week study, and mild faecal changes and increased incidences of vomiting in dogs, which had no consistent or dose-dependent consequences for food consumption or body weight gain. The target organs for toxicity were the liver and gall bladder, which is unsurprising considering the tissue distribution and biliary route of elimination, and consistent with other NS3/4A protease inhibitors, such as paritaprevir and grazoprevir. Exposure ratios (ER) noted below are AUC values in animal species compared to the clinical AUC in cirrhotic patients. The ER in non-cirrhotic patients is approximately twice the ER for cirrhotic patients.

Hepatic effects were not consistently seen. In mice, they were limited to an increase in organ weight at a dose of 300 mg/kg/day for males in the 7 day study, and for females in the 29 day study (ER ≥ 34). Clinical chemistry findings were limited to mild increases in serum cholesterol, and minimal increases in serum ALP and bilirubin at doses of 125 mg/kg/day and above for 7 days or 4 weeks (ER ≥ 24). Hepatic effects in dogs included reversible increases in GGT (up to 4.6-fold) and/or ALT levels (up to 8 fold) at times during the 9 month study (with similar increases in ALT also reported in the 13 week study in this species). Serum ALP levels were also increased up to 5.5 fold for some dogs in the 13 week study. These effects are suggestive of possible cholestasis, and were observed at ER ≥ 35. The above effects in mice and dogs were not associated with any gross or microscopic pathological changes. There was no evidence of hepatic toxicity in rats dosed at up to 120 mg/kg/day for 26 weeks (ER 70).

Minimal gallbladder toxicity was reported in the shorter duration studies in dogs, consisting of mild diffused transmural oedema for both males dosed at 200 mg/kg/day for 2 weeks (ER 155) and at doses ≥ 20 mg/kg/day for 13 weeks (ER 1.5). This was associated with concurrent minimal vacuolation of gallbladder epithelial cells in the 13 week study at doses of 60 mg/kg/day and above (ER 35). No gallbladder abnormalities were seen in recovery animals or in any of the dosage groups in the 9 month study. There was no evidence of gallbladder effects in the repeat-dose studies in mice (and the rat lacks a gallbladder so cannot be used to assess toxicity of this organ).

Additional toxicities reported in the repeat-dose studies included minimal reductions in red cell parameters in the 7 day study in mice and 13 week study in dogs, with minimal increases in red cell distribution width and platelet volume in male mice, suggestive of a regenerative bone marrow effect. These effects were small and reversible and considered not to be of biological relevance, and were not reported in rats or in the longer term studies in mice or dogs. Minimal, dose-dependent decreases in serum potassium and phosphorous seen in the 26 week repeat-dose study in rats were not observed in mice or

dogs. Adverse findings in the stomachs of rats dosed at 600 mg/kg/day for 2 weeks consisted of hyperplasia, minimal to mild neutrophilic infiltration and minimal ulceration or necrosis, which are likely a result of local irritation of the test material, and not considered to be clinically relevant.

Based on the lack of any toxicologically relevant haematological findings or any effects on immune organ weights, histopathology, serum globulins and a lack of evidence of infections, GLE is not considered to have any effects on the immune system, and the absence of any dedicated immunotoxicity studies is acceptable.

There were no toxicities reported in a 4 week repeat-dose study in rats dosed orally with GLE and PIB doses of 12.5 and 20 mg/kg/day, respectively (approximately equal to the exposure for GLE in cirrhotic patients).

Genotoxicity

Glecaprevir was evaluated for its potential to induce reverse mutations in *S. typhimurium* and *E. coli*, and for its clastogenic potential in human lymphocytes in vitro and in vivo in a rat bone marrow micronucleus assay. The range of studies and their designs were consistent with the relevant ICH guideline.[11] Glecaprevir was negative in all three tests, and is unlikely to pose a mutagenic or clastogenic risk to humans.

Carcinogenicity

Carcinogenicity studies were not conducted since no causes for concern were identified in genotoxicity or general toxicity studies, and since the optimal treatment duration for the proposed combination of glecaprevir and pibrentasvir is expected to be less than 6 months.[12]

Reproductive toxicity

Reproductive toxicity studies were designed and conducted in general accordance with the relevant ICH guideline;[13] and examined potential effects on fertility in male and female rats, embryofetal development in rats and rabbits, and pre- and postnatal development (including F1 fertility and reproductive performance) in rats. Doses, group sizes and timing and duration of treatment were appropriate in all studies. Dose range-finding studies for embryofetal toxicity were conducted in both species. The rabbit studies were confounded by poor maternal tolerance of GLE, as well as to the vehicle in the first dose range-finding study (an alternative vehicle was selected for subsequent studies).

Relative exposure

The AUC data used to calculate systemic exposure levels in the table below refers to total (not unbound) GLE. The exposure ratio based on free fraction for rats is approximately half the ratio based on total GLE. There are no plasma protein binding data for rabbits. Relative exposure levels were high in the rat studies (even if the interspecies difference in binding to plasma proteins were to be taken into account, as discussed above). However, relative exposures in the rabbit studies were subclinical, owing to poor maternal tolerance. ^{14}C-glecaprevir crossed the placenta in rats, with radioactivity detected in fetal blood at all sampling times through 72 h post-dose, as well as in liver (which had the highest concentration of radioactivity of all fetal tissues), with low levels detected on occasion in brain and kidneys. Lactational transfer of GLE-related radioactivity was also demonstrated in this species (maximum milk: plasma ratio 0.32; milk: plasma AUC ratio 0.079).

[11] ICH guideline S2 (R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use. EMA/CHMP/ICH/126642/2008.
[12] ICH Topic S1A. The need for carcinogenicity studies of pharmaceuticals. CPMP/ICH/140/95.
[13] ICH Topic S5 (R2). Detection of toxicity to reproduction for medicinal products and toxicity to male fertility. CPMP/ICH/386/95.

Unchanged GLE accounted for 96.5% of radioactivity in milk, with the remaining 3.5% unidentified.

Table 5: Relative exposure in reproductive toxicity studies

Species	Study [Study no.]	Dose mg/kg/ day	$AUC_{0-24\,h}$ (µg·h /mL)	Exposure ratio#	
				HCV infected, no cirrhosis	HCV infected, with cirrhosis
Rat (SD)	Embryofetal development [RD13913]	10†	55.9	12	5
		40†	318	66	30
		120†	559	116	53
	Pre/postnatal development [RD160239]	10†	22.0	5	2
		40†	208	43	20
		120†	492	103	47
Rabbit (Hra:NZW)	Embryofetal development DRF [RD13840]	30	0.406	0.1	0.04
		100	2.19	0.5	0.2
		300	14.6	3	1
	Embryofetal development [RD13679]	20	0.13	0.03	0.01
		60	0.73	0.2	0.07
Human HCV infected, no cirrhosis	Population PK model-estimated steady state exposures, Phase II/III Study RD160234	300 mg	4.8	–	
HCV infected with cirrhosis			10.5		

= animal: human plasma $AUC_{0-24\,h}$ (animal data from GD17 or LD14 in rat, GD7 (DRF) or GD18 (main) in rabbit; †administered in 2 divided doses; DRF = dose range-finding.

Glecaprevir treatment of male and female rats from 2 weeks prior to mating at doses up to 120 mg/kg/day had no effect on fertility or reproductive performance. Sperm quality was not examined, but this is acceptable as tissue distribution studies indicated a very low distribution of GLE-related radioactivity to male reproductive tissues, and no adverse histopathological findings were noted in the repeat-dose toxicity studies in this species. Toxicokinetic data are not available from this study, but the relative exposure at the highest dose is estimated to be around 63 and 137 in cirrhotic and non-cirrhotic patients, respectively (based on the mean exposure levels in the repeat dose toxicity studies with the same dosage regimen and using the same vehicle).

In the definitive embryofetal toxicity study in rats the NOAEL for both maternal and fetal toxicity was 120 mg/kg/day, corresponding to relative exposures of 53 and 116 for cirrhotic and non-cirrhotic patients, respectively. There were no adverse maternal or litter effects in the peri/postnatal development study with maternal dosing at 120 mg/kg/day from Day 6 of gestation throughout lactation (relative exposures 47 and 103 in cirrhotic and non-cirrhotic patients, respectively). The F^1 generation showed no effect of maternal treatment on body weight gain, sexual maturation or behaviour, and there was no effect on F^1 reproductive performance.

As already discussed, the rabbit tolerated GLE poorly, with reduced food consumption and reduced body weight gain or body weight loss, faecal changes, reduced urination and premature delivery evident in the dose range-finding study with maternal doses of 100 mg/kg/day and above (relative exposures 0.2 and 0.5 in cirrhotic and non-cirrhotic patients, respectively). Maternal toxicity was associated with poorer pregnancy outcomes (including increased post-implantation loss) and reduced fetal body weight, but there were no treatment-related fetal malformations or variations in the dose range-finding study with maternal doses of up to 300 mg/kg/day (relative exposures 1 and 3 for cirrhotic and non-cirrhotic patients, respectively). In the definitive embryofetal toxicity study in rabbits there were no adverse maternal or fetal effects with maternal doses of up to 60 mg/kg/day, but the systemic exposure levels achieved in this study were well below those anticipated clinically (relative exposures 0.07 and 0.2 for cirrhotic and non-cirrhotic patients, respectively).

Pregnancy classification

The sponsor has proposed Pregnancy Category B1;[14] for the FDC GLE/PIB tablet. This category is appropriate for GLE based on lack of animal findings.

Phototoxicity

Glecaprevir absorbs light in the range of 290 to 350 nm and exhibits photo-instability in UV-visible light in aqueous solution at neutral pH. These properties are indicative of phototoxic potential, although the potential for risk is reduced by virtue of the fact that GLE-related material has very limited distribution to melanin containing tissues of the skin and eye. An in vitro phototoxicity assay conducted with GLE in Balb/c 3T3 mouse fibroblasts found evidence of phototoxicity (mean photo effect (MPE) of 0.240 was greater than the cut off of 0.15, and the photo-irritancy factor (PIF) greater than 10.3 exceeded the cut-off value of 5). As a result of this positive finding, the sponsor conducted an in vivo phototoxicity assay in pigmented rats, which looked for evidence of periorbital oedema and ophthalmological changes as well as skin reactions following UVR exposure of lightly or darkly pigmented skin. Female Long-Evans rats dosed with GLE at up to 600 mg/kg/day in two divided doses for 3 days had no clinical signs of phototoxicity, and histopathological examination of eyes revealed no effect of treatment. The NOEL for phototoxicity was associated with relative systemic exposure levels of 102 and 223 for cirrhotic and non-cirrhotic patients, respectively. The weight of evidence indicates that GLE does not have phototoxic potential.

Impurities

The proposed specifications for GLE-related impurities or degradants in the drug substance and product are below the ICH qualification thresholds. All identified impurities have been assessed for potential mutagenicity are considered non-mutagenic or are below the TTC level.

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

Paediatric use

No specific studies in juvenile animals were submitted, but this is not considered to be a deficiency as there were no toxicological findings of concern in adult animals or in the peri/postnatal toxicity study in rats.

Nonclinical summary and conclusions glecaprevir

Summary

- The nonclinical dossier was of high quality. Pivotal core safety pharmacology, toxicokinetic and repeat dose toxicity studies were GLP-compliant and were conducted in accordance with ICH guidelines.[15] The assessment of the nonclinical aspects of the FDC tablet will be discussed elsewhere.[16]
- Glecaprevir was shown to be a pangenotypic inhibitor of recombinant HCV NS3/4A protease from clinical isolates of HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a, with IC_{50} value ranging from 3.5 to 11.3 nM. No activity was found against a representative panel of seven human proteases.
- The EC_{50} for glecaprevir inhibition of subgenomic stable chimeric replicons encoding NS3/4A from GT1-4 and GT6 ranged from 0.85 to 4.6 nM, and was reduced by 6 to 11 fold in the presence of 40% human plasma. Similar activity was seen against a panel of 40 clinical samples from HCV GT1a, 1b, 2a, 2b, 3a, 4a, 4d and 5a, with a median EC50 value of 0.3 nM (range 0.05 to 3.8 nM). Glecaprevir does not have any activity against HIV-1 or HBV.
- The activity of glecaprevir against commonly encountered resistance mutations in NS3/4A was investigated. Substitutions at positions 36, 43, 54, 55, 56, 155, 166, or 170 had no impact on GLE activity. Glecaprevir was shown to be generally active against HCV replicons containing GT1a or 1b variants resistant to NS5A or NS5B polymerase inhibitors in transient transfection cell culture assays. However, based on the resistance selection studies, cross-resistance with other NS3/4A protease inhibitors is possible.
- Mutations in NS3/4A at position 156 were often associated with marked resistance to GLE, with A156M/T/V/G associated with 148 to 3106 fold resistance in 1a-H77, 1b-Con1, 2a-JFH-1, 2a, 2b, 3a or 4a replicons. Mutations at position 168 also conferred resistance to glecaprevir, but to a lesser extent than mutations at 156. Substitutions at position 80 did not reduce susceptibility to glecaprevir except in GT3a, where a Q80R substitution led to a 21 fold increase in EC_{50}.
- Glecaprevir and pibrentasvir showed additive to synergistic antiviral activity in an HCV replicon cell culture assay. Colony survival was reduced to zero when both were present at 10-fold above their respective EC_{50} values. Glecaprevir had additive to synergistic antiviral activity in combination with either sofosbuvir or with ribavirin in HCV replicon assays.
- Glecaprevir is not expected to exhibit off-target activity. Similarly, no notable effect on physiological functions was observed in a battery of safety pharmacology studies that encompassed the CNS, cardiovascular and respiratory systems.

[15] ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. EMA/CPMP/ICH/286/1995;
[16] Glecaprevir + Pibrentasvir (Maviret) [PM-2017-00210-1-1) new fixed dose combination Nonclinical Evaluation Report; TRIM ref. D17-695886

- The pharmacokinetic profile of glecaprevir in animals is comparable to that in humans, although some inter-species differences were observed. Absorption was generally rapid in all species, while oral bioavailability was variable, being very high in rodents, only moderate in dogs and low in monkeys. Similarly, plasma clearance was moderate in mice, dogs and monkeys, and low in rats.
- Plasma protein binding of glecaprevir was high in all animal species and humans. Glecaprevir accumulated in the liver (liver: plasma AUC ratios > 100, 34 and 10 in mice, rats and dogs, respectively), with limited distribution to extra-hepatic tissues. Elimination of glecaprevir was shown to be largely biliary in rats, with metabolism playing only a secondary role. In all species (including humans) elimination occurs predominantly via the faeces as unchanged glecaprevir or as the sulphonamide hydrolysis product M6, likely formed through the activity of intestinal microflora.
- Based on in vitro studies, inhibitors of intestinal P-glycoprotein and BCRP, OATP1B1 and OATP1B3 could increase glecaprevir systemic exposure. Glecaprevir may increase the systemic exposure of co-administered drugs that are substrates of intestinal CYP3A4, P-glycoprotein, BCRP, the hepatic transporters OATP1B1 and OATP1B3 and BSEP.
- The acute oral toxicity of glecaprevir in mice, rats and dogs is low.
- Repeat-dose toxicity studies by the oral route were conducted in mice (4 weeks), rats (up to 6 months) and beagle dogs (up to 9 months). Maximum exposures (AUC) were high in all species. Target organs for toxicity were the liver and/or gall bladder. In dogs, elevations in GGT, ALT, and ALP were associated with mild diffused transmural gallbladder oedema associated with minimal vacuolation of epithelial cells. Mice exhibited increased hepatic weight and serum ALP. These effects were mild and reversible, and the gallbladder findings were not seen in the 9 month study in dogs, despite higher levels of systemic exposure being achieved. In rats, administration of oral doses of up to 600 mg/kg/day produced hyperplasia, minimal to mild neutrophilic infiltration and minimal ulceration or necrosis of the stomach, probably as a result of local irritation of the test material.
- There were no toxicological findings in a 4 week repeat-dose study in rats dosed orally with a combination of glecaprevir and pibrentasvir. Glecaprevir exposures were approximately equal to those anticipated during clinical use of Maviret.
- Glecaprevir was not mutagenic in the bacterial mutation assay or clastogenic in vitro (human lymphocytes) or in vivo (rat micronucleus assay). Carcinogenicity studies have not been conducted, which is acceptable based on lack of genotoxicity and the proposed duration of treatment.
- Fertility was unaffected in male and female rats treated with glecaprevir at exposure levels ≥ 63 times the clinical AUC. No maternal or fetal toxicity was seen in an embryofetal toxicity study in rats and there were no adverse maternal or litter effects in the peri/postnatal development study in this species (relative exposures ≥ 47). Increased post-implantation loss and decreased fetal weight were seen in embryofetal development studies in rabbits, but only in the context of significant maternotoxicity. No treatment-related developmental abnormalities were observed in either species, although maternal toxicity precluded evaluation of glecaprevir at clinical exposures in the rabbit.
- Glecaprevir absorbs light in the range of 290 to 350 nm and exhibits photo-instability under UV-visible light. An *in vitro* assay indicated phototoxicity potential, but an in vivo study in rats showed no phototoxicity (relative exposure at NOEL ≥ 102). The weight of evidence indicates that GLE is unlike to cause phototoxicity in patients.

- The proposed limits for impurities are below ICH qualification thresholds. All identified impurities have been assessed for potential mutagenicity and are considered non-mutagenic or are below the TTC level.

Conclusions and recommendation

- There are no deficiencies in the nonclinical data for glecaprevir.
- Glecaprevir was shown to be a pangenotypic inhibitor of HCV NS3/4A protease and showed additive to synergistic antiviral activity with pibrentasvir in an HCV replicon assay. Glecaprevir activity against common NS3/4A resistance mutations has been adequately characterised.
- Secondary pharmacodynamics and safety pharmacology have not identified any clinically relevant hazards.
- The in vitro data indicated that glecaprevir inhibition of the hepatic efflux transporter BSEP is a possible source of DDI that may not have been examined clinically.
- Repeat-dose toxicity studies identified the liver and/or gall bladder as potential target organs for toxicity, but effects on these are not expected in patients.
- Glecaprevir was not genotoxic, and carcinogenicity studies are not warranted.
- The nonclinical data support the use of glecaprevir for the proposed indication; the overall recommendation will be provided in the assessment of the combination product for Maviret.

V. Nonclinical findings pibrentasvir

Introduction

The overall quality of the part of the nonclinical dossier concerning pibrentasvir was high and in general accord with the ICH guideline for nonclinical assessment of pharmaceuticals (ICH M3). The design and scope of the nonclinical testing strategy employed to assess pibrentasvir was appropriate. All relevant safety and toxicity studies were conducted according to GLP standards.

A study on the effect of pibrentasvir on the respiration rate of sludge (Study No. R&D/16/0982) was not evaluated as it pertained to environmental toxicity and is outside the remit of the nonclinical evaluation.

As an NS5A selective inhibitor, pibrentasvir belongs to the same pharmacological class as ledipasvir (first registered in May 2015 as the fixed-dose combination tablet Harvoni), ombitasvir (first registered in July 2015 as the fixed-dose combination tablet Viekira) and daclatasvir (registered June 2015 as single ingredient oral tablets Daklinza).

Pharmacology

Primary pharmacology

Primary pharmacological characteristics of pibrentasvir were assessed under in vitro conditions only, with no in vivo proof of concept studies submitted that demonstrated

anti-viral efficacy in animal models of HCV infection, which is acceptable since appropriate animal models are not readily available except for the chimpanzee.[17]

Anti-viral efficacy

Anti-viral efficacy was tested against genotypes 1-6 of NS5A using an HCV expression system where Huh-7 cells were transfected with replicons of the different HCV genotypes. Pibrentasvir exhibited pico molar inhibition of viral replication for nine tested genotype replicons (GT1a-H77, GT1b-Con1, GT2a-JFH-1, GT2a, GT2b, GT3a, GT4a, GT5a, GT6a; EC_{50} ranges: 1.4 to 4.3 pM). Similar inhibition was demonstrated using GT1 replicons from clinical isolates of HCV-infected individuals. Efficacy of pibrentasvir against replicons of GT1a-H77 and GT1b-Con1 was attenuated in the presence of 40% human plasma by 35 and 47 fold respectively, likely due to high plasma protein binding by pibrentasvir. Anti-viral activity of pibrentasvir was at least 10^5 and 10^7 times less potent against HIV-1 and HBV, respectively, than HCV genotypes. There was no evidence of cytotoxicity when tested in a standard MTT colourimetric assay. The therapeutic index of pibrentasvir was very high (as a ratio of the median toxic dose against the half-maximal effective concentration; TD_{50}: $EC_{50} > 10^7$).

Resistance to pibrentasvir

To assess the emergence of HCV variants resistant to pibrentasvir, Huh-7 cells expressing GT1a and 1b replicons were exposed to pibrentasvir concentrations 10, 100 and 1000 fold above the EC_{50}. Under these conditions, GT1a resistant strains were evident at pibrentasvir concentrations 10- and 100-folds above EC_{50} but not 1000-folds. Resistance to pibrentasvir was further explored with the resistant GT1a mutants: Q30D, Q30 deletion, Y93D, Y93H, Y93N and double mutant H58D + Y93H. All these mutants exhibited reduced replication efficiencies. Of all the identified mutants the Q30D variant was the least affected in replication efficiency, with up to a 44% reduction in replication efficiency; all other mutants had replication efficiencies less than 60% of that of wild-type HCV replicons. No resistant strains were observed for GT1b at any pibrentasvir exposure levels. With respect to emergent resistant strains for other genotypes (GT2a, 2b, 3a, 4a, 5a and 6a), only GT2a and 3a were reportedly found to have pibrentasvir-resistant HCV variants at 10 times above their respective EC_{50}, but not at 100-folds higher.

Combination studies with glecaprevir and pibrentasvir against genotypes 1a-H77 and 1b-Con1 for the selection of resistant mutants did not find evidence of emergent resistant colonies in the presence of the anti-viral substances at concentration 10 folds above their respective EC_{50} levels. Combination studies were not available for other HCV genotypes.

The resistance profile was assessed by looking at pibrentasvir susceptibility with various amino acid-substituted variants. For GT1a, the majority of single amino acid substitutions were susceptible to pibrentasvir except two mutants (M28G and Q30D) while around 50% of mutants with 2 or 3 substitutions had an increase in EC_{50} greater than 50 fold higher than the wild type. For GT2a, one double amino acid substituted variant exhibited significant resistance (F28H + M31I: > 14,000 folds difference in EC_{50}). Genotype 3a had four variants with significant resistance to pibrentasvir (S24F + M28K; A30K + Y93H; S24F + M28LK + A30K; A30K + L31I + Y93H). Replication efficiencies were not reported for these genotypes; thus it is uncertain whether the emergence of these HCV mutants would exhibit clinically significant viability. None of the mutants for genotypes 1b, 2b, 4a, 4d, 5a or 6a showed resistance to pibrentasvir.

HCV variants of genotypes 1a-H77, 1b-Con1, 2a, 2b, 3a, 4a, 5a and 6a known to be resistant to other NS5A inhibitors were tested with pibrentasvir where it was found that most were generally susceptible to pibrentasvir with EC_{50} values in the pico molar range, although cross-resistance was detected for some mutants (for example, GT1a

[17] Vercauteren K *et al*. (2015) Animal models for the study of HCV. *Curr. Opin. Virol.* 13: 67-74.

H58D+Y93H). As expected, variants resistant to NS3 and NS5b inhibitors were susceptible to pibrentasvir.

Secondary pharmacodynamics and safety pharmacology

A receptor, ion channel and transporter screening assay did not identify any significant secondary pharmacological activity by pibrentasvir. Weak antagonist activity was noted for (central) benzodiazepine receptors ($GABA_AR$; around 33% inhibition), H_1 receptors (22% inhibition) and Y_1 receptors (23% inhibition), but as these did not exceed the 50% cut-off mark that denotes significant secondary activity, these weak interactions are not considered clinically significant.

Specialised safety pharmacology studies covered the CNS, cardiovascular and respiratory organ systems. In vivo studies were conducted in mice and dogs and used pibrentasvir doses (up to 100 mg/kg PO in both species and 19 µg/kg/min by IV infusion in dogs) that attained plasma exposures of up to around 60 times and 14 to 18 times the clinical C_{max}. None of these studies revealed specific hazards or organ system toxicities, consistent with findings from repeat-dosing studies in which no organ specific targeted toxicities were evident.

Pharmacokinetics

Pibrentasvir is a large lipophilic molecule (MW: 1113.18) with minimal aqueous solubility (not soluble in phosphate buffer at pH ≥ 3.3). Higher solubility was achieved using a variety of diluents subsequently used in oral repeat-dose toxicity studies. Absorption of pibrentasvir was slow in all tested species and T_{max} ranged between 3 hours in dogs and 9 hours in mice (compared with 5 h in humans). Plasma exposures following oral dosing were highest in mice due to slow clearance (around 10 fold higher AUCs than rats with pibrentasvir formulated in the same dosing vehicle), followed by dogs ($AUC_{0-\infty}$ 41 µg·h/mL in fed mice at 3 mg/kg; 7.86 µg·h/mL in fasted dogs at 2.5 mg/kg; and 4.1 µg·h/mL in fasted rats at 3 mg/kg), which was the likely reason for selecting these two species for the toxicity studies. Bioavailability was low in all species (highest in dogs: ~30%; 9-10% in fed mice and fasted rats). Pibrentasvir exhibited low plasma clearance (mouse CL_p: 6.4 µL/h/kg; rat: 75 µL/h/kg; rabbit: 490 µL/h/kg; dog: 97 µL/h/kg). Elimination half-lives for pibrentasvir were long in all species (> 5 h) and $T_{½}$ was the most comparable between mice and humans (7 to 8 h in rats and dogs compared with 13 h in humans).

Plasma exposures in mouse and dog studies were mostly comparable between males and females; however, in rats female exposures (as AUC) were approximately half that of males. In all tested species plasma exposures were less than dose-proportional, indicating that absorption follows non-linear plasma kinetics.

Pibrentasvir exhibited very high plasma protein binding (> 99.9%) across all species, as well as in human subjects with varying grades of hepatic or renal impairment. Tissue distribution studies were conducted in albino SD rats and in Long Evans pigmented rats where highest levels were detected in bile (Tissue to Plasma: 6.3), liver (3.1), adrenal glands (3.4) and brown fat (1.6) at 2 to 4 hours post-dose. There was no evidence of distribution in the CNS, and nor was there evidence that radiolabelled pibrentasvir had affinity for pigmented tissue.

Biotransformation of pibrentasvir under in vitro conditions (i.e. using liver microsomes or hepatocytes) was low in all species (mouse, rats, dog, monkey, human). Unchanged pibrentasvir was the major entity detected for all species when liver microsomes were used. Of the minor metabolites detected, low levels of an *O*-demethylation product of pibrentasvir (M4) were detected in mouse and human plasma, whilst two mono-oxidation products (M10 and M11) were detected in dog plasma. There were no metabolites that

were unique to humans. Studies using human recombinant isozymes identified a minor role for CYP 3A4 in pibrentasvir biotransformation.

In all tested species (mouse, rat, dog, human) excretion of pibrentasvir was through the faecal route. Studies using bile-duct cannulated rats indicated that biliary transport was the main pathway for excretion by IV administration (84% of dose) while biliary excretion accounted for only around 3% of an oral dose, with the majority (92% of dose) excreted in faeces most likely as unabsorbed drug.

Based on the findings presented in the nonclinical pharmacokinetic studies, there were sufficient similarities in absorption, plasma protein binding, metabolism and/or excretion of pibrentasvir in mice and dogs to the human pharmacokinetic profile, to allow these animal species to serve as the appropriate models for assessing pibrentasvir toxicity.

Pharmacokinetic drug interactions[18]

Pibrentasvir did not exhibit significant inhibitory activity against CYP isozymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4. Inhibition of CYP 2D6 was up to 46.7% at 30 μM pibrentasvir. Pibrentasvir is unlikely to affect the exposure of CYP2D6 or other CYP isozyme substrates. UGT isozymes 1A1 and 1A4 were inhibited by pibrentasvir with IC_{50} values of 2.54 and 0.027 μM, respectively. Pibrentasvir did not inhibit UGT1A6, 1A9 or 2B7 and is therefore unlikely to affect the exposure of UGT1A1, 1A6, 1A9 or 2B7 substrates. There was no evidence of a clinically relevant interaction between pibrentasvir and 1A4 substrate lamotrigine. CYP enzyme induction by pibrentasvir was not demonstrated.

Following oral dosing of pibrentasvir, plasma exposures were higher in MDR1a/1b-BCRP knockout mice than in wild-type mice, whereas exposures did not differ when intravenous dosing was used. This increased bioavailability in MDR1a/1b-BCRP knockouts was attributed to absence of P-gp and/or BCRP mediated efflux; thus it was concluded that pibrentasvir is a P-gp substrate. For this reason, P-gp and/or BCRP inhibitors may increase the pibrentasvir exposure in patients. This was confirmed in a clinical study, where co-administration of pibrentasvir with glecaprevir enhanced pibrentasvir plasma exposures in human subjects by approximately three-folds due to an inhibitory effect of glecaprevir on P-gp and/or BCRP (see *Clinical Overview*), although enhancements to pibrentasvir plasma levels were not apparent in a rat combination study. Pibrentasvir is not a substrate of hepatic uptake transporters OATP1B1, 1B3 or OCT1.

Assessment of pibrentasvir actions against transporters found inhibitory activity against P-gp when vesicular preparations were used (IC_{50} 0.036 μM) but not when intact cells were used (MDCK-MDR1 cells; IC_{50}: > 150 μM). Inhibition was also reported for BCRP (IC_{50}: 14 μM), BSEP (IC_{50}: 39 μM) and uptake transporter OATP1B1 (IC_{50}: 1.3 μM with 4% BSA). Based on pharmacokinetic transporter interaction considerations, clinically relevant inhibition of P-gp, BCRP and OATP1B1 is predicted. Pibrentasvir is not an inhibitor of OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K.

[18] The following assumptions were made:
• molecular weight, 1113.18 g/mol; dose, 120 mg; $C_{max,}$ 0.10 μM (total); free fraction, 1%; intestinal volume, 0.25 L; absorption rate constant, 0.26 hr^{-1}; absolute bioavailability, not determined; k_{deg} for CYP3A, 0.0005 min^{-1}
• for intestinal CYP (CYP3A) and intestinal transporters (P-glycoprotein and BCRP): if the IC_{50} is ≤0.1-fold the intestinal concentration, an *in vivo* interaction is considered possible
• for systemic CYP, renal uptake and efflux transporters, and hepatic efflux transporters (OAT1, OAT3, OCT2, MRP2, BCRP, P-glycoprotein, MATE1 and MATE2K): if the IC_{50} is ≤50-fold the unbound clinical C_{max}, an *in vivo* interaction is considered possible
• for hepatic uptake transporters (OCT1, OATP1B1 and OATP1B3): if the IC_{50} is ≤25-fold the unbound hepatic inlet concentration, an *in vivo* interaction is considered possible.

Toxicology

Acute toxicity

A single dose study using the intravenous route was conducted in rabbits for the purposes of optimising systemic exposures to pibrentasvir. There were mortalities in both animals that received high dose pibrentasvir and because necropsy assessments did not uncover any significant findings to associate with cause, it was surmised that the dose tested (50 mg/kg, IV) was above the limit of solubility and therefore likely to have contributed to mortality. The toxicological significance of these findings is uncertain but likely to be low as the study did not use the clinical route and the number of animals in the treatment group was low (n = 2).

Repeat-dose toxicity

Repeat dose toxicity studies of up to 26 weeks in mice, 13 weeks in rats and 39 weeks in dogs were conducted using the clinical (oral) route. Duration of studies was acceptable in view of the period of clinical use (up to 16 weeks). Other design aspects of the studies (species choice, group sizes, etc) were appropriate and consistent with ICH guideline on Nonclinical safety studies to support marketing authorisation for new pharmaceuticals (M3(R2)).[19] The sponsor also provided a repeat dose study in rats that used pibrentasvir in combination with glecaprevir, although only one dose combination was tested.

Relative exposure

Exposure ratios are based on animal: human AUC values. Human reference values are based on AUC values determined for HCV-infected patients without cirrhosis, who were reported to have exposures similar to patients with cirrhosis ($AUC_{0\text{-}24h,ss}$ 1.43 and 1.53 µg.h/mL, respectively). High exposure multiples were achieved in mouse and dog studies (>10-times the clinical AUC), but in rats plasma exposures were low and variable between males and females. (The overall geometric mean of the pibrentasvir clinical AUC exposure in HCV-infected subjects with and without cirrhosis was 1.44 µg.h/mL; Study RD160234).

Table 6: Relative exposure in repeat-dose toxicity studies

Species	Study duration[Study no.]	Dose mg/kg/day	$AUC_{0\text{-}24\,h}$^ µg·h/mL	Exposure ratio#
Mouse (CD-1)	26 weeks [R&D/13/434]	3	16	11
		10	49	34
		100	123	86
	13 weeks [R&D/12/138]	3	19	13
		10	48	34
		100	128	90
Rat (SD)	13 weeks	3	2.1 / 1.23	1.5/0.9

[19] ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals.

Species	Study duration[Study no.]	Dose mg/kg/day	$AUC_{0-24\ h}$^ µg·h/mL	Exposure ratio#
	[R&D/13/600]	10	7.9 / 2.9	5.5/2
		30	10.2 / 5.6	7/3.9
	4 weeks (with glecaprevir) [R&D/16/0097]	20	3.0 / 1.2	2/0.8
Dogs (Beagle)	39 weeks [R&D/13/172]	10	4.7	3.3
		30	14	9.8
		100	25	17.5
	2 weeks [R&D/11/928]	10	10.8	7.6
		30	24.2	17
		300	45	31
Human (HCV-infected patients without cirrhosis)	steady state [R&D/16/0234 & -7]	120 mg	1.43	–

= animal: human plasma $AUC_{0-24\ h}$; ^ = data are for the sexes combined in mice and dogs and male/female in rats at the last sampling occasion

Major toxicities

There were no specific or targeted toxicities associated with pibrentasvir treatment in any of the tested species.

In mouse studies where animals were exposed at up to 300 mg/kg/day for 2 weeks and 100 mg/kg/day for 26 weeks, clinical signs were generally sporadic and minor in nature (discoloured fur, unkempt appearance). There were no treatment-related effects on body weight gain or food consumption. As well, there were no major gross changes reported in any of the studies. Minor decreases in spleen weights were reported in all dosed females from the 13 week study, but were not considered to be toxicologically significant as there was no histopathological correlate for these changes. As well, the effects were not dose dependent, nor were they seen in male animals. Two males from the 26 week study that were exposed to high dose pibrentasvir (100 mg/kg/day) exhibited proliferative histological changes in the liver (benign hepatocellular adenoma) and lung (benign bronchioalveolar adenoma), respectively. The study authors considered these to be incidental observations that perhaps were evident because of the advancing age of the animals. No other dose groups were examined to determine if there was a dose-dependency to these observations; however, considering that there were no other accompanying gross or histological changes nor were these effects seen in females or in other mouse repeat dose toxicity studies, it is agreed that the adenomas are likely to be a

spontaneous observation. At the NOAEL (the highest dose, 100 mg/kg/day) for the pivotal 26 week study in mice the relative exposure was 86 times the clinical AUC.

Repeat dose studies of up to 13 weeks were also performed in rats. There were no mortalities or significant clinical changes associated with pibrentasvir treatment. In the 3 week study, haematology assessments showed minor variations for some parameters (decreased WBC, eosinophils and lymphocytes at 100 mg/kg/day). The magnitude of these decreases was small; thus, such changes were not considered adverse. However, the toxicological significance of these findings is uncertain, especially considering that pibrentasvir exposures in rats were lower than for other tested species. Furthermore, the study was limited because pathology assessments were not conducted to determine if there were macroscopic or microscopic correlates associated with the haematological changes. In the 13 week study the highest dose tested was 30 mg/kg (up to 7 times the clinical AUC) and there were no treatment related mortalities or clinical changes. Post-mortem assessments found minimal changes that could be directly attributed to pibrentasvir exposure. There was one high dose female that was found to have a mammary adenocarcinoma but this was likely to be an incidental observation as there were no other incidences of mammary adenocarcinoma in any other females nor was this evident in other studies. The combined glecaprevir and pibrentasvir study used pibrentasvir at a dose of 20 mg/kg/day for 4 weeks (up to 2 times the clinical AUC). Findings were minor in nature (small reductions in potassium and cholesterol levels in males only, 23% decrease in reticulocyte count in males) and since only one dose of each antiviral was tested, the dose-dependency of these effects is unknown.

In dogs pibrentasvir was well tolerated at up to 100 mg/kg/day doses (17.5 times the clinical AUC) for up to 39 weeks. A non-GLP 2 week study used doses up to 300 mg/kg/day, which also gave rise to plasma exposures 31 times the clinical AUC, and were well tolerated by the treated animals. There were no mortalities in the studies, and clinical signs were sporadic in nature and thus considered unlikely to be related to treatment. There were no pibrentasvir-related effects on body weight gain, food consumption, ophthalmology, ECG parameters and urinalysis. In the 39 week study minor decreases in platelet and reticulocyte counts were observed from treatment day 92 onwards. Gross findings were variable and thus difficult to definitively ascribe to pibrentasvir exposure. In the 39 week study there were increases in spleen weights (relative to body weight) of up to 60% at the highest dose but only in female animals. In the 13 week study, relative spleen weights were decreased in both males and females, and at all doses. However, there were no macroscopic or microscopic correlates related to these findings. For both repeat dose toxicity studies in dogs, the NOAEL was 100 mg/kg/day (17 times the clinical AUC).

Overall, any treatment-related changes associated with pibrentasvir exposure were minor or sporadic in nature, were not consistently seen in both males and females or they did not exhibit dose-dependency. Exposures attained in the studies were of sufficient multiples of the clinical AUC to have adequate assurance that pibrentasvir is not anticipated to exert any targeted toxicities when used at the proposed dose level.

Genotoxicity

Pibrentasvir was not found to be mutagenic in a bacterial reverse mutation assay or clastogenic under in vitro or in vivo conditions in a human blood lymphocyte chromosomal aberration assay and a mouse micronucleus test, respectively. Studies were consistent with ICH guideline S2 (R1), used sufficiently high concentrations/doses of pibrentasvir and all studies were conducted according to GLP.

Carcinogenicity

Carcinogenicity studies were not conducted based on the fact that the duration of treatment is expected to be no more than 16 weeks, as per the ICH guideline S1A[20] mandated period where carcinogenicity studies should be performed if a pharmaceutical is intended for continuous use of 6 months and more or intermittent use for chronic or recurrent conditions. As well, in the absence of genotoxicity findings or preneoplastic changes in repeat dose toxicity studies following treatment periods of up to 26 weeks in mice and 39 weeks in dogs, pibrentasvir is not anticipated to represent a significant carcinogenic risk above that expected of a patient population already at risk of certain cancers.

Reproductive toxicity

The reproductive toxicity potential of pibrentasvir was assessed in mice and rabbits using GLP-compliant studies that encompassed all stages of development and included all relevant exposure periods. Group sizes, timing and duration of treatment were generally satisfactory and consistent with the ICH guidance on reproductive toxicity (ICH S5 R2). Mice instead of rats were used as the primary rodent species because higher systemic exposures were attained in mice, compared with rats.

Relative exposure

See Table 7, below.

Table 7: Relative exposure in reproductive toxicity studies

Species	Study [Study no.]		Dose mg/kg/day	$AUC_{0-24\,h}$ µg·h/mL	Exposure ratio#
Mice Crl:CD1(ICR)	Fertility (males) [R&D/14/0682]	♂	3	21.2	14.7
			10	69.1	48
			100	153	107
		♀*	3	22	15
			10	43	30
			100	141	99
	Embryofetal development [R&D/13/950]		3	9.63	6.7
			10	23.6	16.5
			100	73.1	51
	Pre-/postnatal development [R&D/15/0822]		3	14.5	10
			10	32.4	23
			100	107	74
Rabbit	Embryofetal		10 (PO)	0.404	0.3

[20] ICH S1A - Note for guidance on the need for carcinogenicity studies of pharmaceuticals.

Species	Study [Study no.]	Dose mg/kg/day	$AUC_{0-24\,h}$ µg·h/mL	Exposure ratio#
(NZW)	development [R&D/13/638]	100 (PO)	2.11	1.5
	Embryofetal development [R&D/13/321]	2 (IV)	2.63	1.8
		5 (IV)	4.76	3.3
		10 (IV)	21.2	15
Human	steady state [R&D/16/0237; R&D/16/0234]	120 mg Non-Cirrhotic HCV	1.43	–

= animal: human plasma $AUC_{0-24\,h}$; * based on toxicokinetic data in the 13-week repeat dose study (R&D/12/138) in females.

Dosing in mice was sufficiently high with relative exposures of 51 times the clinical AUC for embryofetal development studies, 102 times for fertility and 74 times for pre/postnatal studies. It is noted that plasma exposures were lower in females than in males. Repeat-dose toxicity studies of up to 26 weeks did not indicate significant differences in plasma exposures between males and females. For rabbit embryofetal development studies, when the oral route was used relative exposures were subclinical or on par with clinical exposures (up to 1.5 times the clinical AUC). Pibrentasvir administered intravenously resulted in exposures up to 15 times the clinical AUC.

Pibrentasvir was shown to cross the placenta in mice and rabbits. In rats, although radioactivity denoting the presence of pibrentasvir was reported in the placenta, there was limited distribution into fetal organs and therefore limited placental transfer in rats; however, this may have been due to lower bioavailability of pibrentasvir in rats *cf*. mice or rabbits. Pibrentasvir is also likely passed through milk since pibrentasvir was detected in pooled plasma from pre-weaned mouse pups.

Pibrentasvir at doses of up to 100 mg/kg/day was not found to affect male or female fertility in mice. There were no treatment-related mortalities, changes to body weight or clinical signs in either males or females. In females oestrus cycling was not affected by pibrentasvir treatment. In males, sperm count, motility and morphology were not evaluated to establish whether there is a targeted effect on the male reproductive system; however, gross examination of organs (epididymides, testes, seminal vesicles and prostate gland) did not reveal any treatment-related effects. As well, there were no treatment-related effects on mating or fertility indices.

In embryofetal development studies, pibrentasvir did not affect litter parameters or cause developmental abnormalities in either mice or rabbits at doses of up to 100 mg/kg/day. There were no treatment-related findings in mice, with no mortalities, changes to body weight gain, clinical signs or necropsy findings that denoted treatment-related effects. Maternal toxicokinetic parameters were generally consistent with those of female mice reported in other submitted studies; therefore, exposures attained in the embryofetal development studies were adequate.

In the rabbit, a preliminary tolerability study used 2 doses (10 and 100 mg/kg/day) where there were no overt toxicities reported. One dam from the 100 mg/kg group was found dead on GD 11 with necropsy findings consistent with dose-administration related injury. However, another rabbit from the 100 mg/kg group also exhibited weight loss and scant faeces, as well as reduced food consumption. For the main study, the same doses were

used on the basis that the doses of up to 100 mg/kg/day were well tolerated in rabbits. In the main study mortalities were seen in all groups including controls. These were preceded by a similar raft of clinical signs such as ataxia, ptosis, hunched posture, bradypnoea, and reduced grooming. In the surviving animals weight loss was noted across all groups including controls. Clinical signs included ungroomed coats, soft or liquid faeces. Despite these maternal changes, there were no treatment-related changes to litter parameters. Fetal variations and malformations were comparable between control and pibrentasvir-treated groups. Although adverse maternal findings were not related to exposures to pibrentasvir, it is noted that exposures attained in the main embryofetal development study were approximately twice as high as those in the preliminary study where adverse findings were not as pronounced (Preliminary study AUC: 10 mg/kg 0.191 µg.h/mL; 100 mg/kg 0.802 µg.h/mL; Main study AUC: 10 mg/kg 0.404 µg.h/mL; 100 mg/kg 2.11 µg.h/mL). The study authors attributed adverse findings to the choice of vehicle used in the study (Phosal 53MCT:PEG400: Poloxamer 124: Cremophor RH40), which is likely the case. This was likely unique to rabbits as all other test species exhibited good tolerance to the vehicle in chronic oral dosing studies. Despite the adverse maternal findings, these did not extend to embryofetal development and the NOAEL was the highest tested dose of pibrentasvir (100 mg/kg/day, PO; 1.5 times the clinical AUC). Higher exposures were attained when the intravenous route was used (at up to 14 times the clinical AUC) but there were high maternal mortalities and morbidities in all groups, including vehicle treated dams. For this reason litter and fetal assessments were not conducted. It is noted that one dam from the low dose group (2 mg/kg/day, IV) and 3 from the high dose group (10 mg/kg/day, IV) were euthanised ahead of scheduled necropsy because they had aborted their pups. Further detail was not provided but in amendments to the study report (Study No. R&D/13/321), the study authors clarified that the dams that aborted or exhibited total litter loss did so in the presence of maternotoxicity. Nevertheless, abortions and/or litter loss occurred only in dams that received intravenous doses of pibrentasvir. Since pibrentasvir is not intended to be administered intravenously, these findings have uncertain toxicological significance but are noted.

A pre-/postnatal development study in mice did not show evidence of a treatment-related effect on postnatal development at doses of up to 100 mg/kg/day. There were no pibrentasvir-related effects on maternal health during gestation or lactation periods. Treatment did not affect gestation length or parturition, and there was no effect on litter parameters or the viability or lactation index in any of the dose groups. With regard to F_1 generation offspring, there were no treatment-related mortalities or clinical signs reported at pre-weaning or post-weaning periods of the postnatal development period. Developmental milestones were generally unaffected by pibrentasvir treatment, although F_1 generation males from the mid dose and high dose groups exhibited slightly but significantly longer timing of preputial separation that was attributed to slightly higher body weights at the time of the assessment. However, these changes did not impact on the reproductive functions of F_1 generation offspring, who exhibited fertility and litter parameters and embryofetal viability comparable to vehicle treated animals. Overall, pibrentasvir was not found to have any detrimental effects on litter parameters, postnatal development and subsequent reproductive function in offspring exposed to pibrentasvir through maternal exposures and the NOAEL was the highest dose tested, 100 mg/kg/day (74 times the clinical AUC).

Pregnancy classification

The sponsor has proposed Pregnancy Category B1.[21] Based on the absence of adverse findings on litter parameters and embryofetal development in mice and rabbits (albeit, the

[21] B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the

latter in the context of vehicle-related maternotoxicity), a B1 category is considered acceptable for pibrentasvir. As the product is formulated as a fixed dose product, acceptability of a B1 category will also depend on whether there were no significant findings in the reproductive toxicity studies on glecaprevir.

Local tolerance

There were no dedicated local tolerance studies conducted on pibrentasvir nor were they required.

Phototoxicity

Tissue distribution studies did not identify an affinity of pibrentasvir for pigmented tissues. Nevertheless, based on its spectral attributes (absorbance in the range of 290 to 320 nm), an *in vitro* study was conducted to assess the phototoxic potential of pibrentasvir using the Neutral red uptake cell-based assay. Pibrentasvir at up to 3 mg/L did not induce cytotoxicity in Balb/c 3T3 mouse fibroblast cells following UV irradiation, whereas positive control promethazine impaired uptake of Neutral red dye and thus denoted photo-induced cytotoxicity. Therefore, pibrentasvir was not found to have significant phototoxic potential.

Impurities

The proposed specifications for process-related impurities and degradants in the drug substance and product have been adequately qualified. All identified impurities have been assessed for potential mutagenicity are considered non-mutagenic or will be controlled below the TTC level.

Paediatric use

Pibrentasvir has not been proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions pibrentasvir

Summary

- The quality of data relevant to pibrentasvir was generally high. Studies were conducted in accordance with ICH guideline for the nonclinical assessment of pharmaceuticals (M3(R2))[15] and all pivotal safety and toxicity studies were conducted according to GLP.
- Under in vitro conditions, pibrentasvir exhibited pico molar inhibition of viral replication for genotypes 1 to 6 against replicons GT1a-H77, GT1b-Con1, GT2a-JFH-1, GT2a, GT2b, GT3a, GT4a, GT5a, GT6a (EC_{50} ranges: 1.4 to 4.3 pM). Antiviral activity is attenuated in the presence of 40% human plasma, which may be associated with high plasma protein binding.
- Pibrentasvir-resistant variants were reported for GT1a, 2a and 3a. With respect to GT 1a, the emergent mutants had significantly impaired replication efficiencies; therefore, the likelihood of clinical viability is low. Replication efficiencies were not determined for mutants of GT 2a and 3a, thus it is uncertain whether emergence of these HCV mutants would harbour clinically relevant resistance. HCV variants that are resistant to other NS5A inhibitors were generally susceptible to pibrentasvir, although some mutants were resistant to pibrentasvir. Combination of pibrentasvir with glecaprevir

human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

against replicons of GT 1a-H77 and 1b-Con1 confirmed susceptibility. Combination studies were not available for other HCV genotypes.

- Pibrentasvir did not have any significant off-target effects. Specialised safety pharmacology studies covering the CNS, cardiovascular and respiratory organ systems did not reveal any specific hazards or organ specific toxicities.
- Pibrentasvir has low bioavailability (< 50%) that is augmented in human subjects when co-administered with glecaprevir. Absorption is slow with T_{max} ranging between 3.7 to 9 hours in nonclinical species. Pibrentasvir exhibits very high plasma protein binding (> 99.9% for all species). Unchanged pibrentasvir was the predominant entity detected in plasma and excreta in all species, with a few minor metabolites detected in mouse and human plasma. Pibrentasvir is excreted through the faecal route, with biliary transport involvement.
- Pibrentasvir is not expected to alter the exposure of co-administered drugs that are CYP450 substrates. Although pibrentasvir inhibited UGT 1A4 in vitro (IC_{50}: 0.027 μM) this does not appear to be clinically relevant based on a lack of interaction with the UGT1A4 substrate lamotrigine. Based on pharmacokinetic transporter interaction considerations, clinically relevant inhibition of P-gp, BCRP and OAT1B1 is predicted.
- Pibrentasvir had a low order of acute oral toxicity in rats and dogs. A single dose intravenous study in rabbits, for the purpose of optimising systemic exposures to pibrentasvir, reported mortalities that were surmised to be due to issues of solubility and are not of toxicological relevance.
- Repeat dose toxicity studies by the clinical (oral) route were conducted in mice (up to 26 weeks), rats (up to 13 weeks) and dogs (up to 39 weeks). There were no specific or targeted toxicities associated with pibrentasvir treatment in any of the tested species and generally pibrentasvir appeared to be well tolerated in mice (at exposures 86 times the clinical AUC) and dogs (17.5 times the clinical AUC). Exposures attained were at high enough multiples of the clinical AUC to have sufficient certainty that pibrentasvir is unlikely to exert any targeted toxicities when used at the proposed dose level.
- Pibrentasvir was not mutagenic in a bacterial reverse mutation assay or clastogenic under in vitro and in vivo conditions in a human blood lymphocyte chromosomal aberration assay and a mouse micronucleus test, respectively. In view of the fact that duration of treatment is expected to be no more than 16 weeks, carcinogenicity studies were not conducted as per ICH guideline S1A (S5) on the need for carcinogenicity studies on pharmaceuticals.
- Pibrentasvir crosses the placenta and is passed in the milk. Pibrentasvir at doses of up to 100 mg/kg/day did not affect fertility in male and female mice. In embryofetal development studies, pibrentasvir did not affect litter parameters or cause developmental abnormalities in either mice or rabbits at oral doses of up to 100 mg/kg/day (up to 51 times and 1.5 times the clinical AUC). There was no evidence of treatment-related effects on developmental milestones or fertilities of F_1 generation mice exposed to pibrentasvir during the pre-/postnatal period.
- An in vitro cell-based assay to assess the phototoxic potential of pibrentasvir was negative. Studies on a pibrentasvir excipient (Capryol 90 – propylene glycol monocaprylate II) did not find evidence of mutagenic potential, oral toxicity at doses up to 2500 mg/kg/day or development toxicity.
- The proposed limits for drug substance and drug product impurities have been adequately qualified by submitted toxicity data.

Conclusions and recommendation

- In vitro virology studies demonstrate sufficient nonclinical efficacy against the NS5A protein of the HCV. Emergence of viable resistant variants is likely to be low for HCV GT1a based on reduced replication efficiencies.
- Pibrentasvir exhibits very high plasma protein binding (> 99.9% for all species). Pibrentasvir undergoes very low biotransformation. Significant inhibitory effects against UGT1A4 under in vitro conditions have not been found to be clinically relevant; however, clinically relevant inhibition of P-gp, BCRP and OAT1B1 is predicted.
- There were no targeted toxicities associated with pibrentasvir treatment in any of the tested species and generally pibrentasvir was well tolerated in the tested nonclinical species.
- The Sponsor proposed a Pregnancy Category B1 for the fixed-dose combination tablet product. There were no adverse developmental findings, thus contingent of there being no significant findings in the reproductive toxicity studies on glecaprevir, Category B1 is considered appropriate.
- Overall, there were no major deficiencies identified in the nonclinical dossier of MAVIRET that related to pibrentasvir.
- The draft PI should be amended as directed in the consolidated nonclinical evaluation report for the glecaprevir and pibrentasvir combination (Marviret).

VI. Nonclinical findings glecaprevir + pibrentasvir

Introduction

The overall quality of the submitted dossier was high, and the sponsor clearly identified the rationale behind the submitted studies. All pivotal safety studies were conducted under GLP conditions and their design was in general accordance with ICH guidelines. Nonclinical studies conducted with the individual agents, glecaprevir and pibrentasvir, have been evaluated separately (see above). This evaluation report addresses studies pertinent to the combination product, which includes pharmacology and pharmacokinetic drug interaction studies, and the toxicity of the combination product.

According to the TGA adopted EU guideline on fixed dose combination products;[22] for new active substances being developed for use in a fixed dose combination, a complete nonclinical development programme for each individual active substance would normally be expected to be supplemented by bridging studies with the combination. This approach is consistent with a draft FDA guidance document for direct-acting antiviral drugs.[23]

The only combination toxicity study submitted was a 4 week safety study with a single low dose of the combination.

[22] Guideline on the nonclinical development of fixed combinations of medical products. 24 January, 2008. EMEA/CHMP/SW/258498/2005.
[23] FDA Draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing direct-acting antiviral drugs for treatment. October 2013, Revision 1.

Pharmacology

Antiviral activity

Glecaprevir and pibrentasvir act on separate and distinct targets on the HCV viral protein to prevent replication. The efficacy studies submitted assessed the inhibitory activity of both agents in biochemical and/or standard subgenomic HCV replicon assays. Primary pharmacological characteristics of both agents were assessed under in vitro conditions only, with no in vivo proof of concept studies submitted that demonstrated anti-viral efficacy in animal models of HCV infection, which is acceptable since appropriate animal models are not readily available except for the chimpanzee.[24]

Glecaprevir was shown to be a pangenotypic inhibitor of HCV NS3/4A protease, which is essential for proteolytic cleavage of the HCV encoded polyprotein, and hence for viral replication. In a biochemical assay glecaprevir inhibited the proteolytic activity of recombinant NS3/4A enzymes from clinical isolates of HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a, with IC_{50} value ranging from 3.5 to 11.3 nM (see Table 8). No activity was found against a representative panel of seven human proteases. Pibrentasvir is a pangenotypic inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly.

Table 8: Activity of glecaprevir and pibrentasvir against HCV GT 1-6 NS3/4A protease and/or NS5A in stable replicons (in the absence of human plasma)

HCV subtype	Glecaprevir IC_{50} (nM) (purified NS3/4A protease)	Glecaprevir Median EC_{50} (nM) (stable replicons encoding NS3/4A from laboratory strains)	Pibrentasvir Median EC_{50} (nM) (stable replicons encoding NS5As from laboratory strains)
1a	4.6	0.85	0.0018
1b	8.9	0.94	0.0043
2a	3.5	2.2	0.0023
2b	3.8	4.6	0.0019
3a	7.9	1.9	0.0021
4a	6.1	2.8	0.0019
5a	8.1	NA	0.0014
6a	11.3	0.86	0.0028

NA = not available

Glecaprevir and pibrentasvir inhibited the replication of subgenomic stable replicons cultures encoding NS3/4A and NS5A, respectively, from genotypes 1 to 6 (obtained from laboratory strains). The EC_{50} values for both agents against each genotype are shown in Table 8 (glecaprevir activity against GT5a was not tested as a cell line with a viable replicon containing the GT5a protease domain could not be generated). The results in Table 8 were obtained in the absence of human plasma; the potency of glecaprevir and

[24] Vercauteren K *et al.* (2015) Animal models for the study of HCV. *Curr. Opin. Virol.* 13: 67-74.

pibrentasvir against GT1a and 1b were reduced in the presence of 40% human plasma by 6 to 11 fold and 35 and 47 fold, respectively, which is a reflection of the high degree of plasma protein binding for both agents.

The in vitro efficacy of glecaprevir and pibrentasvir against transient chimeric replicons encoding NS3/4A or NS5A from clinical samples is shown in Table 9 (in the absence of human plasma). The unbound plasma C_{min} and C_{max} values for glecaprevir in non-cirrhotic patients;[25] are approximately equal to and 60 fold greater than the median glecaprevir GT1-6 EC_{50} value of 0.3 nM. Taking into account the finding that the liver exposure for glecaprevir (based on AUC) is likely to be much higher than that of plasma (being more than 25 and 10 fold higher in rodents and dogs, respectively) the in vitro data are supportive of the likely NS3/4A inhibitory activity of the glecaprevir component of Maviret at the proposed dose. Similarly, for pibrentasvir, the unbound plasma C_{min} and C_{max} values in non-cirrhotic patients (0.17 nM and 0.99 nM, respectively);[26] are 155 and 900-fold greater than the median EC_{50} value of 0.0011 nM, and support the inhibition of HCV NS5A by the pibrentasvir component at the proposed dose. Neither glecaprevir nor pibrentasvir showed any activity against HBV or HIV-1.

Table 9: Activity of glecaprevir and pibrentasvir against HCV GT 1 to 6 NS3/4A protease and/or NS5A from clinical samples in transient replicon assays (in the absence of human plasma)

HCV subtype	Glecaprevir		Pibrentasvir	
	No. of clinical isolates	Median EC_{50}, nM (range)	No. of clinical isolates	Median EC_{50}, nM (range)
1a	11	0.08 (0.05-0.12)	11	0.0009 (0.0006-0.0017)
1b	9	0.29 (0.20-0.68)	8	0.0027 (0.0014-0.0035)
2a	4	1.6 (0.66-1.9)	6	0.0009 (0.0005-0.0019)
2b	4	2.2 (1.4-3.2)	11	0.0013 (0.0011-0.0019)
3a	2	2.3 (0.71-3.8)	14	0.0007 (0.0005-0.0017)
4a	6	0.41 (0.31-0.55)	8	0.0005 (0.0003-0.0013)
4b	NA	NA	3	0.0012 (0.0005-0.0018)
4d	3	0.17 (0.13-0.25)	7	0.0014 (0.0010-0.0018)

[25] Unbound C_{min} and C_{max} = 0.4 nM and 17.8 nM, respectively, based on total C_{max} 597 ng/mL (712 nM), C_{min} = 13 ng/mL (15.5 nM) and 2.5% unbound

[26] Unbound C_{min} and C_{max} = 0.17 nM and 0.99 nM, respectively, based on total C_{max} 0.11 µg/mL (0.099 µM), C_{min} = 0.019 µg/mL (0.017 µM), and 1% unbound.

HCV subtype	Glecaprevir		Pibrentasvir	
5a	1	0.12	1	0.0011
6a	NA	NA	3	0.0007 (0.0006-0.0010)
6e	NA	NA	1	0.0008
6p	NA	NA	1	0.0005
GT1-5/6	**40**	**0.30 (0.05-3.8)**	**74**	**0.0011 (0.0003-0.0035)**

NA = not available

Resistance in cell culture

Glecaprevir

Amino acid substitutions at positions 155 (R155K), 156, 168 (D168V) and 80 (Q80K) are signature mutations for NS3/4A protease inhibitors.[27] Changes at position 156 were often associated with marked resistance to glecaprevir, with A156M/T/V/G associated with 148 to 3106-fold resistance in 1a, 1b, 2a, 2b, 3a or 4a replicons. Substitutions at position 168 in GT 1a, 1b, 3a or 4a reduced susceptibility to GLE by up to 55 fold, and by 38 to 191 fold in GT6a, but had no or minimal impact in GT 2a and 2b (up to 5.6 fold increases in EC_{50}). Q168R in GT3a showed 54-fold resistance and Y56H+Q168R showed 1387 fold resistance to GLE. Substitutions at position 80 did not reduce susceptibility to GLE except in GT3a, where a Q80R substitution led to a 21 fold increase in EC_{50}. Glecaprevir retained activity against common R155 variants (including double substitutions), in particular R155K in GT1a (levels of resistance for R155 variants were up to 2.6 fold for variant R155C in GT4a and 1.9 fold for variant R155T in GT1a).

With respect to other single amino acid substitutions, activity was retained (less than 5-fold resistance) in GT 1a, 1b, 2a, 2b, 3a, 4a, 4d and 6a transient replicons containing substitutions at positions 15, 36, 41, 43, 54, 55, 56, 67, 71, 79, 89, 146, 150, 154, 160, 166, 170, 173, 176, 178, or 179, or in the helicase domain at 334, 342, 357, 406, 449, or NS4A position 23. Antiviral efficacy was also examined against HCV replicons containing GT1a or 1b variants resistant to NS5A or NS5B polymerase inhibitors in transient transfection cell culture assays. All NS5A/B variants tested were sensitive to glecaprevir (< 5 fold resistance). However, based on the resistance selection studies, cross-resistance with other NS3/4A protease inhibitors is possible.

Pibrentasvir

The resistance profile was assessed by looking at pibrentasvir susceptibility with various amino acid-substituted variants. For GT1a, the majority of single amino acid substitutions were susceptible to pibrentasvir except two mutants (M28G and Q30D), while around 50% of mutants with 2 or 3 substitutions had an increase in EC_{50} greater than 50 fold higher than the wild type. For GT2a, one double amino acid substituted variant exhibited significant resistance (F28H + M31I: > 14,000 fold difference in EC_{50}). Genotype 3a had four variants with significant resistance to pibrentasvir (S24F + M28K; A30K + Y93H; S24F + M28LK + A30K; A30K + L31I + Y93H). Replication efficiencies were not reported for these genotypes; thus it is uncertain whether the emergence of these HCV mutants would

[27] Götte, M. and Feld, J.J. (2016). *Nature Reviews (Gastroenterology & Hepatology)* 13**:** 338-351.

exhibit clinically significant viability. None of the mutants for genotypes 1b, 2b, 4a, 4d, 5a or 6a showed resistance to pibrentasvir.

HCV variants of genotypes 1a-H77, 1b-Con1, 2a, 2b, 3a, 4a, 5a and 6a known to be resistant to other NS5A inhibitors were tested with pibrentasvir where it was found that most were generally susceptible to pibrentasvir with EC_{50} values in the pico molar range, although cross-resistance was detected for some mutants (for example, GT1a H58D+Y93H). As expected, variants resistant to NS3/4A and NS5B inhibitors were susceptible to pibrentasvir.

In support of the proposed FDC formulation, glecaprevir and pibrentasvir showed additive to synergistic antiviral activity in a three day HCV replicon cell culture assay. The combination was shown to exhibit increased suppression of resistant colonies in a colony survival assay compared with each agent on its own. Glecaprevir and pibrentasvir also showed additive to synergistic activity with sofosbuvir, as did glecaprevir and ribavirin. Glecaprevir did not affect the in vitro activity of the HIV-1 protease inhibitors lopinavir and darunavir, and they in turn did not affect the in vitro efficacy of glecaprevir.

Pharmacokinetics

Both glecaprevir and pibrentasvir undergo minimal metabolism by CYP enzymes, and thus their clearance is unlikely to be affected by CYP450 inhibitors or inducers.

In vitro and in vivo assays indicated that glecaprevir and pibrentasvir are both substrates of P-gp and BCRP, and glecaprevir is also a substrate of the hepatic uptake transporters OATP1B1 and OATP1B3. Drug-drug interactions (DDIs) mediated by these transporters are predicted. This was confirmed in a clinical study, where co-administration of pibrentasvir with glecaprevir enhanced pibrentasvir plasma exposures in human subjects by approximately three-folds due to an inhibitory effect of glecaprevir on P-gp and/or BCRP. Neither agent is a substrate of OCT1.

Glecaprevir is not predicted to have clinically relevant inhibition of hepatic CYP450 or UGTs, but has the potential to inhibit intestinal CYP3A4. Pibrentasvir is unlikely to affect the exposure of CYP isozyme substrates. It is predicted that pibrentasvir is unlikely to affect the exposure of UGT1A1, 1A6, 1A9 or 2B7 substrates. In vitro evidence of inhibition of UGT1A4 by pibrentasvir (IC_{50} 0.027 μM) did not correlate to a clinically relevant interaction between pibrentasvir and 1A4 substrate lamotrigine.

In vitro assays showed that inhibition of P-gp, BCRP and OATP1B1 by glecaprevir and pibrentasvir and OATP1B3 by glecaprevir may be clinically relevant. Inhibition of BSEP by glecaprevir is an additional possible source of DDI. Glecaprevir and pibrentasvir do not inhibit OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K.

Toxicology

Glecaprevir and pibrentasvir are both lipophilic and have minimal aqueous solubility, so the effect of formulation and dose defined the maximum feasible exposures in the nonclinical species, which were used in the repeat-dose toxicity studies. Glecaprevir and pibrentasvir both have a low order of acute oral toxicity. For both agents repeat-dose toxicity studies were conducted in mice, rats and dogs, and the design and conduct of the pivotal studies were consistent with ICH guidelines[28] with respect to GLP compliance, species used, group sizes, duration of treatment and extent of monitoring. ERs noted

[28] ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. EMA/CPMP/ICH/286/1995; Guideline on repeated dose toxicity. CPMP/SWP/1042/99/Rev 1.

below are AUC values in animal species compared to the clinical AUC in cirrhotic patients for glecaprevir and non-cirrhotic patients for pibrentasvir. The glecaprevir ER in non-cirrhotic patients is approximately twice the ER for cirrhotic patients, and the pibrentasvir ER is similar in cirrhotic and non-cirrhotic patients. For glecaprevir, the maximum achieved relative exposures in the repeat dose toxicity studies in all 3 species were high. High exposure multiples were achieved in mouse and dog studies with pibrentasvir (> 10 times the clinical AUC), but in rats plasma exposures were low and variable between males and females.

Both agents were generally well tolerated in all species. For glecaprevir, the major target organs for toxicity included the gastrointestinal system (including the gall bladder) and the haematopoietic system. Glecaprevir effects on the gall bladder are unsurprising considering the tissue distribution and biliary route of elimination, and are consistent with other NS3/4A protease inhibitors, such as paritaprevir and grazoprevir.

Glecaprevir

The gastrointestinal changes in the glecaprevir studies were generally self-limiting (mild faecal changes and increased incidences of vomiting in dogs, with no consistent or dose-dependent consequences for food consumption or body weight gain) or only seen at very high exposures (hyperplasia, minimal to mild neutrophilic infiltration and minimal ulceration or necrosis of the stomach in rats dosed at 600 mg/kg/day for 2 weeks). The latter effect is likely to be a result of local irritation of the test material, and not considered to be clinically relevant. Gallbladder toxicity in dogs treated for up to 13 weeks consisted of mild diffuse transmural oedema for both males dosed at 200 mg/kg/day for 2 weeks (ER 155) and at doses ≥ 20 mg/kg/day for 13 weeks (ER 1.5). This was associated with concurrent minimal vacuolation of gallbladder epithelial cells in the 13 week study at doses of 60 mg/kg/day and above (ER 35). No gallbladder abnormalities were seen in recovery animals or in any of the dosage groups in the 9 month study. There was no evidence of gallbladder effects in the repeat-dose studies in mice (and the rat lacks a gallbladder so cannot be used to assess toxicity of this organ).

Hepatic effects were not consistently seen in the studies with glecaprevir. In mice, they were limited to an increase in organ weight at a dose of 300 mg/kg/day for males in the 7 day study, and for females in the 29 day study (ER ≥ 34). Clinical chemistry findings were limited to mild increases in serum cholesterol, and minimal increases in serum ALP and bilirubin at doses of 125 mg/kg/day and above for 7 days or 4 weeks (ER ≥ 24). Hepatic effects in dogs included reversible increases in GGT (up to 4.6 fold) and/or ALT levels (up to 8 fold) at times during the 9 month study (with similar increases in ALT also reported in the 13 week study in this species). Serum ALP levels were also increased up to 5.5-fold for some dogs in the 13 week study. These effects are suggestive of possible cholestasis, and were observed at ER ≥ 35. The above effects in mice and dogs were not associated with any gross or microscopic pathological changes. There was no evidence of hepatic toxicity in rats dosed at up to 120 mg/kg/day for 26 weeks (ER 70).

Minimal glecaprevir-related reductions in red cell parameters were observed in the 7 day study in mice and 13 week study in dogs, with minimal increases in red cell distribution width and platelet volume in male mice, suggestive of a regenerative bone marrow effect. These effects were small and reversible and considered not to be of biological relevance, and were not reported in rats or in the longer term studies in mice or dogs. Minimal, dose dependent decreases in serum potassium and phosphorous seen in the 26 week repeat-dose study in rats were not observed in mice or dogs.

Pibrentasvir

There were no major adverse effects in repeat-dose studies with pibrentasvir in mice (doses up to 100 mg/kg/day for up to 26 weeks, ER = 86), rats (doses up to 100 mg/kg/day for up to 3 weeks, or 30 mg/kg/day for 13 weeks, ER = 7) and dogs (doses up to 100 mg/kg/day for up to 39 weeks, ER 17). In the 39 week dog study minor decreases in platelet and reticulocyte counts were observed from treatment Day 92 onwards, ER 17.5.

Based on the lack of any toxicologically relevant haematological findings or any effects on immune organ weights, histopathology, serum globulins and a lack of evidence of infections, glecaprevir and pibrentasvir are not considered to have any effects on the immune system, and the absence of any dedicated immunotoxicity studies is acceptable.

Glecaprevir + pibrentasvir

There were no toxicities reported in a 4 week repeat-dose study in rats dosed orally with glecaprevir and pibrentasvir doses of 12.5 and 20 mg/kg/day, respectively (approximately equal to the exposures for glecaprevir and pibrentasvir in cirrhotic patients; see relative exposure table).

Table 10: Relative exposure in repeat-dose toxicity studies

Species	Study No. Duration	Day	Dose mg/kg/day PO		$AUC_{0-24\ h}$ (µg·h/mL)		ER	
			GLE	PIB	GLE	PIB	GLE	PIB
Rat SD	4 weeks RD160097	1	12.5	20	13.4	1.78	1.3	1.2
		24			10.0	2.08	0.95	1.47
Human (HCV infected, with cirrhosis) RD160237, RD160234 population PK model			300 mg	120 mg	10.53	1.43^	–	–

= animal: human plasma $AUC_{0-24\ h}$; ^from HCV infected patients without cirrhosis (The overall geometric mean of the pibrentasvir clinical AUC exposure in HCV-infected subjects with and without cirrhosis was 1.44 µg.h/mL; from Study RD160234, Table 21. In contrast, the glecaprevir exposure ratio in non-cirrhotic patients is approximately twice the exposure ratio for cirrhotic patients).

The absence of more extensive repeat-dose toxicity studies with the proposed combination is acceptable on the following grounds:

- Acceptable studies of sufficient duration with the individual drugs show a substantial safety margin for the intended clinical dose(s) or exposures;
- There are no concerning overlapping toxicities for the individual drugs based on animal toxicology studies;
- The preliminary study showed no synergistic toxicity;
- The proposed product is indicated for patients with limited treatment options, or to improve response rates in patients at risk of serious morbidity;

- The proposed product is expected to be a substantial improvement over approved therapies; and
- There are clinical trial data on the safety of the combination in patients.

Genotoxicity and carcinogenicity

Glecaprevir and pibrentasvir were evaluated for their potential to induce reverse mutations in *S. typhimurium* and *E. coli*, and for its clastogenic potential in human lymphocytes in vitro and in vivo in rat (glecaprevir) or mouse (pibrentasvir) bone marrow micronucleus assays. The range of studies and their designs were consistent with the relevant ICH guideline.[29] Glecaprevir and pibrentasvir were both negative in their respective genotoxicity tests, and are unlikely to pose a mutagenic or clastogenic risk to humans.

Carcinogenicity studies were not conducted since no causes for concern were identified in genotoxicity or general toxicity studies, and since the treatment duration for the proposed combination of glecaprevir and pibrentasvir is expected to be less than 6 months.[30]

Reproductive toxicity

Reproductive toxicity studies with glecaprevir and pibrentasvir were designed and conducted in general accordance with the relevant ICH guideline;[31] and examined potential effects on fertility in male and female rodents, embryofetal development in rodents and rabbits, and pre- and postnatal development (including F_1 fertility and reproductive performance) in rodents. Doses, group sizes and timing and duration of treatment were appropriate in all studies. The rat was the rodent species selected for the reproductive toxicity studies with glecaprevir, whereas mice were used for the pibrentasvir studies since higher levels of systemic exposure were achieved in this species.

Dose range-finding studies for embryofetal toxicity were conducted in the rat and rabbit for glecaprevir and in the mouse and rabbit for pibrentasvir. The glecaprevir rabbit studies were confounded by poor maternal tolerance of glecaprevir, as well as to the vehicle in the first dose range-finding study (an alternative vehicle was selected for subsequent studies), and as a result relative exposures were subclinical. For rabbit embryofetal development studies with pibrentasvir, when the oral route was used relative exposures were subclinical or on par with clinical exposures (up to 1.5 times the clinical AUC), while IV administration resulted in exposures up to 15 times the clinical AUC. Relative exposure levels were high in the rodent studies with glecaprevir and pibrentasvir (even if the interspecies difference in glecaprevir binding to plasma proteins were to be taken into account).

Placental transfer of glecaprevir-associated radioactivity was demonstrated in rats, while pibrentasvir was shown to cross the placenta in mice and rabbits (and to a lesser extent in rats). Lactational transfer of glecaprevir (as well as metabolites comprising 3.5% of radioactivity in milk) and pibrentasvir was demonstrated in rats.

No effects on mating, female or male fertility, or early embryonic development were observed in rats dosed with glecaprevir at up to 120 mg/kg/day PO (ER 63) or in mice dosed with pibrentasvir at up to 100 mg/kg/day (ER ≥ 70). The NOAEL for both maternal and fetal toxicity in rats dosed with glecaprevir was 120 mg/kg /day (ER 53). The rabbit studies with glecaprevir are not able to be used to predict whether glecaprevir has the

[29] ICH guideline S2 (R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use.
[30] ICH Topic S1A. The need for carcinogenicity studies of pharmaceuticals. CPMP/ICH/140/95.
[31] ICH Topic S5 (R2). Detection of toxicity to reproduction for medicinal products and toxicity to male fertility. CPMP/ICH/386/95.

potential for adverse developmental effects in clinical use since the highest dose administered in the main teratology study (60 mg/kg) was associated with systemic exposure levels well below clinical (ER 0.07). The dose level in this study was limited by severe maternal toxicity, and adverse pregnancy outcomes at this dose included increased post-implantation loss and reduced fetal body weight. In embryofetal development studies, pibrentasvir did not cause developmental abnormalities in either mice or rabbits at oral doses of up to 100 mg/kg/day (ER 51 and 1.5, respectively). Higher exposures were attained when the IV route was used (ER ≤ 15) but there were high maternal mortalities and morbidities in all groups, including vehicle treated dams, and fetal assessments were not conducted.

There were no adverse maternal or litter effects in the rat peri/postnatal development study with glecaprevir at maternal doses of 120 mg/kg/day PO from day 6 of gestation throughout lactation (ER 47). The F_1 generation showed no effect of maternal treatment on body weight gain, sexual maturation or behaviour, and there was no effect on F1 reproductive performance. Similarly, a pre-/postnatal development study in mice dosed orally with pibrentasvir did not show evidence of a treatment-related effect on postnatal development at doses of up to 100 mg/kg/day (ER 74). Overall, pibrentasvir was not found to have any detrimental effects on litter parameters, postnatal development and subsequent reproductive function in offspring exposed to pibrentasvir through maternal exposures.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1 for the FDC GLE/PIB tablet.[32]

Although the rabbit developmental toxicity studies did not provide any supportive data on the potential reproductive toxicity of glecaprevir, Category B1 is acceptable for glecaprevir based on the lack of animal findings overall. A B1 category is also considered acceptable for pibrentasvir based on the absence of adverse findings on litter parameters and embryofetal development in mice and rabbits. Therefore, the sponsor's proposed Pregnancy Category of B1 for Maviret tablets is acceptable.

Phototoxicity

The weight of evidence indicates that neither glecaprevir nor pibrentasvir have phototoxic potential.

Impurities

The proposed specifications for process-related impurities and degradants in the individual drug substances and in the product have been adequately qualified. All identified impurities have been assessed for potential mutagenicity and are considered non-mutagenic or will be controlled below the TTC (threshold of toxicological concern) level for mutagenic compounds.

Paediatric use

Maviret has not been proposed for paediatric use and no specific studies in juvenile animals were submitted. This is not considered to be a deficiency as there were no toxicological findings of concern in adult animals or in the peri/postnatal toxicity study in rats.

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

Nonclinical summary and conclusions glecaprevir + pibrentasvir

Summary, conclusions and recommendation

- The overall quality of the submission was high. Pivotal safety studies were conducted in accordance with ICH M3 (R2);33 and under GLP conditions. Studies conducted with the individual agents glecaprevir and pibrentasvir have been evaluated separately.
- Glecaprevir was shown to be a pangenotypic inhibitor of HCV NS3/4A protease, which is essential for proteolytic cleavage of the HCV encoded polyprotein, and hence for viral replication. In a biochemical assay glecaprevir inhibited the proteolytic activity of recombinant NS3/4A enzymes from clinical isolates of HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a, with IC_{50} value ranging from 3.5 to 11.3 nM. Pibrentasvir is a pangenotypic inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly.
- Glecaprevir and pibrentasvir inhibited the replication of subgenomic stable replicons cultures encoding NS3/4A and NS5A, respectively, from genotypes 1 to 6 (obtained from laboratory strains). The potency of glecaprevir and pibrentasvir against GT1a and 1b were reduced in the presence of 40% human plasma by 6 to 11 fold and 35 and 47 fold, respectively, which is a reflection of the high degree of plasma protein binding for both agents.
- The in vitro efficacy of glecaprevir and pibrentasvir against transient chimeric replicons encoding NS3/4A and NS5A, respectively, from clinical samples (median EC_{50}, range in parentheses) were 0.30 nM (0.05 to 3.8 nM) and 0.001 nM (0.0003 to 0.0035 nM). These values are supportive of HCV NS3/4A and NS5A inhibition at the proposed dose of Maviret (based on glecaprevir and pibrentasvir unbound plasma C_{min} values approximately equal to and 155 fold greater than the respective median EC_{50} values, and taking into account the observation that liver exposures for glecaprevir in rodents and dogs were at least ten-fold higher than those of plasma). Neither glecaprevir nor pibrentasvir showed any activity against HBV or HIV-1.
- Mutations in NS3/4A at position 156 were often associated with marked resistance to glecaprevir, with A156M/T/V/G associated with 148 to 3106 fold resistance in 1a, 1b, 2a, 2b, 3a or 4a replicons. Mutations at position 168 also conferred resistance to glecaprevir, but to a lesser extent than mutations at 156. Substitutions at position 80 did not reduce susceptibility to glecaprevir except in GT3a, where a Q80R substitution led to a 21-fold increase in EC_{50}. Glecaprevir was shown to be generally active against HCV replicons containing GT1a or 1b variants resistant to NS5A or NS5B polymerase inhibitors in transient transfection cell culture assays, but based on the resistance selection studies; cross-resistance with other NS3/4A protease inhibitors is possible.
- The majority of individual amino acid substitutions associated with resistance to other HCV NS5A inhibitors (at positions 24, 28, 30, 31, 58, 92, or 93 in NS5A) did not reduce susceptibility to pibrentasvir, although cross-resistance was detected for some mutants (for example, GT1a H58D+Y93H). Resistance was observed with M28G or Q30D in the GT 1a replicon (244 and 94 fold reductions in EC_{50}, respectively), and P32-deletion in GT 1b (1,036-fold). For GT2a, the double amino acid substitution F28H + M31I led to a >14,000-fold change in EC_{50}. In GT 3a the double or triple substituted variants (S24F+M28K), (A30K+Y93H), (S24F+M28LK+A30K) and (A30K+L31I+Y93H) had significant resistance to pibrentasvir. As expected, variants resistant to NS3/4A and NS5B inhibitors were susceptible to pibrentasvir.

[33] ICH Guideline M3 (R2) EMA/CPMP/ICH/286/1995

- Glecaprevir and pibrentasvir showed additive to synergistic antiviral activity in a three day HCV replicon cell culture assay. The combination was shown to exhibit increased suppression of resistant colonies in a colony survival assay compared with each agent on its own. Glecaprevir did not affect the in vitro activity of the HIV-1 protease inhibitors lopinavir and darunavir, and they in turn did not affect the in vitro efficacy of glecaprevir.
- Glecaprevir and pibrentasvir are not expected to exhibit off-target activity. No notable effect on physiological functions was observed in a battery of safety pharmacology studies that encompassed the CNS, cardiovascular and respiratory systems.
- Both glecaprevir and pibrentasvir undergo minimal metabolism by CYP enzymes, and thus their clearance is unlikely to be affected by CYP450 inhibitors or inducers. Based on in vitro data glecaprevir and pibrentasvir are both substrates of P-gp and BCRP, and glecaprevir is also a substrate of the hepatic uptake transporters OATP1B1 and OATP1B3. Drug-drug interactions (DDIs) mediated by these transporters are predicted.
- Glecaprevir is not predicted to have clinically relevant inhibition of hepatic CYP450 or UGTs, but has the potential to inhibit intestinal CYP3A4. Pibrentasvir is unlikely to affect the exposure of CYP isozyme substrates. It is predicted that pibrentasvir is unlikely to affect the exposure of UGT1A1, 1A6, 1A9 or 2B7 substrates. Although pibrentasvir inhibited UGT 1A4 in vitro (IC_{50}: 0.027 μM) this does not appear to be clinically relevant based on a lack of interaction with the UGT1A4 substrate lamotrigine.
- In vitro assays showed that inhibition of P-gp, BCRP and OATP1B1 by glecaprevir and pibrentasvir and OATP1B3 by glecaprevir may be clinically relevant. Inhibition of BSEP by glecaprevir is an additional possible source of DDI. Glecaprevir and pibrentasvir do not inhibit OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K.
- The only combination repeat-dose toxicity study submitted was a 4 week repeat-dose study in rats dosed orally with glecaprevir and pibrentasvir doses of 12.5 and 20 mg/kg/day, respectively (approximately equal to the exposures for glecaprevir and pibrentasvir in cirrhotic patients), which was well tolerated. The absence of more extensive combination repeat dose toxicity studies is acceptable since studies of sufficient duration with the individual drugs show a substantial safety margin for the intended clinical doses or exposures, and there are no concerning overlapping toxicities for the individual drugs based on animal toxicology studies.
- Glecaprevir and pibrentasvir were not mutagenic in the bacterial mutation assay or clastogenic in vitro (human lymphocytes) or in vivo (rodent micronucleus assays). Carcinogenicity studies have not been conducted, which is acceptable based on lack of genotoxicity and the proposed duration of treatment.
- The Pregnancy Category proposed by the sponsor (B1) is considered appropriate for both glecaprevir and pibrentasvir, and hence also for the proposed combination product, Maviret.
- There are no objections on nonclinical grounds to the registration of Maviret.

VII. Clinical findings

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

Introduction

Clinical rationale

Successful clearance of HCV reduces liver-related morbidity and mortality with a reduction in the incidence of HCC. SVR rates of 95% to 100% can now be achieved with DAA combinations in treatment-naïve and treatment-experienced patients infected with any HCV genotype, with or without cirrhosis or HCV/HIV co-infections. Maviret is a combination of the NS3/4A protease inhibitor glecaprevir (GLE, ABT-493) and the NS5A inhibitor pibrentasvir (PIB, ABT-530). Each component has potent activity against HCV genotypes 1 to 6 and each is effective against common resistant forms. Additive or synergistic effects have been demonstrated with the combination which has been formulated as a FDC for once daily administration. It is hoped that Maviret will be effective in patients with any genotype infection, without cirrhosis or with compensated cirrhosis. It is also hoped that the treatment duration may be reduced from 12 weeks to 8 weeks in non-cirrhotic patients.

Guidance

A pre-submission meeting with the TGA and the submission complies with the outcomes of that meeting. The clinical development plan, proposed indication, treatment duration and justifications for a fixed dose combination were reviewed. The development program was conducted in accordance with the relevant US and CHMP guidelines.[34,35] Specific scientific advice from the FDA and CHMP was obtained at the end of Phase I and the end of Phase II. Both bodies approved the Phase III dose and duration selection, including the assessment of 8, 12 and 16 weeks regimens.

Contents of the clinical dossier

The submission contains new clinical studies as follows:

- Clinical Pharmacology Studies
  - 43 PK studies; Two of these studies also contain PD data related to the QTc effects of therapeutic and supra-therapeutic doses of GLE + PIB.
  - a single study (Study R&D/16/0234) examines the population PKs of both GLE and PIB in HCV-infected subjects and examines the relevance of a range of factors that may contribute to PK variability.
- Pivotal Efficacy/Safety Studies
  - Two randomised, controlled studies (Studies M15-464 and M13-594).
  - Seven uncontrolled Phase II/III efficacy and safety studies: Studies M13-583, M13-590, M15-462, M15-410, M14-867, M14-868 and M14-172.
- Other Efficacy/Safety Study
  - One pilot Phase II study: Study M14-213.

Paediatric data

The submission did not include paediatric data.

[34] Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment(October 2013 and May 2016)
[35] Clinical evaluation of medicinal products for the treatment of chronic hepatitis C: EMA/CHMP/51240/2011

Good clinical practice

The clinical studies were performed according to the principles of ICH GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

See Table 11, below.

Table 11: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK – Relative BA	M14-714	Relative BA and food effect of FDC GLE/PIB film-coated bilayer tablets relative to the reference Phase IIb formulation
		M13-601	Relative BA of the GLE Phase IIa and Phase IIb test formulation A and PIB Phase IIb test formulation A and the FIH formulations
		M14-214	Relative BA of the GLE Phase IIb test formulation and the Phase IIa and FIH formulations
		M14-711	Relative BA of four experimental GLE/PIB formulations and reference Phase IIb formulations
		M13-581	Relative BA of the PIB Tablets –test formulations and FIH formulation
		M13-580	Relative BA of co-formulated GLE/PIB test formulation and the reference Phase IIa formulations
		M14-611	Relative BA of the co-formulated GLE/PIB test formulations and the reference Phase IIa formulations
		M14-719	Relative BA of three different co-formulated GLE/PIB formulations and the reference Phase IIb formulations
		M14-725	Relative BA and food effect on blended GLE/PIB film-coated tablets and the reference co-formulated uncoated bilayer tablet formulation
		M14-717	Relative BA and food effect on experimental GLE/PIB uncoated, bilayer tablets and reference Phase IIb formulations
	ADME	M13-890	ADME of [^{14}C]GLE and [^{14}C]PIB in healthy males
	Escalating doses	M15-543	Potential for QTc prolongation following combination administration of GLE and PIB
		M14-716	PKs, safety and tolerability of GLE and PIB when

PK topic	Subtopic	Study ID	*
			given in combination
		M13-356	Safety, tolerability and PKs of single and multiple escalating doses of GLE
		M13-355	Safety, tolerability and PKs of single and multiple escalating doses of PIB
PK in special populations	Target population	M13-595	Safety, tolerability, PKs, and antiviral activity of multiple dose levels of GLE and PIB administered as monotherapy for 3 days in treatment-naïve adults with chronic HCV GT1 infection
		M14-868	PKs of ABT-493, ABT-530 and RBV and the emergence and persistence of viral variants in patients with HCV
		M15-410	PKs of ABT-493, ABT-530, and RBV, and to evaluate the role of RBV in patients with HCV infection
		M14-867	PKs of GLE, PIB, and RBV, and the emergence and persistence of viral variants with this treatment regimen
	Hepatic impairment	M13-604	PKs and safety of single-dose GLE and/or PIB in subjects with normal hepatic function and stable chronic hepatic impairment
	Renal Impairment	M13-600	PKs and safety of a single dose of GLE and PIB in subjects with normal renal function, mild, moderate and severe renal impairment and in subjects with ESRD
	Race	M15-432	PKs and safety of multiple doses of GLE and PIB given alone and in combination in healthy Han Chinese, Japanese and Caucasian adults
		M14-066	PKs and safety of multiple oral doses of GLE and PIB given alone and in combination in healthy Han Chinese, Japanese, and Caucasian adults
PK interactions	GLE and PIB	M13-586	PKs and safety of multiple oral doses of GLE and PIB given in combination under non-fasting conditions in healthy adults
	CYP Substrates	M13-605	DDI between GLE + PIB at steady state and caffeine, midazolam, tolbutamide, omeprazole, dextromethorphan and cyclosporine
		M14-380	Effect of GLE + PIB on the PKs and safety of caffeine, tolbutamide, omeprazole, midazolam and dextromethorphan
		M13-578	DDI between GLE + PIB at steady state and felodipine

PK topic	Subtopic	Study ID	*
			or amlodipine administered as a single dose
		M13-584	PK interaction following administration of a single 100 mg dose of cyclosporine
		M13-599	PK interaction with single doses of two angiotensin receptor blockers
		M14-721	DDI between GLE + PIB and simvastatin or lovastatin
		M14-715	PK interaction with multiple doses of 20 mg to 40 mg of omeprazole
	CYP and P-gp inducers	M14-724	DDI with carbamazepine
		M14-723	DDI between rifampin administered as a single dose and at steady state and GLE + PIB
	Anti-HIV medication	M13-603	DDI between GLE and PIB at steady-state and atazanavir and ritonavir at steady-state
		M13-597	DDI between multiple doses of Atripla and multiple doses of GLE + PIB in HIV-mono-infected subjects
		M15-584	DDI between multiple doses of GLE + PIB and multiple doses of Genvoya or Triumeq
	P-gp substrate	M13-582	DDI between GLE + PIB at steady state and a single dose of digoxin
		M14-532	DDI between sofosbuvir and GLE + PIB
		M13-585	DDI between a single 150 mg dose of dabigatran and GLE 300 mg QD + PIB 120 mg QD.
	OATP-substrates	M13-579	DDI between GLE + PIB and pravastatin, rosuvastatin or atorvastatin
	Other interactions	M14-213	PKs of ABT-450, ritonavir, PIB, and RBV in patients with chronic HCV infection
		M13-598	Effect of GLE and PIB on the PKs of oral contraceptives
		M13-602	Effect of GLE 300 mg QD + PIB 120 mg QD on the PKs of methadone or buprenorphine/naloxone
Population PK analyses	Target population	R&D/16/0234	To characterise the popPKs of GLE and PIB and identify to identify covariates

* Indicates the primary PK aim of the study; †/BE Bioequivalence of different formulations; § Subjects who would be eligible to receive the drug if approved for the proposed indication. BA: Bioavailability

Evaluator's conclusions on pharmacokinetics

- The formulation of GLE/PIB proposed for marketing is a FDC tablet 100 mg/40 mg film-coated tablet. The recommended daily dose is 300 mg/120 mg (3 x 100/40 mg tablets) which is to be taken orally with food.

Absorption, distribution, metabolism and excretion

- Population pharmacokinetics (PopPK) predicted Ka for GLE and PIB in patients with chronic HCV was 8.63/day and 6.13/day, respectively.
- The absolute bioavailability of GLE and PIB has not been determined. Although not specifically stated, this is most likely due to the poor solubility of both GLE and PIB in water.
- The to-be-marketed FDC formulation of GLE/PIB is identical to the Phase III formulation.
- Under fasting conditions, the AUC values for GLE and PIB were 56% and 36% lower, respectively, following administration of a 300mg/120mg dose of the GLE/PIB FDC tablets compared to the free-combination of Phase IIb tablets.
- Following a 300 mg/120 mg dose of GLE/PIB FDC, food increased exposure to the GLE component by 1.8 to 3.2 fold compared to fasted conditions and exposure to the PIB component by 1.4 to 2.1 fold. Moreover, following administration of the FDC tablet, GLE and PIB exposure under fed conditions was similar to the levels of GLE and PIB exposure attained following administration of the free combination of the Phase IIb tablet formulation under fasted conditions.
- Following administration of increasing doses of GLE + PIB to healthy subjects increases in GLE are greater than dose proportional, whereas, the results for PIB are equivocal. For instance, following single doses of the free combination at dose strengths of 600 mg + 240 mg, GLE Cmax and AUC_{inf} values were increased by 3.6 fold and 3.9 fold, respectively, and PIB Cmax and AUC_{inf} were increased by 1.8 and 2.1 fold, respectively, compared to the values following a dose of GLE 400 mg + PIB 120 mg, whereas, the ratio of the point estimates for GLE Cmax and AUCinf values following doses of 800 mg + 240 mg of the free combination of GLE + PIB versus 400 mg + 120 mg of GLE + PIB were 8 fold and 13 fold, respectively, and for PIB were 2.2 fold and 3.0 fold, respectively. Following administration of multiple escalating doses of GLE 200 mg to 800 mg QD for 10 days, GLE exhibited non-linear PKs with greater than dose proportional increases in exposure following multiple doses. Steady-state GLE was attained following 10 days of dosing and median accumulation ratios for Cmax, Ctrough and AUC_{0-24} values ranged from 0.8 to 2.4 over the 200 to 800 mg dose range. Following both the 200 mg QD and 400 mg QD doses there was minimal accumulation of GLE.
- Following administration of multiple escalating doses of PIB 30 mg to 600 mg QD for 10 days PIB, C_{max} and AUC_{0-24} values increased in a greater than dose proportional manner between doses ranging from 30 mg to 180 mg and were then approximately linear following the 180 mg and 600 mg doses. In addition, there was minimal accumulation of PIB and steady-state was attained at 10 days.
- The estimated values for the Vc/F and Vp/F for GLE were 130 L and 39.6 L, respectively, and for PIB were 1380 L and 2250 L, respectively.
- There was no concentration dependence in plasma binding for either GLE or PIB when tested at concentrations ranging from 0.1 to 30 μM and no preferential partitioning into red blood cells was observed.

- Following oral administration both [^{14}C]-GLE and [^{14}C]-PIB were primarily cleared via the biliary-faecal route; however, CYP3A metabolism played a secondary role in the metabolism of [^{14}C]-GLE.
- Following a 400 mg dose of [^{14}C]-GLE, nearly the entire radioactive dose (92.1%) was recovered in faeces, whereas, 0.661% was recovered in urine. Following a 120 mg dose of [^{14}C]-PIB, the mean recovery of administered radioactivity was 96.6%, which was entirely contained in the faeces.
- No metabolites for GLE or PIB were identified in human plasma.
- In pooled faeces samples, unchanged GLE accounted for 22.6% of the radioactive dose and seven GLE metabolites were identified. By contrast, following administration of 120 mg [^{14}C]-PIB, unchanged PIB was the only radiochemical component detected in faeces.

PK variability

- The inter-individual variability on GLE CL/F and F were 0.874 and 1.84, respectively. The estimated inter-individual variability values for PIB CL/F, V2/F and F were 0.084, 0.334 and 0.198, respectively. The estimated residual variability for GLE was 0.562, whereas, for PIB it was 0.252.

PKs in the target population

- In the target population, the relative GLE and PIB exposure following administration of the free combination of the Phase II formulation of 300 mg GLE + 120 mg PIB with or without food and the Phase III FDC with food in patients was similar.
- In subjects with HCV-infection, increase in GLE exposure was more than dose-proportional over the 100 mg to 700 mg range. Similarly, the increase in PIB exposure was more than dose-proportional over the 15 mg to 120 mg range; however, between the 120 mg and 400 mg doses the increase in PIB exposure was less than dose proportional.

Special populations

- Following administration of GLE 300 mg + PIB 120 mg, GLE AUC values were 33% and 100% higher in subjects with mild and moderate hepatic impairment, respectively, and were increased by 11 fold in subjects with severe hepatic impairment compared to subjects with normal hepatic function. Compared to normal subjects, PIB AUC values were similar in subjects with mild hepatic impairment (≤ 20% difference), 26% higher in subjects with moderate hepatic impairment and 114% higher in patients with severe hepatic impairment.
- GLE exposure in cirrhotic subjects following 200 mg QD dosing were between the exposure of 200 mg QD and 300 mg QD in non-cirrhotic subjects, whereas, PIB exposures were similar in both non-cirrhotic and cirrhotic subjects.
- Following a single dose of the free combination of GLE 300 mg + PIB 120 mg under non-fasting conditions, there was a trend towards increasing GLE and PIB AUC_{inf} values as eGFR decreased, with maximum predicted increases of 56% and 46%, respectively, in subjects with ESRD not on dialysis compared to normal subjects.
- GLE and PIB protein binding was similar in subjects with normal renal function, in subjects with mild, moderate and severe renal impairment and in subjects with ESRD. Moreover, haemodialysis did not affect protein binding to either GLE or PIB.

PopPK

- PopPK analysis indicated that a two-compartment model with first-order absorption and elimination adequately described the GLE and PIB plasma concentration-time

data. For GLE, bodyweight, BMI, BSA, race, genotype, dialysis, prior HCV treatment history and co-administration with RBV did not have significant impact on GLE exposure, whereas, for PIB, dialysis, genotype, prior HCV treatment history and co-administration with RBV had no significant impact on PLE exposure.

- The PopPK analysis also identified the following:
  - Age was a significant covariate for GLE and PIB CL/F such that a 10-year increase in age (65 years versus 55 years) is associated 32% higher GLE exposure and PIB exposure was 13% higher.
  - Gender affected GLE and PIB exposure as GLE exposure was 39% higher in females than in males and PIB was 37% higher in females compared to males.
  - Race was a covariate of PIB CL/F such that PIB exposure was 26% higher in Asian subjects than in Caucasians.
  - GLE and PIB exposures in subjects with compensated cirrhosis were increased by 2.2 fold and were 7% higher, respectively, than in subjects without cirrhosis.
  - Compared to subjects with normal renal function, GLE and PIB exposure was 55% and 13% higher, respectively, in subjects with moderate or severe renal impairment and 86% and 54% higher, respectively, in subjects with end stage renal disease.
  - GLE exposure was 5% lower in subjects who took high dose PPIs and 16% higher in subjects who took opioid medications. PIB exposure was 27% higher in subjects who took BCRP inhibitors.

Drug-drug interactions

- The C_{max} and AUC values for GLE were similar following 300 mg GLE in the presence or absence of 120 mg PIB.
- The C_{max} and AUC values for PIB were increased by 2.86 fold and 3.14 fold following co-administration of 120 mg PIB with 300 mg GLE compared to when PIB was administered alone.
- Although 300 mg GLE QD and 120 mg PIB QD had little effect on tolbutamide PKs, the AUC_{inf} values for caffeine and midazolam were increased by 35% and 27%, respectively, whereas, the AUC_t values for omeprazole (2C19) and dextromethorphan (2D6) were decreased by 21% and 25%, respectively.
- Although, GLE + PIB QD had little effect on cyclosporine PKs following a 400 mg dose, steady-state GLE and PIB exposure was significantly increased by 5.08- and 1.93-fold, respectively, when cyclosporine was co-administered.
- Co-administration of GLE + PIB with simvastatin or lovastatin results in increased AUC values for the statins and their metabolites ranging from 1.7 fold to 4.5 fold.
- Compared to when GLE + PIB were administered alone, co-administration with steady-state carbamazepine resulted in decreases in GLE Cmax and AUC_{inf} values of 67% and 66%, respectively, and PIB C_{max} and AUC_{inf} values of 50% and 51%, respectively.
- A single dose of rifampin increased GLE C_{max} and AUC_{inf} values by 6.5 fold and 8.6 fold, respectively, whereas, rifampin had little effect on either PIB C_{max} or AUC_{inf} (≤ 9% change). By contrast, following multiple doses of rifampin, increases in GLE exposure were relatively small (5 to 40%), whereas, PIB C_{max} and AUC values were decreased by 79% and by 83%, respectively.

- A single dose of atazanavir + ritonavir increased the C_{max} and AUC_{24} of steady-state GLE by 4.1 and 6.5 fold, respectively, whereas, PIB C_{max} and AUC_{24} values were 29% and 64% higher, respectively.
- Compared to historical data, GLE and PIB exposures were significantly lower when co-administered with Atripla.
- GLE C_{max} and AUC were increased by 150% to 205% and the corresponding PIB parameters were increased by 24% to 57% when co-administered with Genvoya.
- Co-administration of GLE + PIB with Genvoya increased C_{max} and AUC of elvitegravir and cobicistat by 29% to 47%.
- GLE + PIB C_{max} and AUC were slightly lower (25% to 28%) when administered with Triumeq.
- Results from the atazanavir+ritonavir study and the Atripla study suggested ritonavir (C_{max} raised 21%, AUC_{0-24h} raised 30% and C_{0-24h} raised 26%) and tenofovir (C_{max} raised 22%, AUC_{0-24h} raised 29%, and C_{0-24h} raised 38%) exposure was mildly increased in the presence of GLE + PIB.
- Following co-administration of GLE + PIB, digoxin Cmax and AUC_{inf} values increased by approximately 72% and 48%, respectively, compared to when digoxin was administered alone.
- Following co-administration with GLE + PIB, sofosbuvir Cmax and AUC_{0-24h} values increased by 66% and 125%, respectively, compared to when sofosbuvir was administered alone.
- Dabigatran C_{max} and AUC_{inf} were increased by 2.0 and 2.4 fold when co-administered with GLE + PIB.
- Following co-administration with pravastatin, rosuvastatin or atorvastatin, GLE C_{max} and AUC were similar or increased (up to 59%), whereas, PIB C_{max} and AUC were minimally affected (≤ 24% increase).
- GLE 400 mg QD and PIB 120 mg QD increased: pravastatin Cmax and AUC values by 2.2- and 2.3-fold, respectively; rosuvastatin Cmax AUC by 5.6- and 2.2-fold, respectively, and atorvastatin Cmax and AUC by 22- and 8.3-fold, respectively.
- GLE 300 mg QD + PIB 120 mg QD increased exposure to EE, NGM and LNG by up to 68%.
- Co-administration of GLE + PIB had little effect (< 35%)on the exposure to carbamazepine, CBZE, rifampin, atazanavir, efavirenz or emtricitabine, emtricitabine, abacavir, dolutegravir, and lamivudine, lamotrigine, NET, (R)-methadone and (S)-methadone, buprenorphine and naloxone.
- Co-administration of digoxin, sofosbuvir, omeprazole 20 mg QD, dabigatran, lamotrigine and NET had no to relatively minor effects on exposure to steady-state GLE or PIB.

Limitations of PK studies

- No studies have directly examined the relative bioavailability of the reference Phase IIb formulation under fasted and fed conditions. Thus it is difficult to accurately compare the PKs of FDC Phase III formulation and the Phase IIb formulations under fed conditions. However, if we compared the GLE and PIB exposure under fasted (results from Study M14-714) and fed (results from Study M14-724) conditions following a single dose of the free combination of 300 mg GLE + PIB to healthy subjects we can see that exposure to the GLE component is increased by around 1.3 to 1.40 fold and for the PIB component is increased by around 1.4 to 1.7 fold under fed conditions

compared to when the subjects were fasted. Although this comparison is far from ideal as the study has not been undertaken in the same population, it clearly identifies that food may significantly effect GLE and PIB exposure when given as the free combination, and perhaps calls into question the results of studies, such as Study M14-868, in which patients have been administered the free combination without instructions regarding whether tablets should be taken with food or not.

Pharmacodynamics

Studies providing pharmacodynamic data

All of the studies included in the evaluation materials that contain PD results also contain PK data and therefore have been summarised.

Evaluator's conclusions on pharmacodynamics

- GLE is a pangenotypic inhibitor of the HCV NS3/4A protease, whereas, PIB is a pangenotypic inhibitor of HCV NS5A.
- In treatment-naïve adults with chronic HCV GT1 infection, the decline in HCV viral load was immediate and substantial on Study Day 1 for all subjects that received doses of GLE ranging 100 mg to 700 mg and for subjects who received either 40 mg, 120 mg or 400 mg doses of PIB.
- The maximum decrease in plasma RNA viral load from baseline was similar following doses of GLE ranging from 100 mg to 700 mg QD, whereas, for PIB the maximum decrease in viral load was higher in groups that received doses ranging from 40 mg QD to 400 mg QD than in the group that received the 15 mg dose.
- Following supratherapeutic doses of GLE + PIB no clinically significant effects on QTc interval prolongation were identified.

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics: dose finding studies

Study M13-595 investigated the plasma RNA viral load following doses of 100 mg to 700 mg QD of GLE or 15 mg to 400 mg QD of PIB in treatment-naïve adults with chronic HCV GT1 infection. The results indicated that the decline in HCV viral load was immediate and substantial on Study Day 1 for all subjects that received doses of GLE ranging 100 mg to 700 mg and for subjects who received either 40 mg, 120 mg or 400 mg doses of PIB. In addition, the maximum decrease in plasma RNA viral load from baseline was similar following doses of GLE ranging from 100 mg to 700 mg, whereas, for PIB the maximum decrease in viral load was higher in groups that received doses ranging from 40 mg QD to 400 mg QD than in the group that received the 15 mg dose.

Phase II dose finding studies

Dose ranging arms were included in the Phase II Studies M14-868, M14-867 and M15-410.

Phase III pivotal studies investigating more than one dose regimen

No dose finding Phase III studies were performed.

Evaluator's conclusions on dose finding for the pivotal studies

Dose finding was satisfactory. Dose selection was based initially on in vitro antiviral activity. The combination of GLE 300 mg and PIB 120 mg achieves blood levels providing maximal antiviral effects and higher doses will not achieve additional reductions in HCV RNA. Three exploratory and confirmatory Phase II studies have assessed lower dose combinations of GLE and PIB. Although lower doses were effective in some patient subgroups, the proposed dose of GLE 300 mg +PIB 120 mg achieved optimal SVR12 rates across all patient groups. The Phase III studies were conducted using the single dose FDC proposed for marketing.

Efficacy

Studies providing efficacy data

Pivotal or main efficacy studies:

- Study M15-464 (ENDURANCE-2)
- Study ID M13-594 (ENDURANCE-3)
- Study ID M13-583 (ENDURANCE-4)
- Study ID M14-868 (SURVEYOR-2)
- Study ID M13-590 (ENDURANCE-1)
- Study ID M14-172(EXPEDITION-1)
- Study ID M15-462 (EXPEDITION-4)
- Study ID M14-867 (SURVEYOR-1)
- Study ID M15-410 (MAGELLAN-1)

Other efficacy studies:

- Study ID M14-213

Evaluator's conclusions on efficacy

In the registration studies, the efficacy of GLE/PIB was assessed in treatment-naïve and treatment-experienced patients with any genotype infection, at the same fixed dose but for different durations of treatment (8, 12 or 16 weeks). Dose selection was based on Phase II studies which supported the GLE/PIB dose of 300 mg/120 mg used without RBV. The study designs were in line with the relevant EMA and FDA guidelines for the use of DAAs in patients with chronic HCV and scientific advice was provided by both bodies. The primary efficacy endpoint for all studies was SVR12 with on-treatment virologic failure and post-treatment relapse as the key secondary endpoints. Two randomised, controlled studies compared the efficacy of GLE/PIB against placebo and against SOF + DCV, the most effective active control for HCV GT3 infection at the time the studies were planned. In addition, a series of single-arm studies assessed efficacy in subpopulations including patients with compensated cirrhosis, severe renal impairment, patients with genotypes 1 to 6 infection, patients with HCV/HIV-1 co-infection and patients who failed prior therapy with DAA-containing regimens. Inclusion and exclusion criteria were broadly similar across studies, with protocol-defined criteria for the presence or absence of cirrhosis. All statistical analyses were based on the ITT populations, including all patients who received at least one dose of study drug. Meta-analyses and pooled data analyses were conducted with sensitivity analyses as indicated. The baseline demographics were representative of the HCV population in Australia with treatment-naïve and treatment-experienced male

and female patients. Most patients were White (80.2%) or Asian (11.5%), with small numbers of other racial groups. Only a limited number of patients (2.0%) were aged ≥75 years.

The clinical efficacy data are summarised below. They are satisfactory, they match claims in the proposed PI and they support the broad proposed indication:

> *Maviret is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.*

Patients with all main genotypes were studied in controlled and uncontrolled studies and outstanding SVR12 rates were achieved in treatment-naïve and treatment-experienced patients:

- In patients with GT1 infection (Study M13-590), treatment given for 12 weeks was non-inferior to historical control regimens given for 12 weeks with an SVR12 rate of 99.7%. Treatment given for 8 weeks was also non-inferior to 12 weeks therapy with an SVR12 rate of 99.1%.
- In patients with GT2 infection (Study M15-464), treatment given for 12 weeks was non-inferior to SOF + RBV for 12 weeks with an SVR12 rate of 99.5%.
- In patients with GT3 infection (Study M13-594), treatment given for 12 weeks was non-inferior to SOF + DCV given for 12 weeks with an SVR12 rate of 95.3%. Treatment given for 8 weeks was also non-inferior to 12 weeks therapy with an SVR12 rate of 94.9%.
- In patients with GT4-GT6 infection (Study M13-583), the SVR12 rate was 99.2% with 12 weeks treatment.
- In patients with GT1, GT2, GT4-GT6 infection and compensated cirrhosis (Study M14-172), the overall SVR12 rate was 99.3% with 12 weeks treatment.
- In patients with GT1-GT6 infection (Study M15-462), the overall SVR12 rate was 98.1% with 12 weeks treatment.
- In patients with GT1, GT4-GT6 infection (Study M14-867), the SVR12 rates were 97.1% in GT1-infected patients treated for 8 weeks and 100% in GT4-GT6 patients treated for 12 weeks.
- In patients with GT2-GT3 infection (Study M14-868, Parts 1 and 2), non-cirrhotic patients with GT2 infection achieved an SVR12 rate of 96.0% and non-cirrhotic patients with GT3 infection achieved an SVR12 rate of 93.3% with 12 weeks treatment. In non-cirrhotic patients with GT2 infection, SVR12 was achieved in 98.1% of patients treated for 8 weeks. In non-cirrhotic patients with GT3 infection, SVR12 was achieved in 96.6% of treatment naïve patients treated for 8 weeks. In cirrhotic patients with GT3 infection, SVR12 was achieved in 100% of treatment naïve patients treated for 12 weeks and in 75.0% of treatment-experienced patients (n = 4) treated for 16 weeks.
- In patients with GT3 infection (Study M14-868, Part 3), SVR12 was achieved in 97.5% of treatment-naïve patients with cirrhosis treated for 12 weeks and by 90.9% of treatment-experienced patients without cirrhosis treated for 12 weeks. SVR12 was achieved in 95.7% of treatment-experienced patients with cirrhosis treated for 16 weeks and in 95.5% of patients without cirrhosis treated for 16 weeks.
- In patients with GT2, GT4-GT6 infection (Study M14-868, Part 4), SVR12 was achieved in 97.9% of treatment-naïve and treatment-experienced patients with GT2 infection without cirrhosis treated for 8 weeks and by 93.1% of treatment naïve and treatment-experienced patients with GT4-GT6 infection also treated for 8 weeks.

- In patients with GT1 infection (Study M15-410, Part 1), SVR12 was achieved in 86.4% of DAA treatment-experienced patients without cirrhosis for 12 weeks.
- In patients with GT1 and GT4 infection (Study M15-410, Part 2), SVR12 was achieved in 88.6% of DAA treatment-experienced patients with or without cirrhosis treated for 12 weeks and by 91.5% of patients treated for 16 weeks.

SVR12 rates were comparable in patients with severe renal impairment and in patients with HCV/HIV-1 co-infection compared with the overall population. In the pooled analysis, outstanding SVR12 rates were achieved, irrespective of genotype, treatment experience and duration of treatment. Suboptimal SVR12 rates were experienced only in patient groups who did not receive treatment for the proposed durations. HCV RNA < LLOQ was achieved by Week 4 in >90% of patients across studies and there was close concordance > 90% between SVR4 and SVR12. Across all studies, on-treatment virologic failure and post-treatment virologic relapse was reported in only 0.5% and 0.9% of patients, respectively. In the Phase II and III Analysis Set, there were 2, 2 and 18 virologic failures in patients with GT1, GT2 and GT3 infection, respectively. Baseline polymorphisms had no impact on treatment outcome in patients with any genotypic infection except GT3. Patients with GT3 infection and A30K in NS5A at baseline had a lower SVR12 rate of 75%. In the 18 patients with GT3 infection and virologic failure, most had treatment-emergent variants at the time of failure for NS3 (61.1%) and NS5A (88.9%).

The pivotal studies are still on-going and detailed resistance data are described in the Integrated Resistance Report. The impact of drug resistant HCV variants in patients who do not achieve SVR12 cannot be quantified, but it is a potential risk for the wider community. However, the overall risk is low because the percentage of patients with virologic failure and relapse following treatment with Maviret is extremely low. Missing information highlighted in the RMP includes data in patients with HBV co-infection, renal/liver transplant patients and patients with decompensated cirrhosis.

Based on these data, the sponsor proposes GLE/PIB treatment durations shown below. These recommendations are conservative and maximise the potential for SVR12 in all patient subgroups as shown below.

Table 12: Recommended GLE/PIB duration in treatment-naïve patients

	Recommended Treatment Duration	
Patient Population	**No Cirrhosis**	**Cirrhosis**
Genotype 1 – 6	8 weeks	12 weeks

GLE = glecaprevir; PIB = pibrentasvir

Table 13: Recommended GLE/PIB duration in treatment-experienced patients

	Recommended Treatment Duration	
Patient Population	**No Cirrhosis**	**Cirrhosis**
NS5A inhibitor-naïve[a] GT1, GT2, GT4 – GT6	8 weeks	12 weeks
NS5A inhibitor-experienced GT1, GT2, GT4 – GT6	16 weeks	16 weeks
GT3 (any experienced)		

BOC = boceprevir; GLE = glecaprevir; GT = genotype; NS5A = nonstructural protein 5A; PIB = pibrentasvir; P/R = regimens containing interferon, pegylated interferon, and/or ribavirin; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; TVR = telaprevir

a. Experienced with P/R, SOF + P/R, SOF + RBV, SMV + SOF, SMV + P/R, TVR + P/R, or BOC + P/R.

Table 14: Summary of SVR12 rates for recommended treatment duration in the Phase II and III Analysis Set

	SVR_{12} %										
	GT1		GT2		GT3		GT4 – GT6		GT1 – GT6		
	No Cirr	Cirr	No Cirr	Cirr	No Cirr	Cirr	No Cirr	Cirr	No Cirr	Cirr	All
TN[a] +TE-P/R, SOF/R or PI[b]	99.0	97.2	98.0	100	95.2	96.6	93.1	100	97.4	97.6	97.5
TE-NS5A Inhibitor[c]	87.5		-		-		100		96.3	57.1	88.2
Overall	97.9		98.3		95.7		95.5		97.4	96.6	97.2

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

None submitted.

Pivotal and/or main efficacy studies

- The placebo-controlled set assessed safety in Study M15-464.
- The active-controlled set assessed safety in Study M13-594.
- The Phase II and III set consisted of all Phase II and III efficacy studies with evaluable safety data, including the controlled Studies M15-464 and M13-594; and the uncontrolled Studies M14-868, M13-583, M13-590, M14-172, M15-462, M15-410 and M14-867.

Other studies

Other efficacy studies

Not applicable.

Studies with evaluable safety data: dose finding and pharmacology

Two studies (Studies M15-543 and M14-716) examined the effects of GLE + PIB on QTc in healthy subjects. The first of these, Study M15-543, assessed the potential for QTc prolongation following combination administration of GLE + PIB at therapeutic (400 mg + 120 mg) and supra- therapeutic (600 mg + 240 mg) doses, whereas, the second study, Study M14-716, examined QTc following doses of GLE 400 mg + PIB 120 or GLE 800 mg + PIB 240 mg. The results indicated that, in contrast to 400 mg moxifloxacin (positive control) there were no clinically significant effects on QTc interval prolongation according to the ICH E14 guideline following any of the doses of GLE + PIB investigated.

Patient exposure

Overall exposure in the placebo-controlled analysis set is shown in Table 15. Mean exposure in 202 patients in the GLE/PIB 12 week group was 84.4 days with a range of 47 to 90 days. The total exposure was 46.7 patient-years. Overall exposure in the active-controlled analysis set is shown in Table 16. Mean exposure in 233 patients in the GLE/PIB 12 week group was 83.3 days with a range of 5 to 89 days. The total exposure was 53.2 patient-years. Overall exposure in the Phase II and III analysis set is shown in Table 17. Totals of 850 (37.5%), 1,295 (57.2%) and 120 (5.3%) patients were assigned to treatment for 8, 12 and 16 weeks, respectively. Mean exposure to study drug in 2,265

patients was 75.4 days with a range of 2 to 116 days. The total exposure was 467.9 patient-years.

Table 15: Study drug exposure in the placebo-controlled analysis set

Parameter	GLE/PIB 300 mg/120 mg × 12 Weeks (N = 202)	Placebo × 12 Weeks (N = 100)	Total (N = 302)
Mean ± SD (days)	84.4 (2.83)	84.4 (0.64)	84.4 (2.34)
Median (days)	84	84	84
Minimum – maximum (days)	47 – 90	82 – 86	47 – 90
Total subject-years of exposure	46.7	23.1	69.8

GLE = glecaprevir; PIB = pibrentasvir; SD = standard deviation

Table 16: Study drug exposure in the active-controlled analysis set

Parameter	GLE/PIB 300 mg/120 mg × 12 Weeks (N = 233)	SOF + DCV × 12 Weeks (N = 115)
Mean ± SD (days)	83.3 (9.40)	83.6 (6.82)
Median (days)	85	84
Minimum – maximum (days)	5 – 89	12 – 91
Total subject-years of exposure	53.2	26.3

DCV = daclatasvir; GLE = glecaprevir; PIB = pibrentasvir; SD = standard deviation; SOF = sofosbuvir

Table 17: Study drug exposure in the Phase II and III analysis set

Parameter	Phase 2 and 3 Analysis Set[a] (N = 2,265)
Mean ± SD (days)	75.4 (16.39)
Median (days)	84
Minimum – maximum (days)	2 – 116
Total subject-years of exposure	467.9
Duration interval (days), n (%)	
1 – 15	6 (0.3)
16 – 30	5 (0.2)
31 – 45	4 (0.2)
46 – 60	816 (36.0)
61 – 75	14 (0.6)
76 – 90	1,304 (57.6)
91 – 105	1 (< 0.1)
> 105	115 (5.1)
Assigned treatment duration, n (%)	
8 weeks	850 (37.5)
12 weeks	1,295 (57.2)
16 weeks	120 (5.3)

SD = standard deviation

a. Excluding Study M15-462.

Safety issues with the potential for major regulatory impact

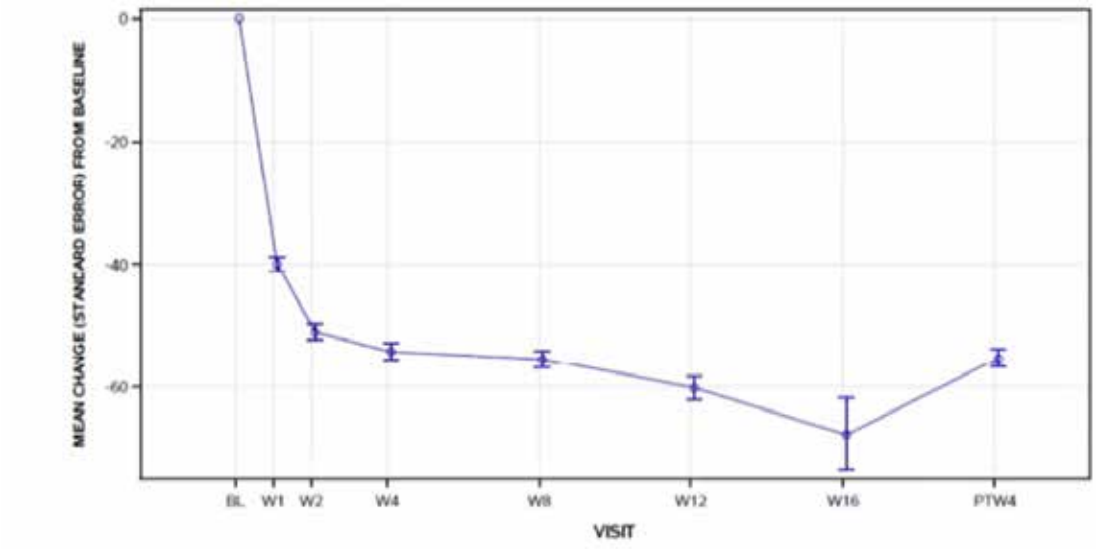
Liver function and liver toxicity

Integrated safety analyses

Hepatic events of special interest included potential hepatotoxicity, hepatic decompensation or failure and HCC. No issues with possible regulatory impact were identified.

Only four patients had clinically relevant ALT elevations in the Phase II and III Analysis Set, but none of the patients discontinued prematurely because of LFT abnormalities. In three patients, the ALT elevations were considered temporary fluctuations of no clinical significance. Only one patient met the criteria for potential hepatotoxicity.[36] A transient Grade 3 ALT elevation with a Grade 2 bilirubin elevation were considered probably related to the passage of gallstones noted on liver ultrasound. The pattern of LFT abnormalities was considered obstructive rather than drug-induced liver injury. Modest bilirubin increases of mean 0.05 mg/dL occurred in all patients in the Phase II and III Analysis Set. These typically occurred at Week 1 but returned towards baseline thereafter, consistent with known GLE-mediated inhibition of bilirubin metabolism. Bilirubin elevations of potential clinical interest were uncommon. Total bilirubin elevations ≥ 2 x ULN and > baseline were reported in 1.2% of patients and total bilirubin ≥ 2 x ULN and > baseline and direct/total bilirubin ratio > 0.4 were reported in 0.2% of patients. Mean changes in ALT and bilirubin over time are shown. Mean ALT rapidly decreased in response to reduced liver inflammation.

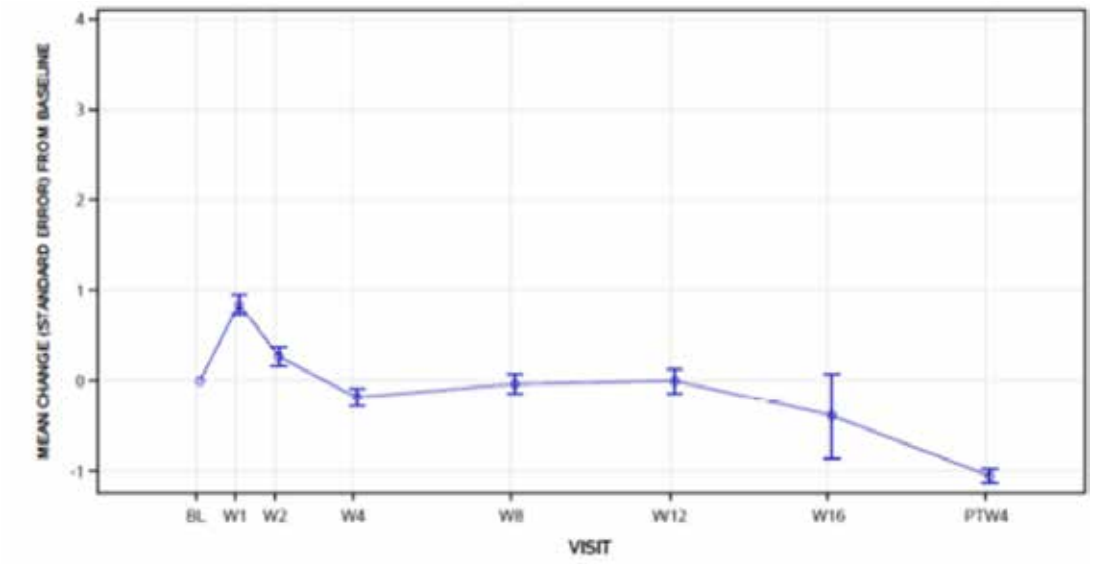
Figure 4: Mean change in ALT (U/L) over time in the Phase II and III set



ALT = alanine aminotransferase; BL = baseline; PTW = Post-Treatment Week; W = week
Note: Data exclude Study M15-462

[36] ALT > 5 x ULN and ≥ 2 x baseline; or ALT > 3 x ULN and concurrent total bilirubin ≥ 2 x ULN with direct/total bilirubin ratio > 0.4

Figure 5: Mean change in total bilirubin (µmol/L) over time in the Phase II and III set



BL = baseline; PTW = Post-Treatment Week; W = week
Note: Data exclude Study M15-462
Note: Mean change from baseline at Week 1 was 0.8 µmol/L (0.05 mg/dL).

Only one case of hepatic decompensation was reported in the Phase II and III set. A patient with cirrhosis (Child-Pugh score 6 at baseline and known oesophageal varices) had a variceal haemorrhage on Day 22. There were no signs of hepatic failure, study drug treatment was continued and SVR12 was achieved. Six cases (0.3%) of HCC were reported, five in patients with underlying cirrhosis. Each case was consistent with underlying chronic HCV infection and none were considered related to study drug.

Renal function and renal toxicity

Integrated safety analyses

- Controlled studies: No Grade 3/4 AEs relating to renal function abnormalities were reported in the controlled studies. There were no reports of creatinine > 3 x ULN, or creatinine clearance < 30 mL/min.
- Phase II and III Analysis Set: There was a single Grade 3/4 AE of renal impairment with creatinine > 3 x ULN and creatinine clearance < 30 mL/min.

Other clinical chemistry

Integrated safety analyses

- Controlled studies: The numbers of patients with any Grade 3/4 laboratory abnormalities are shown in Table 18.

Table 18: Patients with Grade 3/4 laboratory abnormalities in controlled studies

	Treatment Group, n/N* (%)			
	Placebo-Controlled Analysis Set		Active-Controlled Analysis Set	
Variable (Criterion)	GLE/PIB 300 mg/120 mg × 12 Weeks (N = 202)	Placebo × 12 Weeks (N = 100)	GLE/PIB 300 mg/120 mg × 12 Weeks (N = 233)	SOF + DCV × 12 Weeks (N = 115)
Hemoglobin (< 80 g/L)	0/202	0/100	0/232	0/115
Platelet count (< 50 × 10^9/L)	0/202	0/100	0/232	0/115
Total neutrophils (< 1 × 10^9/L)	3/202 (1.5)	0/100	1/232 (0.4)	0/115
Leukocytes (< 2.0 – 1.0 × 10^9/L)	0/202	0/100	1/232 (0.4)	0/115
INR (> 2.5 × ULN)	1/202 (0.5)	1/100 (1.0)	1/232 (0.4)	0/115
ALT (> 5 × ULN)	1/202 (0.5)	2/100 (2.0)	0/232	0/115
AST (> 5 × ULN)	2/202 (1.0)	1/100 (1.0)	1/232 (0.4)	0/115
GGT (> 13.9 U/L)	1/202 (0.5)	0/100	1/232 (0.4)	0/115
Alkaline phosphatase (> 5 × ULN)	0/202	0/100	0/232	0/115
Total bilirubin (> 3 × ULN)	1/202 (0.5)	0/100	0/232	0/115
Creatinine clearance, calculated (< 30 mL/min)	0/202	0/100	0/232	0/115
Albumin (< 20 g/L)	0/202	0/100	0/232	0/115
Cholesterol (> 10.34 mmol/L)	0/202	0/100	1/232 (0.4)	0/115
Glucose (> 13.9 mmol/L)	2/202 (1.0)	1/100 (1.0)	1/232 (0.4)	0/115
Creatinine (> 3 × ULN)	0/202	0/100	0/232	0/115
Triglycerides (> 5.7 mmol/L)	1/202 (0.5)	1/100 (1.0)	1/232 (0.4)	2/115 (1.7)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; DCV = daclatasvir; GGT = gamma-glutamyl transferase; GLE = glecaprevir; INR = international normalized ratio; PIB = pibrentasvir; SOF = sofosbuvir; ULN = upper limit of normal

Note: n/N* indicates the number of subjects with postbaseline values for the respective parameter meeting the criteria; grade must have been more extreme than baseline.

- Phase II and III Analysis Set: The percentages of patients with significant laboratory abnormalities were < 1% for any individual variable.

Haematology and haematological toxicity

Integrated safety analyses

- Placebo-Controlled Analysis Set: There were no Grade 3/4 abnormalities related to haemoglobin, platelets, or leucocytes. There were three reports (1.5%) of neutropaenia in the GLE/PIB group compared with none in the placebo group.
- Active-Controlled Analysis Set: There were no Grade 3/4 abnormalities related to haemoglobin, or platelets. There were single reports of leucopaenia (0.4%) and neutropaenia (0.4%) in the GLE/PIB group compared with none in the SOF + DCV group.
- Phase II and III Analysis Set: There were few clinically significant haematological laboratory abnormalities in the full safety set. Grade 3/4 abnormalities were reported for low haemoglobin (<0.1%), reduced platelet count (0.2%), neutropaenia (0.5%) and leucopaenia (<0.1%).

Other laboratory tests

Integrated safety analyses

- Phase II and III Analysis Set: There were few Grade 3/4 abnormalities for other laboratory variables including cholesterol (< 0.1%), glucose (0.9%) and triglycerides (0.6%). There were no Grade 3/4 laboratory abnormalities related to alkaline phosphatase or albumin.

Electrocardiograph findings and cardiovascular safety

Integrated safety analyses

- Phase II and III Analysis Set: Only four clinically significant ECG changes were reported in the full safety set. Three events were reported as AEs, one case of bundle branch block and two cases of transient atrial fibrillation. Each event was Grade 1 or 2 in severity. One patient had a prolonged QTc interval which was also present at baseline.

Vital signs and clinical examination findings

Integrated safety analyses

- Phase II and III Analysis Set: Few patients had clinically significant changes related to vital signs (≤ 1.5% for any parameter) and no clinically important trends were identified.

Immunogenicity and immunological events

Not applicable.

Serious skin reactions

Integrated safety analyses

Pooled safety data relating to skin reactions were not provided in the integrated safety analyses.

In the Phase II and III safety set, three SAEs relating to skin/wound infections were reported; however, no serious skin reactions were identified.

Other safety parameters

Not applicable.

Post-marketing data

Not applicable.

Evaluator's conclusions on safety

Overall, the safety profile of GLE/PIB was comparable to placebo and no significant safety signals were detected. There were few severe AEs, ADRs, or SAEs and discontinuations due to AEs were uncommon.

The safety of the GLE/PIB fixed dose combination has been evaluated in 2,369 patients with chronic HCV infection, including those with compensated liver disease, renal impairment and co-infection with HIV-1. Two controlled studies were performed. In the double-blind, placebo-controlled Study M15-464, 202 patients with GT2 infection without cirrhosis were given GLE/PIB for 12 weeks as compared with 100 patients given placebo. In the open-label, active-controlled Study M13-594, 390 patients with GT3 infection without cirrhosis were given GLE/PIB for 12 weeks, compared with 115 patients given SOF + DCV. In the Phase II and III analysis set, 2,369 patients in 21 study arms received GLE/PIB or GLE 300 mg + PIB 120 mg without RBV. Excluding patients in the renally impaired study, the mean exposure to study drug was 75.4 days or 467.9 patient-years. Overall, only 1.5% of patients prematurely discontinued study drug for any reason and only 0.4% discontinued due to AEs.

In the Phase II and III analysis set, AEs, AEs ≥ Grade 3, SAEs and discontinuations due to AEs were reported in 67.5%, 2.9%, 2.1% and 0.4% of patients, respectively. There were six deaths but none were considered drug related. By PT, the most common AEs were headache (18.1%), fatigue (14.6%) and nausea (9.2%), but most AEs were only mild in severity. In Study M15-464, the pattern of AEs was comparable in the GLE/PIB and

placebo groups, most commonly headache (11.9% versus 12.0%) and fatigue (11.4% versus 10.0%). Diarrhoea was reported in 9.9% of patients receiving active treatment with a risk difference of 6.9% compared with placebo. However, diarrhoea was reported in only 6% of the Phase II and III analysis set. In Study M13-594, the pattern of AEs was comparable in the GLE/PIB and SOF +DCV groups, most commonly headache (25.8% versus 20.0%), fatigue (18.9% versus 13.9%) and nausea (13.7% versus 13.0%). The pattern of AEs analysed by SOC was similar in patients given GLE/PIB compared with those in the placebo and active control groups. No clinically meaningful changes in haematological and chemistry variables were reported. ALT levels were significantly improved and no cases of drug induced liver injury were detected. Only two patients (< 0.1%) experienced Grade 3 ALT elevations and only eight patients (0.4%) experienced Grade 3 elevations in bilirubin. No safety signals related to ECGs were detected.

As highlighted, the pattern of AEs in important subgroups was comparable to the overall safety population. In particular, there were no clinically meaningful differences related to age, gender, ethnicity, baseline renal function or baseline hepatic function and no dosage adjustments are required. As discussed, there are no safety data in patients with HBV co-infection, renal/liver transplant patients and patients with decompensated cirrhosis.

First round benefit-risk assessment

First round assessment of benefits

See Table 19 below.

Table 19: First round assessment of benefits

Benefits	Strengths and Uncertainties
Very high SVR12 rate in patients with any HCV genotype, including GT3. Effective in all patients, irrespective of age, gender, race, BMI and hepatic function. Although controlled clinical trials cannot be conducted, Maviret will reduce the morbidity and mortality associated with chronic HCV infection, including cirrhosis, HCC and liver related deaths.	Very strong evidence supporting good efficacy with SVR12 rates typically > 95% across all genotypes and patient subgroups in multiple Phase II and III studies.
Effectiveness was not generally impacted by the presence of baseline polymorphism	SVR12 rates lower in a small number of DAA treatment-experienced patients with baseline both NS3 and NS5A polymorphisms.
Simple, once daily treatment with a single dose, fixed dose combination.	Once daily dosing is assumed but not proven to enhance compliance and maximise SVR12 rates.
No additional benefit with co-administration with RBV.	Data are limited but SVR12 rates are typically > 95% without additional RBV.
Effective in patients with or without compensated cirrhosis, including cirrhotic patients with GT3 infection.	Adequate patient numbers with and without cirrhosis have been studied.
Effective in treatment-naïve and treatment-	Strong Phase II and III study data

Benefits	Strengths and Uncertainties
experienced patients (including those who previously received DAA-based therapies).	confirming efficacy in patients with any treatment history. Relatively few patients have been studied with previous DAA treatment.
Effective when given for 8 weeks in patients without cirrhosis.	Statistically significant non-inferiority of 8 weeks versus 12 weeks treatment in non-cirrhotic patients.
Renal elimination is minimal. Well tolerated without dosage adjustment in patients with chronic renal impairment.	Strong evidence of effectiveness in a stand-alone study of patients with chronic kidney disease.
Effective in patients with HCV/HIV-1 co-infection.	Limited patient numbers but 100% SVR12 rate in patients with HCV/HIV-1 co-infection.
Virologic failure uncommon so reduced risk of drug resistant strains in community.	Safety data available in 2369 patients but only limited data from controlled clinical studies.
Well tolerated with low incidence of ADRs and SAEs. No evidence of drug related liver injury.	Controlled data limited but convincing
Safety profile comparable to placebo and SOF + DCV. No specific ADRs have been identified.	

First round assessment of risks

See Table 20 below.

Table 20: First round assessment of risks

Risks	Strengths and Uncertainties
Well tolerated but there is a risk of unidentified, uncommon ADRs.	Well tolerated in 2,369 patients.
Potential for DDIs.	Metabolic pathways have been characterised and the potential for DDIs has been identified in the proposed PI.
Potential for HBV re-activation.	Patients with HCV/HBV co-infection have not been studied.
No data available for use in liver and renal transplant patients, paediatric patients and patients with decompensated cirrhosis.	Studies are planned or on-going.

First round assessment of benefit-risk balance

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

Maviret given for 8, 12 weeks, or 16 weeks provides outstanding SVR12 rates of 90 to 100% in HCV patients with or without cirrhosis, irrespective of genotype and prior treatment experience. Virologic failure (mainly relapse) is uncommon and reported mostly in patients with GT3 infection and patients who have failed previous DAA therapies that included both NS3/4A PI and NS5A inhibitor. Maviret is given as a simple once daily dose and it obviates the need for potentially toxic RBV, PegIFN, or other less well tolerated DAA therapies. In this vulnerable population, high SVR12 rates are associated with improved liver function in a significant proportion of patients. It is effective in all subgroups irrespective of age, gender and race, including those with mildly impaired hepatic and any degree of impaired renal function. Maviret is well tolerated and no specific ADRs have been identified.

First round recommendation regarding authorisation

Authorisation is recommended for Maviret for the following indication:

> *Maviret is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.*

Approval is subject to incorporation of suggested changes to PI and satisfactory response to clinical questions.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

No changes to the first round assessment.

Second round assessment of risks

No changes to the first round assessment.

Second round assessment of benefit-risk balance

No changes to the first round assessment. The benefit-risk balance is positive.

Second round recommendation regarding authorisation

No changes to the first round assessment.

Authorisation is recommended for Maviret for the following indication:

> *Maviret is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.*

Approval is subject to the proposed PI changes.

VIII. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[37]

- In support of this application, the sponsor submitted EU-RMP version 2.0 (dated August 2017; data lock point (DLP) 4 November 2016) with ASA version 2.0 (dated August 2017; DLP November 2016) in the post-first round evaluation response.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised in Table 21, below.

Table 21: Summary of safety concerns

Summary of safety concerns (ASA v2.0)		Pharmacovigilance		Risk Minimisation
		Routine	Additional	Routine only
Important identified risks	HBV reactivation	ü*	–	ü
	Resistance development	ü	# 1	ü
Important potential risks	Recurrence of hepatocellular carcinoma	ü*	# 2	-
	Emergence of hepatocellular carcinoma			
	Drug-drug interactions – Concomitant use with other drugs that are strong inhibitors of OATP1B1 or OATP1B3 (for example, ciclosporin 400 mg, darunavir with or without ritonavir, and lopinavir/ritonavir) – Concomitant use with drugs that are inducers of P-gp/CYP3A (e.g., efavirenz)	ü	–	ü

[37] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns (ASA v2.0)		Pharmacovigilance		Risk Minimisation
	– Concomitant use with drugs that are sensitive substrates of P-gp (e.g., digoxin) – Concomitant use with drugs that are sensitive substrates of OATP1B1 or OATP1B3 (e.g., lovastatin, pravastatin, rosuvastatin)			
Missing information	Safety in patients with moderate hepatic impairment (Child-Pugh B)	ü*	–	ü
	Safety in liver transplant patients	ü	# 3	ü
	Safety in pregnant and breastfeeding patients	ü	-	ü
	Safety in patients with previous hepatocellular carcinoma			

*General hepatic events follow-up questionnaire will be used to characterise any hepatic decompensation events that are reported, in Australia.

'Use in Paediatric patients' should be added to the list of safety concerns, in the ASA.

The pharmacovigilance plan is considered adequate. Routine pharmacovigilance is proposed and includes the use of structured follow-up of reports of HBV reactivation and hepatocellular carcinomas in Australia. Additional pharmacovigilance activities are as follows:

1. *Study M13-576 (ongoing):* Long term follow up study (36 months) to evaluate durability of sustained virologic response (SVR) and development and/or persistence of resistance among subjects who do not achieve SVR in previous trials.
2. *Study PASS (planned, not finalised):* prospective, cohort, safety study using data derived from a cohort of a well-defined group of patients, based on an agreed protocol setting out criteria for entry and follow-up of patients in terms of timing and method of screening (risk of HCC recurrence).
3. *StudyM13-596 (ongoing, MAGELLAN 2):* safety and efficacy of GLE/PIB in adult post-liver or post-renal transplant recipients with chronic HCV genotype 1 to 6 infection

- The sponsor has not proposed any pharmacovigilance activities to investigate 'use in paediatrics' – this is acceptable considering the proposed usage and the agreed EU-Paediatric Investigation Plan (EMA-001832-PIPO1-15).
- Routine risk minimisation activities only (PI, CMI) are proposed and this is considered acceptable. No additional risk minimisation activities are considered necessary, which is consistent with the RMPs of other Direct Acting Antiviral products.

New and outstanding recommendations from second round evaluation

The recommendations made in the first round evaluation, along with consideration of the sponsor response, are reconciled. There are new and outstanding recommendations as follows:

- Recommendation 1: 'Use in Paediatrics' should be added to the list of safety concerns in the ASA.
- Recommendation 2: Administrative recommendation - The ASA refers to the previous safety concern of 'de novo hepatocellular carcinoma'. This should be updated to align with the terminology used in the summary of safety concerns (emergence of HCC).

Proposed wording for conditions of registration

A suggested RMP condition of registration can be provided if the sponsor provides satisfactory responses to the recommendations in the report.

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

IX. Overall conclusion and risk/benefit assessment

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

Quality

There were no objections to registration from a chemistry and quality perspective. GMP clearance was not in place at the time of review, but is anticipated to be resolved prior to the decision phase.

Nonclinical

There were no non-clinical objections to registration of glecaprevir/pibrentasvir. The overall quality of the submission was high. The non-clinical data predicted drug-drug interactions mediated by the transporters including P-glycoprotein (P-gp), BCRP;[38] OATP1B1;[39] and OATP1B3. Both glecaprevir and pibrentasvir undergo minimal metabolism by CYP enzymes, and thus their clearance is unlikely to be affected by CYP450 inhibitors or inducers. Glecaprevir has the potential to inhibit intestinal CYP3A4 but is not predicted to have clinically relevant inhibition of hepatic CYP450 or UGT.[40]

Pregnancy Category B1 was considered appropriate for both glecaprevir and pibrentasvir and therefore the combination product.

The sponsor provided an updated draft PI with their post-first round response. The changes recommended by the nonclinical evaluators were accepted, with minor amendments or corrections.

[38] Breast cancer resistance protein
[39] Organic anion transporting polypeptide
[40] UDP-glucuronosyltransferases

Clinical

Pharmacology

Discussion of pharmacokinetics in the clinical evaluation report primarily focused on the Phase III formulation of GLE/PIB, which is identical to the formulation proposed for marketing. A number of formulations were investigated as part of the clinical development process but were not developed further due to lower bioavailability than the formulation to be marketed.

The submission included 43 PK studies, two of which also contained pharmacodynamic data addressing QTc effects of GLE and PIB and a single population PK study (R&D/16/0234).

Key points regarding the PK of glecaprevir and pibrentasvir are briefly summarised according to the following topics, in a similar format to the FDA Summary and Clinical Pharmacology Reviews.[41]

When GLE and PIB are co-administered, the time to maximum observed plasma concentration (T_{max}) of GLE occurs 3 to 5 hours after dosing and for PIB occurs approximately 5 hours after dosing. GLE exhibited limited metabolism in vitro. Metabolism played no role in the elimination of PIB. Both GLE and PIB are predominantly excreted through the biliary-faecal route, with renal clearance < 1%.

Bioavailability and food effect

The absolute bioavailability of GLE and PIB has not been determined. This was discussed in the Pharmaceutical and Quality evaluation, with a justification for waiving the requirement of absolute bioavailability studies submitted by the sponsor.

A food-drug interaction effect was described in Study M14-714. Following a 300 mg/120 mg dose of GLE/PIB FDC, food increased the exposure to the GLE component by 1.8 to 3.2 fold compared to fasted conditions and exposure to the PIB component by 1.4 to 2.1 fold. It is recommended in the PI that Maviret be taken with food.

Hepatic impairment

Study M13-604 (n = 27) examined the PKs of a single-dose of GLE and/or PIB under non-fasting conditions in subjects with normal hepatic function (n = 7) and in subjects with mild (n = 7), moderate (n = 6) and severe (n = 7) hepatic impairment as assessed by the Child-Pugh score. Following the recommended dose of the free combination of GLE 300 mg + PIB 120 mg, GLE AUC values were 33% and 100% higher in subjects with mild and moderate hepatic impairment, respectively, and increased by 11 fold in subjects with severe hepatic impairment compared to the subjects with normal hepatic function. In subjects with severe hepatic impairment, PIB AUC was increased by 2.14 fold compared to the subjects with normal hepatic function. For this reason, GLE/PIB will be contra-indicated in patients with Child Pugh C cirrhosis and 'not recommended' in patients with Child Pugh B cirrhosis.

Population pharmacokinetics

The TGA did not arrange for a population pharmacokinetic replication and evaluation by a pharmacometrician for this submission. The Pop PK Working Group reviewed the relevant part of the clinical evaluation report and the report of the PopPK analysis at the request of the Delegate.

[41] Centre for Drug Evaluation and Research. Application 209394Orig1s000. Summary Review. Mavyret/glecaprevir and pibrentasvir. July 17, 2017; Centre for Drug Evaluation and Research. Application 209394Orig1s000. Clinical Pharmacology and Biopharmaceutics Review.

A number of concerns were in relation to the PopPK analysis for glecaprevir, in particular the performance of the modelling and conclusions related to covariates. The FDA expressed similar concerns in relation to the effect of cirrhosis on the PK of glecaprevir in their Clinical Pharmacology and Biopharmaceutics Review;[42] namely a 2 fold difference in mean exposures between cirrhotic and non-cirrhotic patients was observed, 'however the overlap in exposures for those subjects without cirrhosis and those with cirrhosis limit the clinical significance of the observed difference.'

The sponsor provided a formal response which will be reviewed by the PopPK Working Group in November 2017.

The TGA concurs with the FDA comments in regards to the uncertainty regarding the magnitude of the effect of cirrhosis on GLE PK and how this might guide dosing advice. The data do not support different dosing recommendations, including when dealing with drug-drug interactions, for patients with mild hepatic impairment (Child Pugh A cirrhosis). Classic PK study data and clinical trials information should inform the recommendations in the PI.

Renal impairment

Study M13-600 (n=46) assessed the PKs following a single dose of the free combination of GLE 300 mg + PIB 120 mg under non-fasting conditions in subjects with normal renal function (n=8), in subjects with mild (n=8), moderate (n=8) and severe (n=8) renal impairment and in subjects with end-stage renal disease (n=6), as assessed by the estimated glomerular filtration rate (eGFR). The study also examined the impact of haemodialysis in subjects with ESRD requiring dialysis (n=8). The results indicated that as eGFR decreased there was a trend towards increasing GLE and PIB AUC_{∞} values, with maximum predicted increases of 56% and 46%, respectively, in subjects with ESRD not on dialysis compared to normal subjects. C_{max} values were similar in all groups regardless of renal function. GLE and PIB exposures were similar in subjects with ESRD requiring dialysis prior to haemodialysis and on a non-dialysis day.

As discussed in the efficacy section of the Overview, a single-arm, open label trial (Study M15-462) evaluated the efficacy and safety of GLE/PIB in 104 HCV-infected subjects (GT 1-6) with eGFR < 30 mL/min/1.73 m^2 including those on dialysis, with a safety profile comparable to that of the overall population.

GLE and PIB are minimally eliminated via the renal route and no dosage adjustments are proposed in patients with mild, moderate, or severe renal impairment, with or without haemodialysis.[43]

Drug-drug interactions

GLE is a substrate and inhibitor of the transporters P-glycoprotein and BCRP and the hepatic uptake transporters OATP1B1 and OATP1B3. PIB is a substrate of P-gp and/or BCRP and an inhibitor of P-gp, BCRP, and OATP1B1. GLE and PIB are weak inhibitors of cytochrome P450 (CYP)-3A, CYP1A2 and UGT1A1, but did not inhibit CYP2C9, CYP2C19, CYP2D6 or UGT1A4.[44]

The drug-drug interaction profile was evaluated in over 23 studies for more than 35 drugs, with clinically significant drug interactions outlined in the proposed PI. Significant drug-drug interactions include those with carbamazepine, rifampicin, St John's wort, HIV protease inhibitors, cyclosporine, dabigatran and statins. Co-administration with ethinyl

[42] Centre for Drug Evaluation and Research. Application 209394Orig1s000. Clinical Pharmacology and Biopharmaceutics Review.
[43] Centre for Drug Evaluation and Research. Application 209394Orig1s000. Summary Review. Mavyret/glecaprevir and pibrentasvir. July 17, 2017
[44] Centre for Drug Evaluation and Research. Application 209394Orig1s000. Clinical Pharmacology and Biopharmaceutics Review.

estradiol-containing oral contraceptives is not recommended due to ALT elevations observed in a PK study in healthy volunteers.

Conclusions on pharmacodynamics

Results of pharmacodynamics studies were described in the CER. Following supra-therapeutic doses of GLE + PIB, no clinically significant effects on QTc interval prolongation were identified.

The EPAR included a useful summary of pharmacodynamics. In vitro, glecaprevir showed optimised pharmacodynamics properties as compared to previous protease inhibitors and activity was poorly affected by common GT1 resistance associated substitutions associated with virologic failure to other protease inhibitors.

Similarly, in vitro activity of pibrentasvir did not appear to be significantly affected by the presence of common resistance associated substitutions.

Dose selection for pivotal trials

The clinical evaluator was satisfied with the dose finding for the pivotal trials. The combination of GLE 300 mg and PIB 120 mg achieved blood levels providing maximal antiviral effects and higher doses would not achieve additional reductions in HCV RNA. Phase II studies assessed lower dose combinations of GLE and PIB. While lower doses were effective in some patient subgroups, the proposed dose of GLE 300 mg +PIB 120 mg achieved optimal SVR12 rates across all patient groups.

Efficacy

Efficacy data included two controlled studies (Studies M15-464 and M13-594) and seven uncontrolled Phase II/III efficacy and safety studies: Studies M13-583, M13-590, M15-462, M15-410, M14-867, M14-868 and M14-172. A pilot Phase II study, Study M14-213, was also included. The main studies were conducted in non-cirrhotic or compensated cirrhotic patients who were treatment naïve or had failed previous treatment with pegIFN + ribavirin (including some patients with pegIFN + ribavirin + sofosbuvir).

Inclusion and exclusion criteria

The inclusion and exclusion criteria (patient and laboratory) were generally similar across the studies, with the main differences relating to HCV genotype, presence or absence of cirrhosis and presence or absence of severe renal impairment.

Study design

Studies employed various designs including comparison to historical control, duration controlled, placebo or active-controlled or open-label single arm across important subpopulations.

Table 22: Overview of clinical studies

Study and dates	Design	Population	Number of subjects randomised and treated	Study duration	Status
Phase III					
M13-590 (ENDURANCE-1)	Multicentre, randomised, open-label study	Non-cirrhotic HCV GT1 with our without HIV-HCV co-	703	36 weeks or 32 weeks	Ongoing*

Study and dates	Design	Population	Number of subjects randomised and treated	Study duration	Status
		infection			
M15-464 (ENDURANCE-2)	Multicentre, randomised, double-blind, placebo-controlled	Non-cirrhotic adult patients with chronic HCV GT2 infection	302	36 weeks (arm A) 48 weeks (arm B)	Ongoing*
M13-594 (ENDURANCE-3)	Multicentre, partially-randomised, open-label, active-controlled, study	Chronic HCV GT3 infection without cirrhosis	505	36 weeks (arms A,B) 32 weeks (arm C)	Ongoing*
M13-583 (ENDURANCE-4)	Single-arm, open-label, multicentre study	Chronic HCV GT4, 5 or 6 infection without cirrhosis	121	36 weeks	Ongoing*
M14-172 (EXPEDITION-1)	single arm, open-label study	Treatment-naïve or treatment-experienced adults with chronic HCV GT1, 2, 4, 5 or 6 infections and compensated cirrhosis	146	36 weeks	Ongoing*
M15-462 (EXPEDITION-4)	single-arm, open-label study	Treatment-naïve or treatment-experienced adults with chronic HCV GT1-6 infection, with or without cirrhosis and severe renal impairment including patients on dialysis	104	36 weeks	Ongoing*
Phase II					

Study and dates	Design	Population	Number of subjects randomised and treated	Study duration	Status
M14-867 (SURVEYOR-1), Part 1	Phase II, open-label, two part, multicentre study	Treatment-naïve and PR null responders, non-cirrhotic HCV GT1	79	36 weeks	Completed
M14-867 (SURVEYOR-1), Part 2		Treatment-naïve and treatment-experienced, HCV GT-1, with and without compensated cirrhosis, HCV GT4-6 treatment-naïve and treatment-experienced, without cirrhosis	95	32 or 36 weeks	Completed
M14-868, (SURVEYOR-2)	Phase II, multicentre, randomised, open-label, multipart study	Chronic HCV GT2, 3, 4, 5, or 6 infection with or without cirrhosis	692 (195:Part 1, 162:Part 2, 131:Part 3, 203:Part 4)	32 or 36 weeks	Ongoing*
M15-410, MAGELLAN-1	Phase II, randomised, open-label, multicentre study	Part 1: HCV GT-1 treatment-experienced, without cirrhosis (DAA-experienced to NS5A and/or PI), or GT1, GT4 – GT6 (Part 2)	Part 1: 50 Part 2: 91	Up to 40 weeks	Ongoing*

*Studies now completed, PR: pegylated interferon and ribavirin.GT: genotype

Study M13-590 (ENDURANCE-1): HCV GT1, treatment naïve or experienced, non-cirrhotic, with our without HIV-HCV co-infection

This multicentre, randomised, open-label study investigated the efficacy and safety of GLE/PIB in treatment-naïve and treatment-experienced, non-cirrhotic adult patients with chronic HCV GT1 infection.

The primary efficacy objectives were:

- To demonstrate the non-inferiority of SVR12 rates in DAA-naïve, HCV GT1 mono-infected patients following treatment with GLE/PIB for 12 weeks, compared with historical efficacy data in the same patient population treated with the standard of care regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir +/- ribavirin (Viekira Pak / Viekira Pak RBV) or ledipasvir/sofosbuvir (Harvoni) for 12 weeks.
- To show the non-inferiority in SVR12 rates in the same patient population treated for 8 weeks (Arm B) versus 12 weeks (Arm A).

Secondary objectives are outlined in the CER (see Attachment 2). With respect to inclusion criteria, the protocol was amended to include patients with HCV/HIV-1 co-infection; and/or patients who had previously received sofosbuvir.

Results for the primary efficacy outcome

A total of 704 patients (352 in each arm) were randomised and 703 patients received at least one dose of study drug. A total of 700 patients completed study drug and three patients discontinued.

Baseline demographics and disease characteristics were comparable in each treatment group. 33 patients (4.7%) had HCV/HIV-1 co-infection, all were receiving anti-retroviral therapy and nearly all (n=28) had baseline CD4 counts ≥ 500 cells/mm^3.

In the ITT-PS population (ITT subset of HCV mono-infected DAA-naïve patients), SVR12 was achieved by 99.7% (95% CI: 99.1, 100.0) of patients in Arm A (12 weeks treatment) and 99.1% (95% CI: 98.1, 100.0) in Arm B (8 weeks treatment). In the ITT-PS-PP[45] population, SVR12 was achieved by 100% (95% CI: 98.9, 100.0) of patients in Arm A and by 100% (95% CI: 98.9, 100.0) of patients in Arm B. There was a single case of on-treatment virologic failure in the 8 week group but no cases of post-treatment relapse. All primary endpoints were achieved.

In the small cohort of HIV-co-infected patients (n = 33), SVR12 was achieved by 18 patients (100.0%) in Arm A and 15 patients (100%) in Arm B. In the ITT-MS population, SVR12 was achieved by 99.7% of patients in Arm A and 99.1% in Arm B. The evaluator concluded that the overall results supported the dosage and treatment duration recommendations in the proposed PI.

Study M15-464 (ENDURANCE-2): HCV GT2, treatment naïve or experienced, non-cirrhotic

This multicentre, randomised, double-blind, placebo-controlled study investigated the efficacy and safety of GLE/PIB in non-cirrhotic adult patients with chronic HCV GT2 infection.

The primary objectives were to measure the proportion of patients achieving SVR12 compared with historical SOF +RBV efficacy data and to assess the tolerability and safety of 12 weeks treatment with GLE/PIB compared with placebo. Other objectives were to assess the rate of on-treatment virologic failure and post-treatment relapse and to assess efficacy in patients previously treated with SOF + RBV +/- pegIFN.

Patients were randomised 2:1 to one of two treatment groups:

- Arm A: GLE/PIB 300 mg/120 mg given once daily for 12 weeks.

[45] ITT-PS-PP: all randomised patients in the ITT-PS, with the exception of patients who discontinued before Week 8, patients who experienced virologic failure prior to Week 8, patients with missing SVR12 values and non-responders due to re-infection. ITT-MS: all patients in the ITT who were HCV-mono-infected and including those who were SOF treatment experienced.

- Arm B: Matching placebo once daily for 12 weeks followed by open-label GLE/PIB given once daily for 12 weeks.

Randomisation was stratified into 3 groups, based on previous treatment experience: treatment-naïve, IFN or pegIFN +/- RBV, SOF + RBV +/- pegIFN.

In the double-blind treatment period, a total of 304 patients were randomised and 302 patients received at least one dose of study treatment (202 patients in Arm A; 100 patients in Arm B). One patient discontinued study drug prematurely.

Baseline disease characteristics were also similar in each group. All patients had HCV GT2 infection, 70.2% were treatment-naïve and 29.8% were treatment experienced.

In the ITT population, SVR12 was achieved by 99.5% (95% CI: 98.5, 100.0) of patients (excluding prior SOF + RBV +/- pegIFN failures) in Arm A who were treated with GLE/PIB 300 mg/ 120 mg once daily for 12 weeks during the double-blind treatment period. The primary efficacy outcome was achieved, as the SVR12 rate was non-inferior to the 95% historical control rate (SOF + RBV for 12 weeks).

SVR12 was achieved by 100% (6/6) of patients in Arm A who were previous SOF + RBV +/- pegIFN failures and by both treatment-experienced patients in Arm B during the open-label treatment period.

The evaluator commented that recruitment of prior sofosbuvir failures was encouraged but more significant numbers could not be found, possibly because SOF-based therapies are generally effective. Eight (6%) of patients had received prior SOF-based therapies. It was concluded that the results of this study supported the use of GLE/PIB given for 12 weeks in treatment-naïve or treatment-experienced patients with HCV GT2 infection without cirrhosis.

Study M13-594 ENDURANCE-3: HCV GT3, treatment naïve, non-cirrhotic

This was a partially randomised, open-label, active-controlled, multicentre study comparing the efficacy and safety of GLE/PIB to sofosbuvir with daclatasvir (SOF +DCV) in treatment-naïve adults with chronic HCV GT3 infection without cirrhosis.

The primary efficacy objectives were to demonstrate non-inferiority in the percentage of patients achieving SVR12 of GLE/PIB given for 12 weeks, compared with SOF + DCV given for 12 weeks; and to demonstrate non-inferiority of GLE/PIB given for 8 weeks compared with GLE/PIB given for 12 weeks. The secondary objectives were to demonstrate the superiority of GLE/PIB given for 12 weeks, compared with SOF + DCV given for 12 weeks; and to assess on-treatment virologic failure and post-treatment relapse.

Patients meeting all eligibility criteria were initially randomised in a 2:1 ratio to Arms A or B, with 230 patients to be randomised to Arm A and 115 patients to be randomised to Arm B. After enrolment in Arms A and B were completed, 115 patients were assigned to Arm C.

- Arm A: GLE/PIB 300 mg/120 mg once daily for 12 weeks.
- Arm B: SOF 400 mg + DCV 60 mg once daily for 12 weeks.
- Arm C: GLE/PIB 300 mg/120 mg once daily for 8 weeks.

A total of 506 patients were randomised and 505 patients received at least one dose of study drug (233 Arm A; 115 Arm B; and 157 Arm C). 491 patients completed the study treatment and 14 (2.8%) patients discontinued. With the exception of country and geographical region, the baseline demographics were comparable in each treatment arm. The Delegate notes that this probably reflects regional variation in HCV genotype subtypes.

In the ITT population, SVR12 was achieved by 95.3% (95% CI: 92.6, 98.0), 96.5% (95% CI: 93.2, 99.9) and 94.9% (955 CI: 91.5, 98.3) of patients in Arms A, B and C, respectively.

Non-inferiority of GLE/PIB 12 weeks as compared to SOF+DCV 12 weeks was achieved in the ITT and PP population. The non-inferiority of GLE/PIB given for 8 weeks compared with GLE/PIB given for 12 weeks was also demonstrated. In the ITT population, SVR12 was achieved by 94.9% (95% CI: 91.5, 98.3) of patients in Arm C, compared with 95.3% (95% CI: 92.6, 98.0) of patients in Arm A.

A sensitivity analysis in the Per Protocol population confirmed the results of the primary analyses.

The evaluator concluded that the results of this study supported the use of GLE/PIB given once daily for 12 weeks in treatment-naïve patients with HCV GT3 infection without cirrhosis. The results also supported the use of GLE/PIB treatment for 8 weeks without the need for RBV. The EPAR noted that more relapses were observed in the 8 week arm, compared to the 12 week arm and that there was a tendency towards lower results in patients with moderate and severe fibrosis treated for 8 weeks.

HCV GT3 patients who were treatment-naïve and non-cirrhotic were included in this study. GT3 patients were excluded from the pivotal study in cirrhotic patients (EXPEDITION-1) and the study in patients with failure to DAAs (MAGELLAN-1). Few GT3 patients with cirrhosis who were treatment naïve were included in the EXPEDITION-4 study (patients with severe renal impairment). GT3 patients with cirrhosis and those who were treatment experienced were included as a subgroup in part 3 of the SURVEYOR-2 study, however numbers were limited: cirrhotic, treatment naïve GT3 patients, n=40 (Arm Q), and cirrhotic, treatment experienced patients, n=48 (Arm R).

It is important that prescribers are informed of inclusion criteria for which for the trials with GT3 patients, given that GT3 and cirrhosis, particularly treatment-experienced patients, are perceived to be a major treatment gap for which treatment failures are the highest (See Phase II trials).

Study M13-583 (ENDURANCE-4): HCV GT4, 5 or 6 without cirrhosis

This was a single-arm, open-label, non-randomised, multicentre study of the efficacy and safety of GLE/PIB in treatment-naïve or treatment-experienced adults with chronic HCV GT4, 5 or 6 infection without cirrhosis.

The primary efficacy objective was to measure the percentage of patients achieving SVR12 following GLE/PIB treatment for 12 weeks. The secondary objectives were to assess on-treatment virologic failure and post-treatment relapse.

Patients were treated with GLE/PIB 300 mg/120 mg once daily for 12 weeks, with a further 24 weeks post-treatment period.

121 patients were enrolled and received at least one dose of study drug. 118 patients completed the study drug and three (2.5%) patients discontinued. Baseline disease characteristics were described. 76 patients had GT4 infection (62.8%), 26 had GT5 infection (21.5%) and 19 had GT6 infection (15.7%). Most patients were treatment-naïve (67.8%) and the remainder (32.2%) were treatment-experienced (all IFN- based).

99.2% (95% CI: 97.6, 100.0) of patients achieved SVR12, regardless of whether they were treatment-naïve or treatment-experienced. One patient did not achieve SVR12 but there were no cases of virologic failure. While an active control group and larger numbers would have been desirable, the evaluator was of the opinion that the study design was appropriate for patients with uncommon HCV genotypes.

Given the low prevalence of these genotypes in Australia, these results are acceptable and are also supported by the in vitro data presented.

Study M14-172 (EXPEDITION-1): HCV 1, 2, 4, 5, 6 and compensated cirrhosis[46]

This was a single arm, open-label study of GLE/PIB in treatment-naïve or treatment-experienced adults with chronic HCV GT1, 2, 4, 5 or 6 infections and compensated cirrhosis.

The primary efficacy objective was to measure the percentage of patients achieving SVR12 following GLE/PIB treatment for 12 weeks. The secondary objectives were to assess on-treatment virologic failure and post-treatment relapse.

146 patients were enrolled and treated and 144 completed study drug. In treatment-naïve and treatment-experienced patients with GT1, 2, 4, 5 and 6 infection and compensated cirrhosis, SVR12 was achieved by 99.3% (95% CI: 98.0, 100.0) of the ITT population. There were no cases of on-treatment virologic failure and one case of relapse. The published study report highlighted the exclusion of important subgroups, including those with GT3 infection and those with decompensated cirrhosis. Few patients with HCV GT5 and GT6 were enrolled, n=2 and n=7 patients respectively, given the low prevalence rates. An active-controlled study design was not deemed feasible due to the absence of a pangenotypic regimen for patients with compensated cirrhosis when the study was designed.

Study M15-462 (EXPEDITION-4): chronic renal impairment, GT1-6 infection, with or without compensated cirrhosis[47]

This was a single-arm, open-label study of the antiviral activity and safety of GLE/PIB in treatment-naïve or treatment-experienced adults with chronic HCV GT1-6 infection, with or without compensated cirrhosis and severe renal impairment including patients on dialysis.

The primary efficacy objective was to assess SVR12 in patients with HCV GT1-6 infection and chronic renal impairment following 12 weeks treatment with GLE/PIB. The secondary objectives were to assess the percentage of patients with on-treatment virologic failure and post-treatment relapse. Of patients with HCV GT3 infection, only treatment naïve without cirrhosis or with compensated cirrhosis were eligible.

104 patients were randomised and received at least one dose of study drug. 100 patients completed study drug and four patients (3.8%) discontinued study drug. All withdrawals were due to AEs. Genotypes 1, 2, 3, 4, 5 and 6 were present in 51.9%, 16.3%, 10.6%, 19.2%, 1.0% and 1.0% of patients, respectively. Overall, 57.7% of patients were treatment-naïve and 42.3% were treatment-experienced (nearly all IFN-based). Cirrhosis was present in 19.2% of patients and 80.8% were non-cirrhotic. Baseline eGFR was < 15 mL/min/1.73m^2 in 82.7% of patients and ≥15 mL/min/1.73 m^2 in 17.3% of patients. Most patients required dialysis (81.7%). Of patients not requiring dialysis, 12.5% were Stage 4 and 5.8% were Stage 5. All patients requiring dialysis were receiving haemodialysis.

In the ITT population, SVR12 was achieved by 98.1% (95% CI: 95.4, 100) of patients.

The evaluator concluded that patient numbers were limited, especially for GT5 and GT6 infection and that treatment experienced patients with HCV GT3 infection were excluded, however along with the study in individuals with renal impairment without HCV infection, the data support the recommendation for no dosage adjustment in HCV infected patients with any degree of renal impairment, including those on renal dialysis.

[46] Forns X, et al. Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): a single-arm, open-label, multicentre phase 3 trial. Lancet Infect Dis. 2017 Oct;17(10):1062-1068.
[47] Gane E, et al. Glecaprevir and Pibrentasvir in Patients with HCV and Severe Renal Impairment. N Engl J Med 2017; 377:1448-55.

Study M15-410 (MAGELLAN-1): GT1, GT4-6 patients with failure to DAAs

This was a Phase II, randomised, open-label, multicentre study of co-administered GLE + PIB with or without RBV, or GLE/PIB in adult patients with HCV infection who had failed prior DAA-containing therapy. It was considered pivotal, as it is it directly assessed SVR12 rates in patients with GT1 or GT4-6 infection who had previously failed therapy with approved DAA treatment regimens.

- Part 1 explored the efficacy of GLE + PBE with or without RBV in approximately 50 patients randomised 1:1:1 to one of three treatment arms:
  - Arm A: GLE 200 mg QD + PIB 80 mg QD for 12 weeks.
  - Arm B: GLE 300 mg QD + PIB 120 mg QD + RBV 800 mg QD for 12 weeks.
  - Arm C: GLE 300 mg + PIB 120 mg QD for 12 weeks.
- Part 2 of the study was conducted after review of the Part 1 data. Approximately 91 DAA treatment-experienced patients with GT1 or GT4-6 infection with compensated liver disease with or without cirrhosis were randomised 1:1 to one of two treatment arms:
  - Arm D: GLE/PIB 300 mg/120 mg QD for 12 weeks.
  - Arm E: GLE/PIB 300 mg/120 mg QD for 16 weeks.

Randomisation was stratified by HCV genotype and by previous DAA treatment experience.

In Part 1, the baseline disease characteristics are detailed. Most patients had GT1a infection (Arm A 66.7%, Arm B 90.9%, Arm C 81.8%) and the remainder had GT1b infection. In each of Arms B and C, 50% of patients were NS5A experienced, 50% were NS5A naïve /PI experienced and 18.2% of patients were NS5A experienced/PI naïve.

In Part 2, the baseline disease characteristics are detailed. Most patients had GT1a infection (73.6%) or GT1b infection (20.9%). 29.7% of patients were PI experienced/NS5A naïve, 70.3% of patients were NS5A experienced, 33.0% were NS5A experienced/PI experienced and 37.4% of patients were NS5A experienced/PI naïve.

In Part 1, ITT SVR12 rates in Arm A (n=6), B (n=22) and C (n=22) were 100% (95% CI: 61.0, 100.0), 95.5% (95% CI: 78.2, 99.2) and 86.4% (66.7, 95.3), respectively.

In Part 2, the SVR12 rates in Arm D (n=44) and Arm E (n=47) were 88.6% (95% CI: 76.0, 95.0) and 91.5% (80.1, 96.6) and 90.1% in Arms D+E (n=91) (95% CI: 82.3, 94.7), respectively.

In Part 1 of the study, there was one case of relapse in patients receiving GLE 300 mg + PIB 120 mg + RBV and one case of on-treatment failure in patients receiving the same combination without RBV, with the sponsor deciding to pursue the 2-DAA combination without RBV. In Part 2, treatment for 16 weeks was compared with treatment for 12 weeks. SVR12 rates were comparable in the two groups (91.5% and 88.6%, respectively). There were more cases of on-treatment virologic failure in patients given treatment for 16 weeks (8.5% versus 2.3%), but relapse was experienced more frequently in patients in patients treated for 12 weeks (0% versus 9.3%). NS5A/PI treatment-experienced patients had a significantly higher rate of virologic failure than those who had received NS5A-based or PI-based monotherapy. In general, multiple polymorphisms at baseline were associated with virologic failure but no predictive patterns were identified.

The following table from the FDA summary review[48] presents the data for the key subpopulations. This analysis was produced by the FDA.

Table 23: MAGELLAN-1 SVR12 data for NS5A Inhibitor and/or NS3/4A PI Experienced Subjects for 12 or 16 Weeks Duration

Treatment Experience	GLE/PIB 12 weeks N = 65 (%)	GLE/PIB 16 weeks N = 44 (%)
NS5A-experienced & NS3/4A PI-naïve	18/20 (90.0) (95% CI: 69.9, 97.2) OTVF: 1/20 (5.0) Relapse: 1/20 (5.0)	16/17 (94.1) (95% CI: 73.0, 99.0) OTVF: 1/17 (5.9)
NS3/4A PI-experienced & NS5A-naïve	23/25 (92.0) (95% CI: 75.0, 97.8) 2 missing SVR12	12/12 (100) (95% CI: 75.8, 100)
NS5A & NS3/4A PI-experienced	16/20 (80.0) (95% CI: 58.4, 91.9) OTVF: 1/20 (5.0)	12/15 (80.0) (95% CI: 54.8, 93.0) OTVF: 3/15 (20.0)

OTVF: on treatment virologic failure.

The number of patients in each subgroup stratified for previous DAA treatment was small for both Parts 1 and 2, making it difficult to draw definitive conclusions regarding efficacy in these subgroups. The majority of patients enrolled in the study had GT-1 infection. The EU highlighted that patients with prior protease inhibitor experience in the MAGELLAN-1 study may not be representative of the majority of protease inhibitor experienced patients eligible for re-treatment in the future.

The sponsor outlined in the second round response that the FDA has not approved use in GT1 patients (treatment-experienced with both NS5A and PI therapies) due to high rates of virologic failure. The EU did not support use in NS5A/PI-experienced patients; however, the sponsor may submit a variation with additional analyses to justify use in this patient population. In Part 2 of Study M15-410, virologic failure was 20% (6/30) in NS5A/PI-experienced patients compared with NS5A-experienced/PI-naïve patients 8.8% (3/34), and PI-experienced/NS5A-naive patients 0% (0/27). In the opinion of the evaluator, these virologic failure rates do not preclude approval for use in NS5A/PI-experienced patients, as this is a patient group with no other treatment options. The higher virologic failure rates are included in Table 11 of the PI.

Study M14-867 (SURVEYOR-1): Treatment-naïve and treatment-experienced, HCV GT-1, HCV GT4-6 with and without compensated cirrhosis

This was a Phase II, open-label, two part, multicentre study of co-administered GLE + PIB with or without RBV in treatment-naïve or treatment-experienced adult patients with HCV infection with compensated cirrhosis or without cirrhosis.

The study consisted of two independent parts enrolled sequentially. In Part 1, patients received GLE + PIB for 12 weeks; in Part 2, patients received GLE + PIB for 8 or 12 weeks. RBV was initially planned but not administered in any study arms.

[48] Centre for Drug Evaluation and Research. Application 209394Orig1s000. Summary Review. Mavyret/glecaprevir and pibrentasvir. July 17, 2017

The evaluator concluded that the study assessed the efficacy of various doses of GLE (200 mg or 300 mg QD) + PIB (40 mg or 120 mg) in a mixed population of treatment-naïve or treatment-experienced patients with GT1 or GT4-6 infection with or without cirrhosis. SVR12 rates >96% were achieved in cirrhotic or non-cirrhotic patients with any HCV genotype infection (noting GT2 and GT3 were not included in the study). There were no cases of on-treatment virologic failure. There were two cases of relapse but both occurred in patients receiving lower than recommended doses of GLE or PIB.

Few patients with compensated cirrhosis were included; 27 patients with GT-1 infection in Arm F of Part 2, who received GLE 200mg once daily and PIB 120 mg once daily for 12 weeks rather than the proposed dose for registration of 300 mg/120 mg.

Study M14-868 (SURVEYOR-2): HCV 2-6 with and without cirrhosis

This was an expanded Phase II, multicentre, partially randomised, open-label study to investigate the efficacy and safety of GLE + PIB co-administered with or without RBV adult patients with chronic HCV GT2, 3, 4, 5, or 6 infection with or without cirrhosis. It consisted of four parts and is described in detail.

It was a complex exploratory/confirmatory study with multiple treatment arms assessing efficacy in patients with GT2-6 infection treated for 8, 12 or 16 weeks. Treatment-naïve and treatment-experienced patients with and without cirrhosis were given various doses of GLE + PIB or GLE/PIB with or without RBV. Although it was a Phase II study, it may be considered pivotal as it supports the dosage and treatment duration recommendations in the proposed PI. Overall, the evaluator was of the opinion that the results supported the dosage (GLE 300mg/PIB 120 mg given QD) and treatment duration recommendations in the proposed PI (8, 12 or 16 weeks depending on genotype (GT2-6), prior HCV treatment history (naïve or experienced) and presence or absence of cirrhosis).

With reference to GT3, in Part 3, treatment-naïve patients with GT3 infection with cirrhosis, and treatment-experienced patients with GT3 infection with or without cirrhosis were treated with GLE 300 mg + PIB 120 mg for 12 or 16 weeks.

The following table is adapted from the FDA Clinical review;[49] and represents the results for GT3 in the SURVEYOR-2 study given at doses proposed for registration, stratified by treatment duration, presence of cirrhosis and prior treatment experience.

Table 24: Study M14-868 (SURVEYOR-2); Genotype 3 SVR12 by treatment arm

	SVR12	OTVF	Relapse	Other
Arm D GT3, TN and TE without cirrhosis, 12 weeks	28/30 (93.3%) (95% CI:78.7, 98.2)	0	1/30(3.3)	1/30(3.3)
Arm L GT3, TN without cirrhosis 8 weeks	28/29 (96.6%) (95% CI: 82.8, 99.4)	0	0	1/29(3.4)
Arm L GT3 TE without cirrhosis, 12 weeks	22/24 (91.7%) (95% CI: 74.2, 97.7)	1/24 (4.2)	1/23(4.3)	0

[49] Centre for Drug Evaluation and Research. Application 209394Orig1s000. Clinical Review. Mavyret/glecaprevir and pibrentasvir. July 17, 2017

	SVR12	OTVF	Relapse	Other
Arm O GT3, TN with cirrhosis 12 weeks	27/28 (96.4%) (95% CI: 82.3, 99.4)	0	1/28 (3.6)	0
Arm Q GT3, TN with cirrhosis 12 weeks	39/40 (97.5%) (95% CI: 87.1, 99.6)	0	0	1/40(2.5)
Arm Q GT3, TE, without cirrhosis 12 weeks	20/22 (90.9%) (95% CI: 72.2, 97.5)	0	2/22 (9.1)	0
Arm R GT3, TE, without cirrhosis 16 weeks	21/22 (95.5%) (95% CI: 78.2, 99.2)	0	1/22 (4.5)	0
Arm R GT3 TE with cirrhosis 16 weeks	45/48 (93.8%) (95% CI: 83.2, 97.9)	1/48 (2.1)	1/46 (2.2)	1/48 (2.1)

OTVF: on treatment virologic failure, TN: treatment naïve, TE: treatment experienced

High SVR12 rates were achieved in all treatment arms. In treatment-naïve GT3 patients with cirrhosis treated for 12 weeks, the SVR12 rate was 98%. In treatment-experienced patients with or without cirrhosis, the 16 week regimen achieved higher SVR12 rates compared with patients without cirrhosis treated for 12 weeks (SVR 91%).

Analyses performed across trials: pooled and meta-analyses

A pooled analysis of all randomised patients in the Phase II and III studies was performed and is described in detail. A total of 2369 randomised patients received at least one dose of study medication and 2332 patients completed study drug treatment. A total of 560 patients completed the studies for the primary analysis, 37 discontinued and 1779 were ongoing. It was felt that the efficacy data were satisfactory, matched the claims in the proposed PI and supported the broad proposed indication.

Safety

General comments

The safety of the GLE/PIB fixed dose combination was evaluated in 2,369 patients with chronic HCV infection. This included 104 with severe renal impairment (Study M15-462) and 308 patients with compensated cirrhosis. Headache, fatigue and nausea were the most common adverse reactions occurring in the Phase II and III trials. Most adverse events and adverse reactions were mild and moderate and did not lead to discontinuation of treatment. The occurrence of ADRs was similar across all treatment durations.

The rate of de novo hepatocellular carcinoma (HCC) was 0.3% in the clinical development program and 1.7% in the patients with cirrhosis, which was thought to be consistent with the expected incidence of HCC in this patient population.

The evaluator was of the opinion that the safety profile of GLE/PIB was comparable to placebo and that no significant safety signals were detected. The pattern of AEs in important subgroups was comparable to the overall safety population. The safety profile was similar in patients with compensated cirrhosis and in non-cirrhotic patients and in patients with severe renal impairment and/or haemodialysis, except for a higher rate of pruritus. There were no safety data in patients with HBV co-infection, renal/liver transplant patients and patients with decompensated cirrhosis.

The FDA and EMA reached similar conclusions in regards to safety. Study M15-462, (EXPEDITION-4), in patients with chronic renal impairment, was analysed separately from the Phase II and III data sets in the overseas assessment reports.

Safety analysis sets

The sponsor elected to analyse safety in three sets:

- The placebo-controlled set assessed safety in Study M15-464 (ENDURANCE-2)
- The active-controlled set assessed safety in Study M13-594 (ENDURANCE-3)
- The Phase II and III set consisted of all Phase II and III efficacy studies with evaluable safety data, including the controlled Studies M15-464 (ENDURANCE 2) and M13-594 (ENDURANCE 3); and the uncontrolled Studies M14-868, M13-583, M13-590, M14-172, M15-462, M15-410 and M14-867.

The evaluator commented that while each study had a stand-alone safety analysis, different doses, drug combinations and treatment durations were tested in each study, making interpretation challenging. For this reason, the evaluator summarised the safety data according to the 3 main safety sets. Safety data from each study were reviewed, but no safety signals stood out compared with the overall data.

Placebo-controlled analysis set, Study M15-464 (ENDURANCE-2)

AEs were reported more commonly in patients treated with GLE/PIB 300 mg/120 mg for 12 weeks (64.9%), compared with patients treated with placebo for 12 weeks (58.0%), with a risk difference of 6.9%. Severe AEs (Grade 3 or higher) were also reported more commonly in the active treatment group (2.5% versus 1.0%). In the GLE/PIB and placebo groups, the most common AEs were headache (11.9% versus 12.0%), fatigue (11.4% versus 10.0%), diarrhoea (9.9% versus 3.0%), asthaenia (9.4% versus 8.0%), nausea (7.4% versus 3.0%) and pruritus (5.9% versus 6.0%). Diarrhoea and nausea were more common in the active treatment group but the differences were not statistically significant for nausea.

Active-controlled analysis set, Study M13-594 (ENDURANCE-3)

AEs were reported more commonly in patients treated with GLE/PIB 300 mg/120 mg for 12 weeks (76.0%), compared with patients treated with SOF + DCV for 12 weeks (69.6%), a risk difference of 6.4%. Severe AEs (Grade 3 or higher) were also reported more commonly in the GLE/PIB (4.7% versus 1.7%). In the GLE/PIB and SOF + DCV groups, the most common AEs were headache (25.8% versus 20.0%), fatigue (18.9% versus 13.9%), nausea (13.7% versus 13.0%), diarrhoea (6.4% versus 3.5%), upper respiratory tract infection (6.4% versus 3.5%) and nasopharyngitis (5.2% versus 6.1%), insomnia (3.9% versus 5.2%) and asthaenia (1.7% versus 6.1%). The only statistically significant difference was for asthaenia.

Phase II and III analysis set

AEs were reported in 67.5% of patients but only 2.9% of AEs were Grade 3 or higher. Only four severe events were considered drug related; one case each of asthaenia, abdominal pain, migraine and raised ALT. The most common AEs were headache (18.1%), fatigue

(14.6%), nausea (9.2%) and diarrhoea (6.4%). There were more events in the GLE/PIB groups compared with the control groups; however most events were mild in severity.

Deaths and serious adverse events

No on-treatment deaths were reported in the Phase II and III set. Seven deaths were reported but most occurred months after completing study drug treatment and all were considered unrelated to study treatment. SAEs were reported in 1.5% to 2.1% across all analysis sets. No pattern was observed and only two SAEs were considered drug related by the investigator (two transient ischaemic attacks in one patient).

Hepatic safety

Hepatic events of special interest included potential hepatotoxicity, hepatic decompensation or failure and HCC. No issues with possible regulatory impact were identified. Four patients had clinically relevant ALT elevations in the Phase II and III set, but none of the patients discontinued prematurely because of LFT abnormalities. In three patients, the ALT elevations were considered temporary fluctuations of no clinical significance. One patient met the criteria for potential hepatotoxicity, but the clinical and laboratory findings suggested an obstructive pattern, probably related to the passage of gallstones.

It is known that NS3/4A protease inhibitors have the potential for hepatotoxicity in patients with hepatic decompensation and hence they are not recommended in this patient group.

Risk management plan

Following the second round RMP evaluation, outstanding issues in relation to the product information were identified. The suggested wording for the RMP condition of registration will be provided upon receipt of satisfactory responses to recommendations in the report, and any changes to which the sponsor has agreed should be included in a revised RMP and ASA.

Risk-benefit analysis

Delegate's considerations

The submitted data for Maviret demonstrate a potent, pan-genotypic and well-tolerated treatment regimen which demonstrates high SVR12, regardless of genotype, treatment duration and degree of renal impairment. Favourable pharmacokinetics and a shorter duration of therapy (8 weeks) in patients without cirrhosis and in treatment experienced patients (excluding an NS3/4A PI or NS5A inhibitor) represent significant advantages for patients and with the possibility of genotype testing no longer being needed.[50]

In addressing the three main treatment gaps raised by the sponsor, patients with severe renal failure; those who have previously failed DAA-containing regimens; and patients with GT-3 and cirrhosis, the data support the recommendation for no dosage adjustment in patients with any degree of renal impairment, including those on dialysis.

There is a paucity of data to support to use of Maviret in patients who are treatment-experienced with NS5A and PI therapies, with higher rates of virologic failure in patients who are both NS5A and PI-experienced. It is anticipated that Maviret and other

[50] Ferenci, P. New anti-HCV drug combinations: who will benefit? Lancet Infect Dis. 2017 Oct;17(10):1008-1009.

pangenotypic DAAs will be most likely used to treat non-response to or relapse after first-line treatment;[51] with NS5A-experienced patients representing a population for whom there are no currently available treatment options. The Delegate therefore recommends that the indication reflect the data submitted, in line with the FDA and Health Canada approved indications, with additional analyses supporting an indication in patients who are both NS5A and PI-experienced to be submitted to the TGA when available.

The data to support efficacy in patients with GT3 and cirrhosis are predominantly derived from Part 3 of the SURVEYOR-2 study. Whilst the data are supportive of efficacy with conservative 16 week duration of therapy, experience is limited to 48 patients with GT-3 cirrhosis who are treatment experienced in this subpopulation. This information should be made clear to prescribers, noting that GT3 represents a significant proportion of the HCV population in Australia and there is a high rate of treatment failure in those with cirrhosis who are treatment experienced, due to the emergence of resistance associated substitutions.

The majority of studies were ongoing at the time of submission but have now been completed, and it is requested that these data be submitted to the TGA when available, in addition to ongoing studies in patients with HIV co-infection, post-liver and renal transplant and HCV 5 and 6. Few patients with GT4-6 were included in the registration studies (notably the EXPEDITION 4 study in patients with renal impairment) however given the SVR12 results and low prevalence of these genotypes in Australia, these data are accepted, with extrapolation from data for other genotypes deemed to be reasonable. Approximately 300 patients with compensated cirrhosis were included in the clinical development program. Based on pharmacokinetics and prior experience with NS3/4A inhibitors, Maviret will be contra-indicated in patients with severe hepatic impairment and not recommended in those with moderate hepatic impairment. It is anticipated that Maviret will be prescribed by appropriately qualified practitioners familiar with these safety issues.

The Delegate recommends that Maviret be approved for the treatment of adult patients with chronic hepatitis C virus (HCV) infection with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor but not both classes of inhibitors. Approval is subject to resolution of outstanding risk management conditions of registration and the product information.

Issues for the sponsor:

- Please provide an update of the overseas regulatory status.
- Please submit additional analyses and justifications supporting an indication in DAA-experienced patients who are both NS5A and PI-experienced, as discussed with the EMA, as a future submission to the TGA.
- The majority of studies were ongoing at the time of submission but have now been completed. It is requested that the final results for these studies are provided when available as a future submission to the TGA. Please also submit the results of the EXPEDITION 2 study in HCV 1 to 6/HIV co-infected patients, MAGELLAN-2 study and Study M16-126 when available.

[51] Ferenci, P. New anti-HCV drug combinations: who will benefit? Lancet Infect Dis. 2017 Oct;17(10):1008-1009.

Summary of issues

- The submitted data for Maviret demonstrate a potent, pan-genotypic and well-tolerated treatment regimen which demonstrates high SVR12, regardless of genotype, treatment duration and degree of renal impairment.
- Maviret demonstrates favourable pharmacokinetics and may be given for 8 weeks in patients without cirrhosis and in treatment experienced patients (excluding an NS3/4A protease inhibitor (PI) or NS5A inhibitor).
- There is a paucity of data to support use in patients who are treatment-experienced with NS5A and NS3/4A protease inhibitor therapies, with higher rates of virologic failure observed in patients who are both NS5A and PI-experienced.

Proposed action

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

It is recommended that Maviret be approved for the amended indication:

> *Maviret is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor but not both classes of inhibitors (see DOSAGE AND ADMINISTRATION and CLINICAL TRIALS).*

Request for ACM advice

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

1. The proposed indication, noting the wording of the indications approved by the EMA, FDA and Health Canada and the Delegate's proposal for wording consistent with the Health Canada and FDA indications.
2. Related to the above, the data to support use in patients who are treatment experienced with NS5A and protease inhibitor therapies (MAGELLAN-1 study) and the implications for registration.
3. The adequacy of the data to support use in GT3 patients with cirrhosis who are treatment experienced.
4. The presentation of the proposed tables in the Dosage and administration section of the product information, noting the format proposed for Australia is consistent with the EU Summary of Product Characteristics. The Delegate recommends adoption of the table in the FDA PI, consistent with the amended indication for treatment experienced patients:

Table 25: Treatment-Experienced Patients

	Treatment Duration		
HCV genotype	Patients previously treated with a regimen containing:	No Cirrhosis	Compensated Cirrhosis (Child-Pugh A)
1	An NS5A inhibitor[1] without prior treatment with an NS3/4A protease inhibitor	16 weeks	16 weeks

	Treatment Duration		
	An NS3/4A PI[2] without prior treatment with an NS5A inhibitor	12 weeks	12 weeks
1, 2, 4, 5, or 6	PRS[3]	8 weeks	12 weeks
3	PRS[3]	16 weeks	weeks

[1] In clinical trials, subjects were treated with prior regimens containing ledipasvir and sofosbuvir or daclatasvir with pegylated interferon and ribavirin. [2] In clinical trials, subjects were treated with prior regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin [3] PRS = Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

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

Response from sponsor

The sponsor would like to take this opportunity to respond to the Delegate's request for ACM advice on the issues raised in the Overview.

Proposed indication and dosing

The sponsor prefers keeping the proposed indication, with reference to different patient subgroups within the Dosage and Administration and Clinical Trials section of the PI. The safety and efficacy of GLE/PIB in HCV treatment-naïve (TN) and treatment experienced (TE) GT1- through GT6-infected patients with compensated liver disease (with or without cirrhosis), including patients with severe renal impairment or end-stage renal disease (chronic kidney disease (CKD) Stages 4 or 5), and subjects co-infected with HIV were demonstrated in 8 pivotal studies and 3 supportive Phase II studies.

The sponsor acknowledges the Delegate's proposed wording, which is consistent with Health Canada. While the sponsor maintains its preference, if the Committee does not agree, the sponsor would accept an amended indication and adoption of the dosing table, as approved by FDA and Health Canada.

Use in GT3-infected patients with cirrhosis who are treatment experienced

Adequacy of the data to support use of GLE/PIB in treatment-experienced (prior experience with IFN or pegIFN +/– RBV, or SOF plus RBV +/– pegIFN) GT3-infected patients with compensated cirrhosis is based on GLE/PIB achieving the highest SVR12 rate (96%) across the largest number of patients in this subpopulation, when compared to other approved regimens. In the Phase III SURVEYOR-2 Part 3 Study M14-868, treatment-experienced GT3-infected patients with compensated cirrhosis receiving 16 weeks of GLE/PIB achieved SVR12 rates (96%; 45/47) higher than observed in the Phase III trials for the approved regimens of SOF + DCV (SVR12 of 69%; 9/13) and SOF/VEL (SVR12 of 89%; 33/37). Moreover, despite the challenges with recruitment given the lower prevalence of this most difficult to treat GT3 subpopulation, SURVEYOR-2 Part 3 evaluated the largest number of treatment-experienced GT3-infected patients with cirrhosis, n = 47, compared to 13 and 37 subjects in the ALLY-3 (SOF + DCV) and ASTRAL-3 (SOF/VEL) trials, respectively.

Overall, the GLE/PIB regimen for 16 weeks would offer a new, highly efficacious and RBV-free therapy for a GT3 subpopulation (TE cirrhotics) that is the most difficult to cure and has limited treatment options.

Use in GT3-infected patients experienced to SOF/VEL or DCV + SOF

Available information on prevalence of A30K and Y93H at baseline and at the time of failure in ALLY-3, ALLY-3+, ASTRAL-3 and ASTRAL-4 is shown in Table 26, below.

Table 26: Prevalence of A30K and Y93H at Baseline and at the time of failure in ALLY-3, ALLY-3+, ASTRAL-3 and ASTRAL-4

Study	Baseline Prevalence	Fold-Resistance	Prevalence in Virologic Failures	
			Baseline	Time of Failure
ASTRAL-3	Overall, A30X = 11% (61/551). In the 12 wk SOF/VEL arm, A30X = 10.2% (28/275)	A30K: ~18-fold to VEL	A30K = 9.1% (1/11)	Y93H in 81.8% (9/11) A30K+Y93H in 9.1% (1/11)
	Overall, Y93H = 5.8% (32/551). In the 12 wk SOF/VEL arm, Y93H = 5.5% (15/275)	Y93H: 724-fold to VEL	Y93H = 27.3% (3/11)	
ASTRAL-4	A30K or Y93H baseline prevalence is not available	--	Y93H = 7.7% (1/13)	Y93H in 100% (13/13)
ALLY-3 and ALLY-3+	A30K = 9.3% (9/97)	A30K: 44-fold to DCV	A30K = 5.9% (1/17)	A30K in 5.9% (1/17) Y93H in 88.2% (15/17)
	Y93H = 8.2% (8/97)	Y93H: 2154-fold to DCV	Y93H = 29.4% (5/17)	

Baseline A30K was not associated with treatment failure and was not reported as a treatment emergent substitution. Among the 41 virologic failures in these 3 studies, A30K alone was detected in 1 subject, Y93H alone was detected in 37 subjects, and A30K+Y93H was detected in 1 subject at the time of failure.

Given that the majority of GT3-infected subjects treated with SOF/VEL or SOF + DCV selected Y93H alone (which confers high levels of resistance to VEL and DCV but not to PIB) at the time of failure, this subject population is expected to respond to GLE/PIB similarly to DAA-naïve subjects who have Y93H at baseline. Among 309 DAA-naïve GT3-infected subjects receiving GLE/PIB (duration of 8 weeks for TN subjects without cirrhosis, 12 weeks for TN subjects with cirrhosis, and 16 weeks pegIFN, RBV and/or SOF TE subjects irrespective of cirrhosis status), all subjects with Y93H in NS5A achieved SVR12 (100%, 15/15).

A30K confers moderate levels of resistance to VEL and DCV (18- and 44-fold, respectively). However, it appears that the SOF/VEL and SOF + DCV regimens are able to overcome baseline A30K resistance, as this polymorphism at baseline was not enriched in the subjects experiencing virologic failure. The majority (38/40) of the virologic failures have only Y93H at the time of failure, a substitution that on its own confers high level resistance to VEL and DCV. The prevalence of A30K+Y93H at the time of failure with SOF/VEL or SOF + DCV regimen was 2.4% (1/41). However, given that a single subject with A30K accounts for the prevalence for this polymorphism at both baseline and virologic failure in the studies shown in table above, it is difficult to draw a conclusion regarding impact of A30K for these regimens.

Availability of Treatment Regimens for Patients Experienced to Both NS5A Inhibitor (NS5A-I) and NS3/4A Protease Inhibitor (PI)

The combination regimen of SOF/VEL/VOX administered for 12 weeks was recently approved in the EU for treatment of DAA-experienced patients including those who previously failed NS5A-I and/or PI-containing regimens.6 This combination has demonstrated high efficacy across all genotypes in this population, however, this regimen may not be suitable for patients with advanced renal disease, a key population with significantly higher prevalence of HCV infection compared to those without renal disease. For patients with severe renal impairment or end-stage renal disease (ESRD) requiring

dialysis, the EU SmPC of SOF/VEL/VOX indicates that safety and efficacy of the regimen was not assessed in these populations, and is not approved as re-treatment in this patient population. Therefore, NS5A-I-experienced patients with severe renal impairment or ESRD currently have limited or no re-treatment options.

In addition, SOF/VEL/VOX is the only IFN-free regimen approved for patients who failed NS5A-I-containing regimens. Increasing the number of therapeutic options available for treatment of these patients will result in increased access to treatment, decreased cost of therapies, especially in the areas with limited resources and high burden of HCV infection, and will contribute towards HCV infection elimination goals as set by the World Health Organization. For the consideration by the ACM, we provide letters from relevant academics as appendices to this response.

Resistance analysis in NS5A-I/PI-experienced GT1-infected subjects in Study M15-410

In the original submission to TGA, resistance analyses used a key subset of amino acid positions (155, 156, 168 in NS3; 24, 28, 30, 31, 58, 92, 93 in NS5A) at which a single substitution confers resistance to at least 1 inhibitor in the PI or NS5A-I class and are typically present in patients who experienced virologic failure with these classes (that is, treatment-emergent substitutions). An additional analysis was performed using a modified key subset of amino acid positions in NS3 (GLE-specific RASs), which included only single or double substitutions that confer resistance to GLE in the in vitro replicon assays (A156any, D168F/Y, Y56H+D168any for GT1a; A156any, Y56H+D168any for GT1b). For NS5A, amino acid position 32 was added for the resistance analysis; thus amino acid positions 24, 28, 30, 31, 32, 58, 92, and 93 were included for this analysis.

Among HCV GT1-infected subjects experienced to PI and NS5A-I in Study M15-410, the presence of baseline substitutions at the key subset of amino acid positions in both NS3 and in NS5A was associated with lower SVR12 rates. Combinations of Y56H and D168any (that confer 39 to 47 fold resistance to GLE) in NS3 were detected in 5 GT1a-infected subjects at the 2% detection threshold, and 4 of these subjects experienced virologic failure. Among these 5 HCV GT1a-infected subjects with GLE-specific RASs in NS3, all 5 had failed a treatment regimen containing a PI < 12 months prior to enrolment in Study M15-410.

Table 27: Prevalence of Baseline GLE-Specific RASs by time from previous PI-containing regimen to start of GLE/PIB treatment for HCV GT1-infected NS5A-I-experienced/PI-experienced subjects in Study M15-410

Presence of Baseline GLE-specific RASs[a], n/N (%)	Time from Previous PI-Containing Regimen[b]			Total
	< 12 Months	≥ 12 and < 24 Months	≥ 24 Months	
Yes	5/17 (13.5%)	0/4	0/14	5/35 (7.7%)
No	12/17 (83.8%)	4/4 (100%)	14/14 (100%)	30/35 (90.8%)

GLE = glecaprevir; PI = protease inhibitor; RAS = resistance-associated substitution

a. "GLE-specific RASs" at baseline includes the following substitutions: A156any, D168F/Y, Y56H+D168any in NS3 for GT1a; A156any, Y56H+D168any in NS3 for GT1b.

b. PI-containing regimen may not have been the most recent treatment regimen.

The single GT1b-infected subject experiencing virologic failure had P32 deletion in NS5A, a substitution seen among a small proportion (3% to 10%) of subjects experiencing virologic failure after receiving a DCV-containing regimen. 9,10,11 P32deletion confers 1036-fold resistance to PIB, and higher levels of resistance to all other marketed NS5A-I.

SVR12 rates in the presence of NS5A substitutions and/or GLE-specific RASs are shown in the table below. In subjects experienced to PI and NS5A-I who did not have GLE-specific RASs, the pattern of baseline NS5A substitutions was similar to that in NS5A-I experienced/PI-naïve subjects. SVR12 rates in the NS5A-I/PI-experienced population

(excluding those subjects with GLE-specific RASs) were 83.3% (15/18) in the 12 week group and 100% (12/12) in the 16-week group, which are similar to those of the NS5A-I-experienced/PI-naïve population (90.0% (18/20) in the 12 week group and 94.1% (16/17) in the 16-week group).

Table 28: Impact of baseline substitutions at 2% detection threshold on treatment response in NS5A-I/PI-experienced subjects in Study M15-410 (mITT-VF population)

HCV GT	Amino Acid positions	Baseline Substitution, Target	12 Week Treatment	16 Week Treatment
			% SVR_{12} (n/N)	
1a	NS5A Key Subset or GLE-specific RASs[a]	NS3 only[b]	-	-
		NS5A only[b]	84.6 (11/13)	100 (7/7)
		NS3 + NS5A[c]	50.0 (1/2)	(0/3)
		None[d]	100 (3/3)	100 (1/1)
	Excluding subjects with GLE-specific RASs[a]	NS5A-only or None	87.5 (14/16)	100 (8/8)
1b	NS5A Key Subset or GLE-specific RASs[a]	NS3 only[b]	-	-
		NS5A only[b]	50.0 (1/2)	100 (3/3)
		NS3 + NS5A[c]	-	-
		None[d]	-	100 (1/1)
	Excluding subjects with GLE-specific RASs[a]	NS5A-only or None	50.0 (1/2)	100 (4/4)
Overall	NS5A Key Subset or GLE-specific RASs[a]	NS3 only[b]	-	-
		NS5A only[b]	80.0 (12/15)	100 (10/10)
		NS3 + NS5A[c]	50.0 (1/2)	(0/3)
		None[d]	100 (3/3)	100 (2/2)
	Excluding subjects with GLE-specific RASs[a]	NS5A-only or None	83.3 (15/18)	100 (12/12)

mITT-VF = modified intention-to-treat-virologic failure

a. Substitutions relative to subtype-specific reference sequences at the following amino acid positions: A156any, D168F/Y, Y56H+D168any in NS3 for GT1a; A156any, Y56H+D168any in NS3 for GT1b; and 24, 28, 30, 31, 32, 58, 92, and 93 in NS5A for GT1a and GT1b.

b. 'Only' indicates total number of subjects with baseline substitutions within the indicated target, and none in the other target. Analysis only includes subjects for whom both NS3/4A and NS5A sequences were available.

c. 'NS3 + NS5A' indicates the total number of subjects with baseline substitutions in NS3 as well as in NS5A. Analysis only includes subjects for whom both NS3/4A and NS5A sequences were available.

d. None indicates no baseline substitutions were present at the indicated amino acid positions in NS3 or NS5A.

Issue for the sponsor: Post-approval variations

No submission containing additional analyses and justifications supporting an indication in DAA-experienced patients who are both NS5A-I and PI-experienced has been made in the EU. The additional analysis is provided as requested.

The sponsor would like to clarify that all of the final primary analysis clinical study reports were submitted as part of the original filing. Regarding Studies EXPEDITION 2, MAGELLAN-2 and M16-126, the sponsor agrees to submit the primary analysis clinical study reports as a future submission to TGA.

Advisory Committee Considerations[52]

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

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Maviret tablet containing glecaprevir 100 mg and pibrentasvir 40 mg to have an overall positive benefit-risk profile for the Delegate's amended indication:

> *Maviret is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor but not both classes of inhibitors (see DOSAGE and ADMINISTRATION and CLINICAL TRIALS).*

In making this recommendation, the ACM noted that:

- the usefulness of the pangenotypic activity of the proposed Maviret fixed dose combination of two drugs, glecaprevir (HCV NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor).
- Maviret will most likely be used to treat non-response to, or relapse after first-line treatment, with NS5A-experienced patients representing a population for whom there are no currently available treatment options.
- there is currently a treatment gap for patients who have chronic renal failure and Genotypes 2, 3, 5 and 6.
- Maviret showed safety in patients with advanced renal failure. No dosage adjustment is needed in patients with any degree of renal impairment, including those on dialysis. There were no specific safety signals in patients with compensated cirrhosis.
- patients given Maviret had low discontinuation rates.
- efficacy in NS3/4A PI and NS5A resistant HCV was only shown in Genotype 1 patients in the submitted studies. There is a lack of data to support to use of Maviret in patients who are treatment-experienced with NS5A and NS3/4A PI therapies as there were higher rates of virologic failure in these patients.
- although high clearance rates were recorded in patients with Genotypes 4, 5 and 6, the number of patients with these genotypes studied was very small. Treatment should be restricted to PRS experience only for Genotypes 2, 3, 4, 5, 6 with specified requirements for durations of treatment.
- uncertainty and concerns with the population pharmacokinetic analysis for glecaprevir and how this might guide dosing advice in patients with mild hepatic impairment (Child Pugh A cirrhosis). No weight can be given to the population pharmacokinetic modelling due to unexplained variation in the model employed.

[52] The ACM provides independent medical and scientific advice to the Minister for Health and TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in 2010. ACM encompasses pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- Maviret showed evidence of efficacy after 12 weeks in treatment naïve and 16 weeks in treatment-experienced Genotype 3 patients.
- 16 weeks of Maviret treatment also gives lower relapse rates in NS5A treatment experienced Genotype 1 patients.
- Inclusion of a detailed Dosage and Administration table in the PI specifying treatment durations according to treatment experience and cirrhosis status is recommended.
- The product is approved in Europe (July 2017), USA and Canada (August 2017). The indication in the EU is less detailed and links to tables in the SmPC. The approved indications in the USA and Canada specify genotype, previous treatment experience and the presence or absence of compensated cirrhosis.

Proposed conditions of registration

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

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

Proposed PI/CMI amendments

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

The Committee agreed with the Delegate that a statement regarding the lack of data in patients with Genotype 3 and compensated cirrhosis and in patients with Genotype 3 who failed a previous regimen containing NS5A and/or NS3/4A protease inhibitors is needed in the PI.

Supported by the available data from clinical studies, the Committee also recommended adopting a more detailed Dosage and Administration table which specifies treatment durations according to treatment experience and cirrhosis status, in particular with regards to NS5A or NS3 PI prior treatment for Genotype 1.

Specific Advice

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

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

1. The proposed indication, noting the wording of the indications approved by the EMA, FDA and Health Canada and the Delegate's proposal for wording consistent with the Health Canada and FDA indications.

The Committee agreed with the Delegate's proposed indication.

2. Related to the above, the data to support use in patients who are treatment experienced with NS5A and protease inhibitor therapies (MAGELLAN-1 study) and the implications for registration.

The Committee advised that there are adequate data to support the use of Maviret in GT1 NS5A experienced patients but not the other genotypes since the patient numbers in the MAGELLAN-1 study were too low. The evidence supports durations of 16 weeks for NS5A experienced and 12 weeks for NS3/4A protease inhibitor experienced Genotype 1 patients.

3. The adequacy of the data to support use in GT3 patients with cirrhosis and who are treatment experienced.

The Committee advised that the data only support the use in PRS treatment experienced patients and not patients who have had NS3/4A PI and/orNS5A failure.

SURVEYOR II Part 3 supports the use of Maviret for GT3 cirrhotic patients as follows:

- 12 weeks therapy in treatment naïve
- 16 weeks therapy in treatment experienced
- *4. The presentation of the proposed tables in the Dosage and Administration section of the product information, noting the format proposed for Australia is consistent with the EU Summary of Product Characteristics. The Delegate recommends adoption of the table in the FDA PI, consistent with the amended indication for treatment experienced patients (located in the Delegate overview).*

The Committee agreed with the Delegate's proposal to adopt the FDA PI tables for inclusion in the Australian PI, that a table which provides details of the proposed treatment durations according to NS5A or NS3/4A PI prior treatment for Genotype 1.

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

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Maviret (glecaprevir/pibrentasvir 100 mg/40 mg) film-coated tablet blister pack indicated for:

> *Maviret is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of an NS5A inhibitor or with an NS3/4A protease inhibitor but not both classes of inhibitors (see 4.2 DOSE AND METHOD OF ADMINISTRATION and CLINICAL TRIALS).*

Specific conditions of registration applying to these goods

- The Maviret EU-RMP, version 2.0 (August 2017); DLP 4 November 2016, with ASA version 2.1 (October 2017), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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