Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Grazoprevir / Elbasvir

Proprietary Product Name: Zepatier

Sponsor: Merck Sharp and Dohme (Australia) Pty Limited

May 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

Common abbreviations

Abbreviation	Meaning
AE	adverse event
Ae_{0-24}	amount of analyte that is eliminated in urine over 24 hours
AE_D	cumulative amount of drug recovered from dialysate samples
ALP	alkaline phosphatase
ALT	serum alanine aminotransferase
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the plasma concentration/time curve
AUC_{0-24}	area under the plasma concentration versus time curve over 24 hours
AUC_{0-inf}	AUC extrapolated to infinity
$AUC_{0-\tau}$	area under the concentration-time curve from 0 to dosing interval, τ (τ = 24 hours)
BCRP	breast cancer resistance protein
BID	twice-daily
BLOQ	below the lower limit of quantitation
BLQ	below the limit of quantitation
BMI -	body mass index
BMS-790052	daclatasvir
C0	plasma concentration prior to dosing
C24 or C24h	plasma concentration 24 hours following the preceding dose
C2h	plasma concentration 2 hours post dosing
CatA	cathepsin A
CES	carboxylesterase
CHC	Chronic hepatitis C
CI	Confidence interval

Abbreviation	Meaning
CKD	Chronic kidney disease
CL	clearance
CL/F	apparent clearance
CL_D	(Dialysis) Clearance estimated from the dialysate data
CLr	renal clearance
C_{max}	maximum plasma concentration achieved
COWS	Clinical Opiate Withdrawal Scale
CPK	creatine phosphokinase
C-SSRS	Columbia Suicide Severity Rating Scale
CWRES	conditional weighted residuals
Cτ or Ctrough	trough plasma concentrations
DAA	Direct acting antiviral
DFC	dry-filled capsule
DRV	darunavir
EBR	Elbasvir
ECG	electrocardiogram
ECI	events of clinical interest
EE	ethinyl estradiol
eGFR	estimated glomerular filtration rate
EOT	End of Treatment
ESRD	end-stage renal disease
EVR	early virologic response
F	absolute bioavailability
FAS	Full Analysis Set
FDC	fixed dose combination
fe	urinary excretion

Abbreviation	Meaning
FFP	fit-for-purpose
FMI	final market image
Free combination	co-administration of the individual tablets of EBR/GZR given at the same dosage strength as the FDC
FSH	follicle-stimulating hormone
FW	Follow-up Week
geometric CV%	coefficient of variation/variability
GM	geometric mean
GMR	geometric mean ratio
GT	Genotype
GT1	genotype 1
GT3	genotype 3
GZR	Grazoprevir
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HD	haemodialysis
HIV	Human immunodeficiency virus
IBD	Inherited blood disorders, including haemophilia, thalassemia and sickle cell anaemia
ICF	informed consent form
IFN	interferon
IL28B	Interleukin 28B (interferon, lambda 3)
IPRED	geometric means of individual predicted values
IV	intravenous
IWRES	individually weighted residuals
LC-MS/MS	liquid chromatographic tandem mass spectrometry

Abbreviation	Meaning
LLoQ	Lower limit of quantification
LLOQ	lower limit of quantitation
ln	natural log
LNG	levonorgestrel
LPV	lopinavir
LS	least squares
mFAS	Modified full analysis set
MK-5172	Grazoprevir
MK-8742	~~EBR~~ Elbasvir
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MPAG	mycophenolic acid glucuronide
NA, N/A	Not applicable
NC	Non cirrhotic
NONMEM	non-linear mixed effects modelling
NR	Null responder
NS5A	nonstructural protein 5A - a phosphoprotein that plays a role in HCV RNA replication
NS5B	nonstructural protein 5B
OATPs	organic anion transporters
OC	oral contraceptive
OCT	oral compressed tablet
OFV	objective function value
OST	Opiate substitution therapy
OTVF	On Treatment Virologic Failure
PD	pharmacodynamics

Abbreviation	Meaning
PEG	polyethylene glycol
peg-IFN	Pegylated interferon alfa
PEP	Pooled efficacy population
P-gp	P- glycoprotein
PI	Protease inhibitor
PI/RTV	protease inhibitor/ritonavir
PK	pharmacokinetics
PMF	preliminary market formulations
PMF1	prototype pre-market formulation 1
PO	per oral (by mouth)
PP	Per Protocol
PPC	post predictive check
PR	Peginterferon alfa + ribavirin
PR interval	time from the onset of the P wave to the start of QRS complex (onset of ventricular depolarisation)
PRED	geometric means of typical individual predictions
PTF	Prior treatment failure
QD	once daily
QTc	corrected QT interval
QTcF	QT interval with Fridericia's Correction
QTcP	population-corrected QTc
RAP	Resistance Analysis Population
RAV	Resistance-associated variant
RBV	Ribavirin
RNA	ribonucleic acid
RR	respiratory rate

Abbreviation	Meaning
RTV	ritonavir
RVR	rapid virologic response
SAE	serious adverse event
SD	Standard deviation
SEM	standard error of the mean
SOC	system organ classes
SVR	sustained virologic response
SVR12	Sustained virologic response, having plasma HCV RNA <25 IU/mL at 12 weeks after the end of all study therapy after becoming undetectable (TND) at end of treatment
SVR24	Sustained virologic response, having plasma HCV RNA <25 IU/mL at 24 weeks after the end of all study therapy after becoming undetectable (TND) at end of treatment
$t_{1/2}$	apparent half-life
TD(q)	Target detected, quantifiable (HCV RNA ≥25 IU/mL)
TD(u)	Target detectable, unquantifiable (HCV RNA <25 IU/mL)
TE	Treatment experienced
TEAE	treatment emergent adverse event
T_{max}	time that at which the maximum plasma concentration is obtained
TN	Treatment naïve
TND	Target not detected (HCV RNA not detected)
TRD	Treatment-Related Discontinuation
TW	Treatment Week
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
Vd	volume of distribution
Vss	apparent volume of distribution at steady state following an intravascular administration

Abbreviation	Meaning
Vz/F	apparent volume of distribution
WAM	Wald's Approximation Method
WBC	white blood cell count

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	25 August 2016
Date of entry onto ARTG	29 August 2016
Active ingredient(s):	Elbasvir/Grazoprevir
Product name(s):	Zepatier
Sponsor's name and address:	Merck Sharp and Dohme (Australia) Pty Limited 26 Talavera Road, Macquarie Park NSW 2113
Dose form(s):	Tablet
Strength(s):	50 mg/100 mg
Container(s):	Blister pack
Pack size(s):	28
Approved therapeutic use:	Zepatier is indicated for the treatment of Chronic Hepatitis C genotype 1 or 4 infection in adults (see Dosage and administration and Clinical trials).
Route(s) of administration:	Oral (PO)
Dosage:	One 100 mg/50 mg tablet taken daily.
ARTG number (s):	AUST R 259928

Product background

This AusPAR describes the application by the sponsor to register two new chemical entities, elbasvir (EBR; 50 mg) and grazoprevir (GZR; 100 mg), for use in the treatment of Chronic Hepatitis C Virus (HCV) infection in an oral Fixed Dose Combination (FDC) under the name Zepatier for the proposed indication:

> *Zepatier is indicated for the treatment of Chronic Hepatitis C infection in adults (see Ddosage and administration and Clinical trials).(See Clinical trials for information on HCV genotype-specific activity.)*

The proposed product is intended for once daily oral administration once daily for 8 or 12 weeks. In special patient groups Zepatier® may be used in combination with ribavirin for 16 weeks or with sofosbuvir for 12 weeks.

EBR and GZR are two Direct Acting Antiviral (DAA) agents targeting different and complimentary aspects of Hepatitis C replication:

- GZR is a novel, pan-genotypic inhibitor of the HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein and is essential for viral replication.
- EBR is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly.

Combining GZR and EBR was stated to give an additive effect in blocking HCV RNA replication and suppressed the emergence of resistance by creating a high genetic barrier. GZR and EBR apparently do not impact the clinical pharmacokinetics of each other when co-administered.

The proposed combination is stated to offer a simple, well-tolerated, ribavirin and interferon-free regimen for patients with HCV genotypes 3, 4 and 6 and treats HCV infected patients in hard to treat populations, including those co-infected with Human immunodeficiency virus (HIV) or those with chronic kidney disease.

A number of DAAs are currently approved in Australia (see Table 2 below).

Regulatory status

This is an application to register a fixed combination of two new chemical entities which have not been registered in Australia previously.

At the time the TGA considered this application a similar application had been approved in Canada, Switzerland and USA was under consideration in the European Union and New Zealand (Table 1).

Table 1: International status of Zepatier

Country	Approval date	Approved Indications
Canada	19 January 2016	Zepatier (EBR/GZR) is indicated for the treatment of chronic hepatitis C (CHC) genotypes 1, 3, or 4 infection in adults.
EU * via Centralized procedure	Projected Approval Date: Early Aug-2016	Zepatier is indicated for the treatment of chronic hepatitis C (CHC) in adults (see sections 4.2, 4.4 and 5.1). For hepatitis C virus (HCV) genotype-specific activity see sections 4.4 and 5.1.
New Zealand	Projected Approval Date: 1 December 2016	Zepatier is indicated for the treatment of chronic hepatitis C (CHC) in adults.
Switzerland	1 April 2016	Zepatier is indicated for the treatment of chronic hepatitis C (CHC) of genotype 1 and 4 in adults.
USA **	28 January 2016	Zepatier is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 or 4 infection in adults.

Table 2: DAAs currently approved in Australia (as of May 2016)

Medicine	Product	Oral tablet	Sponsor	MOA	HCV genotype	D & A
Boceprevir	VICTRELIS	200mg	MSD	NS3 inhibitor	1	BOC/pegINF/RBV
Sofosbuvir	SOVALDI	400mg	Gilead	NS5B inhibitor	1,4; 2,3; Pre-liver transplant	SOF/pegINF/RBV
Lediprevir/Sofosbuvir	HARVONI	90/400mg	Gilead	NS5A inhibitor (LDV) NS5B inhibitor (SOF)	1	LDV/SOF
Simeprevir	OLYSIO	150mg	J-C	NS3/4A inhibitor	1, 4	SMV/pegINF/RBV SMV/SOF
Daclatasvir	DAKLINZA	30mg 45mg	BMS	NS5A inhibitor	1, 1b, 3, 4	DCV/SOF (1, 3) DCV/ASV (1b) DCV/ASV/pegINF/RBV (1, 4)
Asunaprevir	SUNVEPRA	100mg	BMS	NS3/4A inhibitor	1b 1, 4	DCV/ASV (1b) DCV/ASV/pegINF/RBV (1, 4)
Paritaprevir/Ritonovir/ Ombitasvir; Dasabuvir	VIEKIRA VIEKIRA PAK	75/50/12.5mg; 250mg	Abbvie	NS3/4A inhibitor (PAR) NS5A inhibitor (OMB) NS5B inhibitor (DAS)	1, 1a, 1b	PAR/RTV/OMB ± RBV ± DAS

Product information

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

II. Quality findings

Introduction

The proposed drug product is a film-coated tablet containing 100 mg of GZR and 50 mg of EBR with the appearance '*beige, oval shaped, film coated tablets, debossed with '770 on one side and plain on the other*' The tablets are not scored.

The tablets will be packed in aluminium/aluminium blisters in packs of 28 tablets.

The proposed dose is one 100 mg/50 mg tablet taken daily with or without food.

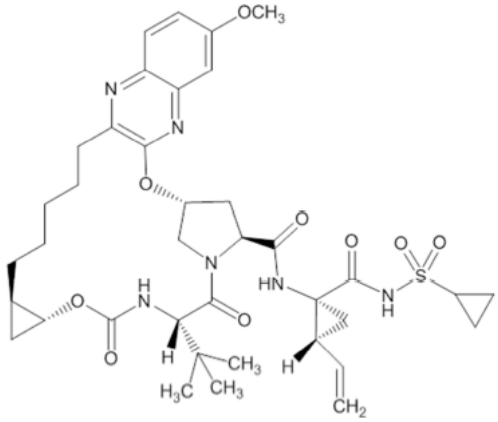
The company has not applied to register either active drug as a monotherapy tablet.

Drug substances (active ingredients)

Grazoprevir (GZR)

GZR has the structure shown in Figure 1 below.

Figure 1: Structure of GZR



GZR is a direct acting antiviral agent, and is a novel, pan-genotypic inhibitor of the HCV NS3/4A protease; necessary for the proteolytic cleavage of the HCV encoded polyprotein and essential for viral replication.

GZR free acid is a white to off-white, slightly hygroscopic, crystalline powder and is isolated as a monohydrate. This monohydrate polymorph is thermodynamically stable. The aqueous solubility of GZR is very low and pH dependent with its highest solubility being under basic conditions.

At the proposed dosage strength of 100 mg, GZR has low aqueous solubility across the physiological pH range as defined by the Biopharmaceutics Classification System (BCS) and high permeability and is hence classified as BCS class II. GZR is sensitive to moisture and is photosensitive in the solid state.

It is is optically active with seven chiral centers but shows no racemisation or epimerisation during product manufacture or storage.

The drug substance is dissolved in acetone and water during manufacture of the drug product to form an intermediate amorphous solid dispersion to maximise oral exposure. Thus particle size and morphology of the drug substance are not considered critical attributes.

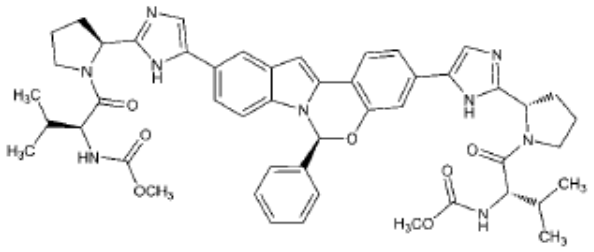
The proposed drug substance specifications comply with TGA requirements and are considered adequate to ensure the quality and consistency of manufacture of the finished product.

The drug substance shows good solid state stability and adequate stability data have been provided to support a retest period for the drug substance of 24 months stored below 25ºC.

Elbasvir (EBR)

EBR has the structure shown in Figure 2 below.

Figure 2: Structure of EBR



EBR is a direct acting antiviral agent, which acts by inhibiting HCV NS5A; a phosphoprotein essential for viral RNA replication and virion assembly.

EBR is isolated in the free base form as a hygroscopic, photosensitive, white to off-white amorphous powder that is '*practically soluble'* in water. It has pH-dependant aqueous solubility with highest solubility under acidic conditions. It is is optically active with five chiral centers but shows no racemisation or epimerisation during product manufacture or storage.

At the proposed dosage strength of 50 mg, EBR has low aqueous solubility across the physiological pH range as defined by the Biopharmaceutics Classification System (BCS) and low permeability and is hence classified as BCS class IV.

The poor solubility of EBR led to development of a spray drying process for generating an intermediate amorphous solid dispersion, to maximise oral exposure. The drug substance is dissolved in acetone and water during manufacture of the drug product. Thus particle size and morphology of the drug substance are not considered critical attributes.

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

The drug substance shows good solid state stability and adequate stability data have been provided to support a retest period for the drug substance of 18 months stored under refrigerated conditions.

Drug product

The proposed product is an un-scored immediate-release fixed combination tablet containing 100 mg of GZR and 50 mg of EBR with the appearance '*beige, oval shaped, film coated tablets, debossed with '770 on one side and plain on the other'*.

All excipients are conventional ingredients used in numerous registered oral dosage forms.

Due to the low solubility of both active drug substances, they are both separately dissolved in acetone/water and combined with suitable polymeric stabiliser and surfactant excipients (EBR: hypromellose and vitamin E polyethylene glycol succinate (TPGS); GZR: copovidone and sodium lauryl sulphate, respectively) before being spray-dried to form separate, stable, spray-dried intermediates, in which the drug substances are in their amorphous forms.

The two spray-dried intermediates are separately converted into suitable granulations by blending with appropriately chosen diluent, disintegrant, glidant and lubricant excipients before roller compaction and milling. The two granulations are blended, lubricated and compressed into tablet cores which are film-coated to produce the proposed combination tablets.

Dissolution performance of the proposed tablets during development and for quality control purposes was monitored by an adequately justified test method. Little or no change in dissolution was observed on storage, with respect to either drug substance.

The tablets will be packed in aluminium/aluminium blisters in packs of 28 tablets.

Two separate in-house gradient-elution reverse-phase HPLC test methods are employed to test for assay of each drug substance and for specified degradants associated with each.

Release and expiry limits are applied for individual unspecified degradants associated with each drug substance of NMT 0.20%, which is within the applicable International Conference on Harmonisation qualification threshold.

Degradation pathways for each drug substance have been adequately investigated and limits are applied for specified impurities for each drug substance. These limits have been qualified by toxicological studies, which have been assessed as acceptable by the TGA toxicological section.

Batches of tablets typically have low levels of total degradant impurities associated with each drug substance at release. On long-term storage (12 months 30°C) there were no significant increases in degradants associated with EBR or GZR.

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

The tablets show good stability and a shelf life of 24 months when stored below 30ºC, is considered justified.

Formulation development

Single entity formulations containing either GZR or EBR (tablets/capsules) were used in the Phase I and II clinical trials.

The proposed commercial formulation of the fixed combination tablets is the same as that used during formal stability studies and pivotal Phase III studies except for differences in the film coat colour and tablet debossing. These are not expected to impact drug product quality or performance.

Biopharmaceutics

Summary of bioavailability and bioequivalence studies

The following bioavailability studies have been provided in support of the submission:

Absolute bioavailability

Study No. 5172-P040

To estimate the absolute bioavailability (F) of single and multiple doses of GZR using radiolabelled (^{14}C)-micro dosing.

Conclusions

The geometric mean of F of GZR ranged from 9.58% to 17.0% and 14.9% to 27.3% following single oral dose administration of 25 mg and 200 mg GZR, respectively, relative to 100 µg (100 nCi) ^{14}C-GZR administered as an IV bolus micro-dose.

The geometric mean of F of GZR ranged from 21.4% to 38.3% following multiple oral doses of 200 mg GZR once a day (QD) for 7 days relative to 100 µg (100 nCi) ^{14}C- GZR administered as an IV bolus micro-dose.

Comparative bioavailability

Study No. 5172-P069

Food effect study: Study of the effect on drug substance pharmacokinetics of a high fat meal after administration of the proposed combination tablet.

Conclusions

GZR area under the concentration versus time curve from time zero to infinity ($AUC_{0\text{-}inf}$) and peak plasma concentration (C_{max}) are increased 1.5-fold and 2.8-fold, respectively,

following a single dose of a GZR (administered as a GZR and EBR 100 mg/50 mg tablet) in the fed state compared with administration in the fasted state.

EBR $AUC_{0\text{-}inf}$ and C_{max} are approximately 10% to 15% lower following a single dose of an EBR (administered as a GZR and EBR 100 mg/50 mg tablet) in the fed state compared with administration in the fasted state.

The sponsor has stated that these changes in exposure are not clinically relevant; therefore, GZR and EBR may be administered with or without food. This statement has been included in the Product Information. The acceptability of the statement 'GZR and EBR may be taken without regard to food' will be confirmed with the clinical Delegate.

Study No. 5172-P027

To compare the pharmacokinetic profile of 100 mg *monotherapy tablet of GZR* with and without *famotidine*, and also food effect of a high fat meal.

Conclusions

Co-administration of famotidine with GZR increases the $AUC_{0\text{-}\infty}$ of GZR by 22% and increases C_{max} by 63%.

Consumption of a high-fat meal prior to single-dose administration of GZR increases the $AUC_{0\text{-}\infty}$ of GZR by 11% and C_{max} by approximately 60%.

Study No. 8742-P018

Food effect study of a *high fat meal* on *EBR* pharmacokinetics in a 50 mg monotherapy tablet of EBR.

Conclusions

Single oral dose administration of the 50 mg EBR premarket tablet formulation after a high-fat breakfast marginally reduces the $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}t}$, and C_{max} (approximately10% to 15%) relative to the fasted state. The T_{max} and apparent half-life were similar under fed and fasted conditions.

Study No. 5172-P072

To evaluate the effect of the presence of famotidine and of pantoprazole on drug substance pharmacokinetics of the proposed combination tablet.

Conclusions

The pharmacokinetics of GZR and EBR administered as a single dose of GZR and EBR 100 mg/50 mg tablet are not meaningfully altered by co-administration with famotidine.

The pharmacokinetics of GZR and EBR administered as a single dose of GZR and EBR 100 mg/50 mg tablet are not meaningfully altered by co-administration with multiple doses of pantoprazole.

Study No. 5172-P055

A comparison of drug substance pharmacokinetics after a single dose of the proposed combination tablet compared to a single co-administered dose of 50 mg EBR monotherapy tablet and a 100 mg GZR monotherapy tablet.

Conclusions

EBR AUC and C_{max} are approximately15% to 18% higher following a single dose of a GZR and EBR 100 mg/50 mg tablet compared with GZR 100 mg tablet co-administered with an EBR 50 mg tablet. (Treatment A: $AUC_{0\text{-}t}$ = 1810 nM.hr, C_{max} = 106 nM; Treatment B: $AUC_{0\text{-}t}$ = 2090 nM.hr, C_{max} = 125 nM)

GZR AUC and C_{max} are similar following a single dose of a GZR and EBR 100 mg/50 mg tablet compared with GZR 100 mg tablet co-administered with an EBR 50 mg tablet. (Treatment A: AUC_{0-t} = 327 nM.hr, C_{max} = 24.6 nM; Treatment B: AUC_{0-t} = 293 nM.hr, C_{max} = 23.0 nM)

The within-subject variability of C_{max} for EBR and GZR in the reference treatment B was considered high.

Quality summary and conclusions

All pharmaceutical chemistry issues raised during the initial evaluation of this application have now been satisfactorily resolved, apart from:

- Six overseas manufacturing sites do not have Good Manufacturing Practice (GMP) clearances valid until the end of the anticipated decision phase for this submission.
- The site(s) of manufacture of the spray-dried intermediates to be included in the Australian Register of Therapeutic Goods (ARTG) has not been finalised.

It is anticipated that the sponsor will take steps to resolve the above issues prior to the Delegate's decision.

Pending resolution of the above issues, the proposed 'Zepatier® EBR and GZR 50 mg/100 mg fixed dose combination tablet is recommended for registration with respect to pharmaceutical chemistry aspects.

III. Nonclinical findings

Introduction

The overall quality of the nonclinical dossier was good with all pivotal studies conducted according to Good Laboratory practice (GLP).

Pharmacology

Primary pharmacology

GZR

GZR is a reversible inhibitor of the HCV NS3/4A protease with inhibitory activity against enzymes from all genotypes but with approximately100 fold lower potency at the enzyme from the gt3a subtype (compared to the gt1 variants). The concentration required to inhibit 50% of activity (ICR50R) values at the gt1a, 1b, 2a, 2b, 4a, 5a and 6a variants were below the clinical free plasma trough (CRtroughR) levels (0.23 nMP0F P). The ICR50R value against the gt3a variant was above the free CRtroughR levels but below the peak plasma (CRmaxR) level. It is noted that the gt3a subtype contains a glutamine at position 168 (rather than the aspartate found in most other genotypes). Amino acid changes in this position have been shown to confer resistance to GZR. While reduced efficacy of GZR may be seen in patients bearing this genotype, the lower efficacy may be compensated by the combination with EBR.

In replicon assays, GZR was effective against most known resistance mutations (including R155K); however there were significant shifts from wild type (>100-fold lower potency) with A156T/V, D168A, Q41H/A156V, Y56H/D168N, A156S/D168A and A156V/D168V mutations. Gt1 variants with reduced susceptibility to GZR were also resistant to other

macrocyclic inhibitors, indicating some cross-resistance. GZR retained activity against genotypes resistant to other NS3/4A inhibitors (S122A/G/R/T, S122A/G/R/T/N/R155K, I132V, R155K/D168A/E/V, I170E). Common mutations arising in de novo resistance induction assays were located at positions 56 (Y56H; multiple genotypes), 71 (V71A; gt2a), 156 (A156T/V; gt1b, gt2a), 158 (V158I; gt6a) and 168 (D168A/G/V; gt1a, gt1b, gt4a; Q168R, gt3a; D168N/A/V, gt5a; D168E/H, gt6a).

One primary pharmacology study in chimpanzees demonstrated that GZR (1 mg/kg PO twice a day (BD); approximately equivalent to the human dose on a mg/kg basis) reduced the viral load in animals infected with either the gt1a or the gt1b subtypes or the gt1a R155K mutant.

EBR

EBR is an inhibitor of HCV NS5A with inhibitory activity on subtypes 1a, 1b, 2a, 3a, 4a, 5a, 6 and 6d in replicon assays. The ICR50R values against these subtypes were well below the clinical free CRtroughR value (0.55 nMP1F P). Lower potency was observed against subtypes 2b, 3i and 3g with ICR50R values above the clinical free CRmaxR. EBR may have low to minimal efficacy against these subtypes. It is unknown if the combination of EBR with GZR would be efficacious against subtypes 3i and 3g but the combination is likely to show some efficacy against subtype 2b due to GZR activity. Reduced potency (≥100-fold) was observed with mutations at position 28 (F28S, gt2a; M28, gt4b), 30 (Q30D/R, gt1a; A30D, gt3a; L30H, gt4a; S30, gt4b, gt6m/n/v), 31 (L31V, gt1a; L31M, gt2a, gt3a; L31F, gt3a, gt5a, gt6) and 93 (Y93H, gt1a, 2a, 3a; Y93N, gt1a; S93, gt4b, gt6m/n/v; H93, gt4b). Double mutations conferring resistance were Q30D/Y93N (gt1a) and A30D/R56K (gt3a). Mutations arising in resistance selection assays were seen at similar positions: 28 (L28F, gta; F28S, gt6a), 30 (Q30D, Q30D/Y93N, gt1a; L30F/P/S, gt4a), 31 (L31F/Y93H/V121I, gt3a; M31V, gt4a; L31F, gt5a, gt6a), 69 (N69K, gt4a), 92 (E92K, gt3a), 93 (Y93H, gt1b, gt3a, gt4a; Y93H/V121I, gt1b) and 121 (V121I, gt1b). EBR-resistant mutants were still sensitive to protease and polymerase inhibitors. No proof of concept studies were conducted in animal models of HCV. This is not considered a major deficiencyP2F P.

Combination studies

In replicon assays, the combination of GZR and EBR was at least additive. Fewer numbers of resistant colonies were selected with the combination than for either GZR or EBR alone. Resistance to both agents was conferred by mutations in NS3 and NS5A, requiring at least two nucleotide mutations. Colonies resistance to GZR were still susceptible to EBR, and vice versa. The combination of GZR or EBR with ribavirin or sofosbuvir, an NS5B inhibitor, was additive to synergistic. The combination studies support the use of Zepatier with ribavirin or sofosbuvir.

Secondary pharmacodynamics

No clinically relevant inhibitory activity was observed with either GZR or EBR at >100 receptors, ion channels and transporters (ICR50R values were >600 times the clinical free CRmaxR). Off-target effects with the GZR/EBR combination are not predicted during clinical use.

In in vitro assays, neither GZR nor EBR had anti-viral activity against HIV at concentrations far-exceeding the clinical free CRmaxR. No antiviral activity was observed with GZR against HBV. EBR had no significant effect on the anti-HIV activity of tenofovir disoproxil, emtricitabine, efavirenz, rilpivirine, dolutegravir, raltegravir, atazanavir, darunavir, maraviroc and enfuvirtide. With the exception of maraviroc, GZR had no effect on the anti-HIV activity of these compounds. The concentration required for 50% activity (ECR50R) for maraviroc increased 1.2 times in the presence of 100 nM GZR (43 times the clinical free CRmaxR). Minimal effect is anticipated at clinically-relevant concentrations. None of these anti-HIV drugs affected the potency of GZR or EBR in HCV replicon assay.

Safety pharmacology

Specialised safety pharmacology studies covered the cardiovascular (GZR and EBR) and the respiratory systems (EBR). Functional observation battery analyses were included in repeat-dose toxicity studies in rats. Central nervous system (CNS) function was unaffected in rats with 1000 mg/kg PO GZR (exposure ratio based on CRmaxR [$ERRC_{max}R$] 33) or 1000 mg/kg PO EBR ($ERRC_{max}R$ 10). In vitro, there was no clinically-relevant inhibition of tail current (hERG KP+P) of the slowly activating, delayed rectifier potassium current (IRKsR) or the cardiac sodium channel current (IRNaR). No electrocardiogram (ECG) abnormalities were noted in dogs with 5 mg/kg PO GZR (estimated CRmaxR 7.1 µM; exposure ratio at CRmaxR ($ERRC_{max}R$) 31) or ≤ 50 mg/kg PO EBR (estimated CRmaxR 0.5 µM; $ERRC_{max}R$ 3). There was no evidence of respiratory effects in dogs at very high GZR doses in repeat-dose toxicity studies and respiratory function was unaffected in dogs with ≤ 50 mg/kg PO EBR in the specialised safety pharmacology study. Overall, effects on CNS, cardiovascular and respiratory function are not predicted from animal studies.

Pharmacokinetics

Absorption of GZR by the oral route was fairly rapid in mice, rats, rabbits, dogs and human subjects (TRmaxR 0.5–8 h), though oral bioavailability was low in rats, dogs and humans (10–40%). Exposure was generally greater than dose-proportional in all tested animal species and no consistent sex differences were observed. Following IV dosing to rats and dogs, plasma half-lives were fairly short (1.4 to 3 h). Longer apparent half-lives were observed following oral dosing (approximately8 h in rats and dogs and 31 h in human subjects). There was no evidence of accumulation with repeat dosing.

The rate of oral absorption of EBR was also fairly rapid (TRmaxR=1 to 5 h) in rats, dogs and humans. Oral bioavailability was low in rats (3 to 9%) and moderate in dogs and human subjects (32 to 35%). Following IV dosing to rats, dogs and monkeys, the plasma half-lives were short to moderate (4 to 16 h). Clearance rates were similar in dogs, monkeys and humans (5 to 10 mL/min/kg). Exposures in rats and dogs were less than dose proportional possibly due to solubility-limited absorption. There were no consistent sex differences in pharmacokinetic parameters in mice, rats and dogs and there was no clear evidence of accumulation in rats or dogs.

Plasma protein binding by GZR was high in humans and animal species (approximately98%) with both serum albumin and alpha1-acid glycoprotein involved in binding. The volume of distribution was similar to or marginally above that of total body water in rats and dogs. Following oral dosing to rats, the tissue distribution of GZR associated radioactivity was limited. GZR distributed readily to the liver with liver/gall bladder exposures 26 to 560 times those found in plasma. Uptake into hepatocytes is likely mediated by organic anion-transporting polypeptide B1 and B3 (OATP1B1/OATP1B3) like transporters. There was minimal penetration of the blood-brain barrier. There was no evidence for a specific retention of radioactivity in pigmented tissues.

Plasma protein binding by EBR was very high in humans and laboratory animal species (>99%). Plasma protein binding was shown to involve human serum albumin affinity and probably involves alpha1-acid glycoprotein binding. There was no evidence for partitioning into blood cells. The volume of distribution was larger than total body water in rats, dogs, monkeys and human subjects. Consistent with this, the tissue distribution of radioactivity in rats after PO administration of radiolabelled EBR was rapid and wide into most tissues. Organs with the highest level of radioactivity included those involved in absorption/elimination (including the liver) and the adrenal gland. There was limited penetration of the blood-brain barrier, possibly due to P glycoprotein transport.

Elimination of radioactivity from the uveal tract was slow, suggesting some retention in this pigmented tissue. No such affinity was observed for pigmented skin.

Metabolites of GZR were formed by hydroxylation, oxidative O-dealkylation, oxidative loss of the vinylcyclopropylamide, conjugation with glutathione subsequent to oxidation and products thought to result from bacterial hydrolytic metabolism in human faeces. Unchanged drug was the only notable circulating drug-related species in rats, dogs and humans. The only human-specific metabolites were observed in the faeces, with some thought to result from bacterial metabolism. These metabolites are not expected to be toxicologically significant. In vitro studies demonstrated a significant role for cytochrome P450 isozyme CYP3A4 and a lesser role for CYP2D6 in the formation of oxidative metabolites. GZR was shown to possess the potential to form chemically reactive metabolites capable of forming covalent bonds with proteins. The formation of reactive species increased in the presence of Nicotinamide adenine dinucleotide phosphate (NADPH) and was reduced when glutathione was present suggesting that cellular antioxidants/ nucleophiles can serve a protective role.

EBR metabolism was limited, with four metabolites identified in animal species (rats, rabbits and dogs) and human subjects across various matrices. Human metabolites were shown to be formed by CYP3A4. There were no human-specific metabolites. Unchanged drug was the only notable circulating drug-related species.

Excretion of GZR and EBR related material was predominantly via the bile/faeces in humans, rats, rabbits and dogs. Urinary excretion was minimal to minor in all species.

Overall, the pharmacokinetic profiles in the laboratory animal species were sufficiently similar to allow them to serve as appropriate models for the assessment of drug toxicity in humans.

Pharmacokinetic drug interactions

GZR is a substrate for CYP3A4, P-glycoprotein, OATP1B1 and OATP1B3. GZR exposures could therefore be affected by concomitant administration of drugs that inhibit or induce CYP3A4 (shown to be the primary metabolic enzyme), P-glycoprotein or inhibitors of OATP1B1 and OATP1B3. There was no clinically-relevant inhibition of uridine diphosphate glucuronosyl transferase A1 (UGT1A1), CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 enzymes, bile salt export pump (BSEP), hepatic multidrug resistance-associated proteins 2, 3 and 4 (MRP2, MRP3, MRP4), hepatic breast cancer resistance protein (BCRP) or P glycoprotein transporters, or hepatocyte taurocholate uptake. Possible clinically-relevant inhibition of OATP1B1, OATP1B3, intestinal MRP2 and intestinal BCRP was indicated in in vitro studies. There was no significant induction of CYP3A4, 1A2 or 2B6 in human hepatocytes. GZR was not a time-dependent inhibitor of CYP3A or 2C8.

In vitro, the HIV inhibitors, atazanavir, darunavir, lopinavir, and ritonavir, inhibited OATP1B-mediated GZR uptake into cells. Based on ICR50R values, this inhibition is considered clinically relevant.

EBR is transported by P-glycoprotein and metabolised by CYP3A4. Co-administration with inducers of these may affect EBR exposures. As EBR is not extensively metabolised, inhibitors of CYP3A are unlikely to significantly affect EBR exposures, though inhibitors of P-glycoprotein may alter EBR exposures. There was no clinically relevant inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 or UGT1A1 activity or BSEP, systemic P glycoprotein, hepatic MRP2, MRP3 or MRP4 transporter activity. EBR was not a time dependent inhibitor of CYP3A4, did not induce CYP1A2, 2B6 or 3A4 expression/activity and was not a substrate for OATP1B1 or OATP1B3. Some inhibition of OATP1B1 may occur with the proposed clinical dose but the effect is unlikely to be significant. Inhibition of intestinal P glycoprotein, BCRP and intestinal MRP2 may occur in human subjects.

In dogs, exposures to GZR were higher when this drug was provided in combination with EBR. EBR exposures were unaffected by co-administration with GZR.

Toxicology

Acute toxicity

No single-dose toxicity studies were submitted. This is not considered a deficiency. Toxicity was assessed in repeat-dose toxicity studies.

Repeat-dose toxicity

Repeat-dose toxicity studies with GZR and EBR were conducted in three species: mouse, rat and dog. All studies were conducted using the clinical (oral) route. The durations of the pivotal studies, the species used and the group sizes were consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. Doses used resulted in exposures that were significant multiples of those at the anticipated clinical dose.

Relative exposure to GZR

Exposure ratios have been calculated based on animal: human plasma CRmaxR and $AUCR_{0-24\,h}$R GZR values. Levels of exposure achieved in animal studies were high relative to the anticipated clinical exposure values and No observable adverse effect level (NOAEL) values (highlighted) were at high relative exposure values.

Table 3: Relative GZR exposure in repeat-dose toxicity studies

Species	Study duration	Dose mg/kg/day	C_{max} µM	$AUC_{0-24\,h}$ µM·h	Exposure ratio#	
					C_{max}	AUC
Mouse rasH2 wild-type	4 weeks	20	2.07	5.0	9	3
		100	40.8	164	179	83
		200	72.3	334	317	169
		500	262	2805	1149	1422
Mouse CD1(ICR)	3 months	20	1.52	7.97	7	4
		100	45.1	452	198	229
		200	59.2	820	259	416
		500	129	1470	566	745
Rat Wistar	4 weeks	50	11.6	32	51	16
		200	27.7	117	121	59
		200 (BD)	20.3	212	89	107

Species	Study duration	Dose mg/kg/day	C_{max} µM	AUC_{0-24h} µM·h	Exposure ratio#	
	6 months	50	25.0	104	109	52
		200	46.5	370	204	188
		200 (BD)	36	445	158	226
Dog	4 weeks	5	8.80	67	39	34
		20	42.3	497	185	252
		600	173	2930	759	1486
	9 months	5	10.9	69	48	35
		15	34.4	367	151	186
		300	163	2620	715	1329
Human HCV positive patients	12 weeks	[100 mg]*	0.23	1.97	–	

= animal: human; *Administered in combination with 50 mg Elbasvir

Relative exposure to EBR

Exposure ratios have been calculated based on animal: human plasma CRmaxR and $AUCR_{0-24\,h}$R EBR values. Reasonable levels of exposure were achieved in the toxicity studies relative to the anticipated clinical exposure values, noting that the maximum doses were the limit dose. At the NOAEL values (highlighted) the safety margin is considered to be reasonable.

Table 4: Relative EBR exposure in repeat-dose toxicity studies

Species	Study duration	Dose mg/kg/day	C_{max} µM	AUC_{0-24h} µM·h	Exposure ratio#	
					C_{max}	AUC
Mouse rasH2 wild-type	4 weeks	10	0.52	2.90	3	1.2
		50	3.41	17.4	23	7
		300	7.06	72.2	47	30
		1000	10.3	151	68	63
Rat (Wistar)	3 months	50	0.50	4.36	3	1.8
		300	0.94	10.1	6	4

Species	Study duration	Dose mg/kg/ day	C_{max} µM	AUC_{0-24h} µM·h	Exposure ratio#	
		1000	1.24	17.3	8	7
	6 months	30	0.45	3.64	3	1.5
		300	1.16	15.1	8	6
		1000	1.55	22.0	10	9
Dog	3 months	2	0.03	0.13	0.2	0.1
		25	0.53	5.28	4	2.2
		1000	1.16	19.3	8	8
	9 months	5	0.08	0.89	0.5	0.4
		25	0.47	4.12	3	1.7
		1000	1.31	16.6	9	7
Human HCV positive patients	12 weeks	[50 mg]*	0.15	2.38	–	

= animal:human; *Administered in combination with 100 mg Grazoprevir;

Major toxicities of GZR

GZR showed generally low toxicity in all species. The effects that were seen did not show a clear relationship with dose and inconsistently varied with sex. In the 3 month repeat-dose study in mice, increased liver weights were observed in male and female mice with the effect most pronounced at the highest dose. In the pivotal 9 month repeat-dose study in dogs inconsistent changes in liver weights occurred at the low and mid doses but there were marked increases in both males and females at the high dose (ERRAUCR 1329). In neither species was this increase in weight accompanied by any consistent histopathological change though enlarged hepatocytes were apparent in mice at doses ≥200 mg/kg. Changes in serum liver enzymes consistent with liver pathology were sporadic but elevations of bilirubin were seen consistently in both species. In dogs microlithiasis was observed in both the gall bladder and bile duct but no pathological changes to the underlying tissue were observed. Liver weights were only slightly increased in rats at all doses in the 26 week repeat-dose study but elevations in bilirubin were apparent in both sexes at the high dose (ERRaucR 226).

Haematological changes were seen in mice and dogs but were inconsistent: for example, in mice at 500 mg/kg for 4 weeks, total white blood cells decreased in females but increased in males but at the same dose after 12 weeks white blood cells decreased in males and increased in females. This and other haematological changes are unlikely to be of clinical significance.

Other changes noted in some studies were focal haemorrhage in the glandular mucosa of the stomach in male rats (200 mg/kg b.i.d.), likely due to high local exposures. Reduced

testes weights and degeneration of the seminiferous tubules were observed in dogs (ERRAUCR 35) but not in other species. No effects on male reproductive capacity were seen in the reproductive toxicity studies. Degeneration of the epithelium of kidney tubules was seen in both mice strains at 500 mg/kg (ERRAUCR 745–1422). None of these toxicity findings are expected to have clinical relevance at the proposed dose.

Major toxicities of EBR

EBR showed no significant toxicity in either mice or rats at any dose tested. Body weight was slightly reduced in rats at the highest doses tested but this was not accompanied by any other consistent observations. In the 9 month study in dogs there was evidence of phospholipidosis in lymphoid tissue associated with the gastrointestinal tract characterized by the presence of large, foamy cells, morphologically consistent with macrophages in the follicular areas of the lymphoid tissues (ERRAUCR 7). The effect was reversed in 3 months without treatment.

The prevailing idea is that drug-induced phospholipidosis is an adaptive response and does not indicate a toxic condition. Definitive evidence for this theory is, however, still lacking except for isolated studies (e.g., Cartwright et al. 2009). Various mechanisms may be involved in the production of phospholipidosis. These include impairment of lysosomal enzyme activity, increased phospholipid synthesis and impaired membrane recycling and lysosomal enzyme sorting dynamics. These mechanisms are not mutually exclusive.

Combination toxicity studies

One 4-week toxicity study in dogs examined the effect of GZR and EBR in combination. No unexpected toxicities were observed. The only notable effect was the appearance of signs of phospholipidosis in female animals receiving EBR (25 mg/kg/day) alone and in combination with GZR. There were no new or exacerbated toxicity findings with the combination. The NOAEL was 5/25 mg/kg/day PO GZR/EBR, resulting in exposures (AUC) 31 and 3.3 times the clinical exposure for GZR and EBR, respectively.

No toxicity study was conducted with the registered drugs sofosbuvir or ribavirin combined with GZR/EBR. The ICHM3(Questions & answers (R2)) guidelineP3F P (TGA-adopted) states ‘ Combination toxicity studies are also not generally warranted for antiviral agents for treatment of Hepatitis C.’

Genotoxicity

GZR and EBR were both evaluated for their potential to induce reverse mutations in S. typhimurium and E. coli, their mutagenic potential in vitro in CHO cells, and their mutagenic potential in vivo in a rat bone marrow micronucleus study (Option 1 in ICH S2(R1)[1]). Both GZR and EBR were negative in all the tests and are unlikely to pose a mutagenic or clastogenic risk to humans.

Carcinogenicity

As neither GZR nor EBR showed any evidence of genotoxic potential and the intended human use is less than 6 months, no carcinogenicity studies were conducted with either drug, in accordance with ICH S1AP4F P[2].

[1] Guidance On Genotoxicity Testing And Data Interpretation For Pharmaceuticals Intended For Human Use
[2] Guideline On The Need For Carcinogenicity Studies Of Pharmaceuticals S1A.

Reproductive toxicity

The reproductive toxicity of GZR and EBR was assessed separately in GLP compliant studies conducted in rats and rabbits. The studies investigated potential effects on male and female fertility in rats, embryofetal toxicity (rats and rabbits) and pre/postnatal development (rats). Adequate animal numbers were used in the pivotal studies and treatment periods were appropriate. Toxicokinetic data were obtained either from animals in the studies or from similarly treated animals in accompanying studies. Exposures to GZR were high, while exposures to EBR were moderate to high (see tables below). The lower relative exposure achieved with EBR is not considered a deficiency as the limit dose was selected as the highest tested dose.

Table 5: Relative exposure to GZR

Species	Study	Dose mg/kg/day	AUC $_{0-24\,h}$ µM.h	Exposure ratio#
Rat Crl:WI(Han)	Fertility[a]	50 PO	32	16
		200 PO	117	59
		200 (BD) PO	212	107
	Embryofetal development	50 PO	160	81
		200 PO	133	67
		200 (BD) PO	217	110
Rabbit Dutch belted	Embryofetal development	25 IV	6.14	3
		50 IV	24.4	12
		100 IV	76.1	37
		50 PO	0.507	0.3
		200 PO	1.08	0.5
		200 (BD) PO	3.61	1.8
Human HCV positive patients	12 weeks	[100 mg]*	1.97	–

= animal: human plasma $AUC_{0-24\,h}$; *Administered in combination with 50 mg elbasvir; [a]estimated from data in Study TT #09-1120 (4 week repeat-dose toxicity study)

Table 6: Relative exposure to EBR

Species	Study	Dose mg/kg/day PO	AUC $_{0-24\,h}$ µM.h	Exposure ratio#
Rat (Crl:WI(Han))	Fertility	50	4.36	1.8
		300	10.1	4

Species	Study	Dose mg/kg/day PO	AUC $_{0-24h}$ µM.h	Exposure ratio#
		1000	17.3	7
	Embryofetal development	50	4.85	2
		300	11.4	5
		1000	21.8	9
Rabbit (Dutch belted)	Embryofetal development	30	1.27	0.5
		100	4.16	2
		1000	39.4	17
Human (HCV positive patients)	12 weeks	[50 mg]*	2.38	–

= animal: human plasma AUC_{0-24h} ; *Administered in combination with 100 mg grazoprevir; [a]estimated from data in Study TT #11-6024 (4 week repeat-dose toxicity study)

Functional fertility was unaffected in male and female rats given either agent. The NOEL was 200 mg/kg bid PO GZR (ERRAUCR 107) and 1000 mg/kg/day (ERRAUCR 7). A small decrease in sperm counts (14%) was observed at the highest tested EBR dose but this had no effect on reproductive performance.

Only limited placental transfer of GZR and EBR was demonstrated in rats and rabbits. No adverse embryofetal effects were observed in either rats or rabbits at the highest tested doses of GZR (ERRAUCR 110 and 37 in rats and rabbits, respectively) and EBR (ERRAUCR 9 and 17 in rats and rabbits, respectively). Excretion of GZR and EBR into milk was demonstrated in lactating rats. There was no effect on postnatal development in rats with either GZR (≤ 200 mg/kg bid PO; estimated ERRAUCR 110) or EBR (≤ 1000 mg/kg/day PO; estimated ERRAUCR 9).

Pregnancy classification

The sponsor has proposed Pregnancy Category B1[3] which is appropriate, given no adverse effects were observed in the embryofetal development and pre/postnatal studies. Ribavirin has an Australian pregnancy category of X[4], based on teratogenicity in multiple animal species, and this category will be applicable to the combination of Zepatier and ribavirin. Sofosbuvir has an Australian pregnancy category of B1.

Local tolerance/skin sensitisation

GZR showed no evidence of skin irritation following topical application to the skin of rabbit and EBR was not an irritant in the in vitro EpiDerm assay. Neither GZR or EBR were eye irritants in the in vitro bovine corneal opacity assay. There was no evidence of skin sensitisation by GZR or EBR in the local lymph node assay in mice.

[3] 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.
[4] Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Phototoxicity

There was no evidence of phototoxicity (either skin or ocular) in rats given EBR or GZR, despite there being some retention of EBR-related material in the uveal tract.

Mechanistic studies

Several mechanistic studies were conducted with GZR in mice. The aim of these studies was to develop an animal model for late elevation of transaminases noted in a subset of patients who were co-administered high doses of GZR with pegylated-interferon and ribavirin in clinical protocol PN003. The findings in these mechanistic studies were essentially similar to those of the repeat-dose toxicity studies in mice. Some small differences in sensitivity to effects on the liver were noted between different mouse strains. Changes in bile acids, transcriptional endpoints for bile acid transport and metabolism genes, serum amyloid A (SAA) and cytokines were measured in these studies. Some changes were noted but the toxicological significance of the changes seen is uncertain.

Impurities

The proposed specifications for a number of impurities in the drug substance for GZR and EBR have been adequately qualified.

Paediatric use

The GZR/EBR FDC is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary

- The overall quality of the nonclinical dossier was good, with all pivotal studies conducted according to GLP.
- In vitro, GZR was an inhibitor of the HCV NS3/4A protease with inhibitory activity against enzymes from all genotypes but with approximately100 fold lower potency at the enzyme from the gt3a subtype (compared to the gt1 variants). Mutations at 56, 156, 158 and 168 in NS3 conferred resistance to GZR. GZR retained activity against some genotypes that are resistant to other NS3/4A inhibitors. In chimpanzees, GZR (at approximately the clinical dose) reduced the viral load in animals infected with either the gt1a or the gt1b subtypes or the gt1a R155K mutant. EBR is an inhibitor of HCV NS5A with nanomolar inhibitory activity on subtypes 1a, 1b, 2a, 3a, 4a, 5a, 6 and 6d in replicon assays. Lower potency was observed against subtypes 2b, 3i and 3g. Mutations at 28, 30, 31, and 93 in NS5A conferred resistance to EBR.
- In replicon assays, the combination of GZR and EBR was at least additive and fewer resistant colonies were selected with the combination than for either agent alone. The combination of EBR with ribavirin and the combination of either GZR or EBR with sofosbuvir were additive to synergistic.
- No clinically relevant inhibitory activity was observed with either GZR or EBR at >100 receptors, ion channels and transporters. Off-target effects with the GZR/EBR combination are not predicted during clinical use. In in vitro assays, neither GZR nor EBR had anti-viral activity against HIV. No antiviral activity was observed with GZR against HBV. Neither EBR nor GZR had any relevant effect on the anti-viral activity of a number of HIV drugs. None of these anti-HIV drugs affected the potency of GZR or EBR in HCV replicon assay.

- Based on findings in the combined set of safety studies, neither EBR nor GZR are expected to have any adverse effects on CNS, respiratory, gastrointestinal or cardiovascular function during clinical use.
- Oral bioavailability of GZR and EBR was low to moderate in animals and human subjects. Both actives are P-glycoprotein substrates. Plasma protein binding by GZR and EBR was high to very high. Tissue distribution of GZR related material in rats was limited, though very high levels were observed in the liver, likely due to uptake by OATP1B-like transporters. Tissue distribution of EBR related material in rats was rapid and wide. Elimination of radioactivity from the uveal tract was slow, suggesting some retention in this pigmented tissue but no phototoxic reactions were observed in a specific study to assess this. In vitro studies indicated a major role for CYP3A4 in the metabolism of GZR and EBR, though overall metabolism of the latter compound was limited. Excretion of GZR and EBR and/or their metabolites was predominantly via the biliary/faecal route in animals and humans.
- GZR exposures may be affected by concomitant administration of drugs that inhibit or induce CYP3A4 (shown to be the primary metabolic enzyme), P-glycoprotein or inhibitors of OATP1B1 and OATP1B3. In vitro, the HIV inhibitors, atazanavir, darunavir, lopinavir, and ritonavir, inhibited OATP1B-mediated GZR uptake into cells at clinically relevant concentrations. GZR has the potential to alter the exposures of compounds that are OATP1B1 or OATP1B3 substrates or orally-administered compounds that are substrates of MRP2 or BCRP.
- Co-administration of EBR with P-glycoprotein or CYP3A4 inducers or P-glycoprotein inhibitors may alter EBR exposures. EBR has the potential to alter the exposures of orally administered compounds that are substrates of P glycoprotein, BCRP and MRP2.
- Repeat-dose toxicity studies were performed in mice (3 months), rats (6 months) and dogs (9 months) using the oral route. Adequate exposures were achieved. No clinically relevant findings were observed. A 4 week study in dogs with the combination showed no new or unexpected toxicity. The lack of combination toxicity studies with ZepatierP®P and ribavirin or sofosbuvir is acceptable.
- Both GZR and EBR were negative in all genotoxicity tests conducted and are unlikely to pose a mutagenic or clastogenic risk to humans.
- No carcinogenicity studies were conducted with GZR or EBR, which is acceptable.
- A standard set of GLP-compliant reproductive toxicity studies was submitted and examined fertility (in rats), embryofetal toxicity (rats and rabbits) and pre/postnatal development (rats). There were no drug related findings. Only limited placental transfer of GZR and EBR was demonstrated in rats and rabbits. Excretion of GZR and EBR into milk was demonstrated in lactating rats.
- Neither compound produced phototoxic reactions in pigmented rats.
- The proposed specifications for a number of impurities and residual solvents in the drug substance for GZR and EBR have been adequately qualified.

Nonclinical conclusions and recommendation

- Primary pharmacology studies support the use of the combination of GZR and EBR against a wide range of HCV genotypes. Combination studies support the use of these agents with ribavirin or sofosbuvir.
- No clinically relevant hazards were identified in safety/toxicity studies.
- A number of pharmacokinetic drug interactions are possible.

- There was no evidence of reproductive toxicity of either GZR or EBR and Pregnancy category B1 is appropriate. Category X is applicable when used in combination with ribavirin.
- There are no nonclinical objections to the registration of Zepatier for the proposed indication.
- Changes to the draft nonclinical sections of the Product Information were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

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

Introduction

Clinical rationale

Hepatitis C is the most prevalent blood-borne virus in Australia and it is estimated there are approximately230, 000 Australians living with Chronic Hepatitis C (CHC) infection. Despite recent TGA registration of several oral DAA regimens for treatment of HCV infection there remains significant unmet medical need and a lack of therapeutic options for several patient subgroups for example, interferon and ribavirin-free regimens for patients with severe renal disease on haemodialysis and patients with HCV genotype 4 or 6. Until 2011, the standard of care treatment for chronic hepatitis C (CHC) infection was peginterferon alfa (peg-IFN) plus ribavirin (RBV) (together, abbreviated as PR) for 24 to 48 weeks and this therapy resulted in SVR in 40 to 50% and 60 to 70% of treated GT1/GT4 and GT2/GT3 patients, respectively. However, net benefit of this therapy was limited by major AEs and poor tolerability.

A better understanding of the biology of HCV led to the development of DAAs, medicines that directly target HCV proteins critical to viral replication. These DAAs inhibit one of three major viral proteins: the NS3/4a protease, the NS5A protein, and NS5B RNA polymerase. Due to genotype-specific differences among these proteins, the potency of DAAs may vary by genotype. The first generation of DAAs, including the NS3/4A protease inhibitors (PIs) boceprevir, telaprevir and simeprevir, were evaluated as add-ons to PR. However, these agents were GT1-specific and also had low potency against commonly-found viral variants. Nevertheless, these PI/PR regimens increased the proportion of GT1 patients that achieved SVR with 80% achieving SVR12 among treatment-naïve (TN), non-cirrhotic patients.

Since 2013, other DAAs have become available and there is now clear evidence that interferon-free regimens, consisting of combinations of DAAs targeting different targets in the HCV life cycle, can be highly effective in clearing chronic HCV infection Although these interferon-free regimens were better tolerated, adverse events (AE) related to RBV (for example, anaemia, fatigue, gastrointestinal symptoms) remained. Therapy required administration of multiple tablets daily, as well as stringent pregnancy precautions. An understanding of HCV biology and the results of the clinical studies with single DAAs suggest that a highly efficacious interferon-free regimen for treatment of HCV infection requires combined therapy with at least two highly potent direct acting antivirals targeting the HCV life-cycle. For example, an 8 or 12 week regimen combining sofosbuvir and the NS5A protein inhibitor (NS5AI) ledipasvir has been demonstrated to result in SVR12 in >90% of TN non-cirrhotic subjects. Among cirrhotics who failed prior PR-based therapies, a 24 week duration, or addition of ribavirin, is needed to achieve SVR12 in

>90% of treated patients. Given the diversity of the HCV population as well as the virus types that cause the disease, there is a need for several effective and well-tolerated regimens for treatment of HCV infection.

GZR is a once daily with a high potency against GT1, GT2, GT4GT6, with somewhat less potency against GT3; in vitro, it retains high potency against resistance associated variants (RAVs) that are commonly detected among individuals who fail therapies with first generation PIs such as boceprevir, telaprevir, and simeprevir. However, efficacy was lower in cirrhotics and in patients with GT1a infection.

EBR is a once daily NS5AI with high potency against GT1, GT2a, GT3, GT4, GT5 and GT6; in vitro, it retains potency in the presence of RAVs associated with failure of other NS5A inhibitors such as daclatasvir and ledipasvir. Pre-clinical data suggested that co-administration of GZR with EBR would create a highly potent regimen for HCV GT1 patients with potential utility in GT3 patients. A fixed-dose combination (FDC) of GZR/EBR has been developed, to improve compliance and convenience with a simple daily dosing regimen, low pill burden of one tablet, low potential for medication error and no potential for off-label use of individual components.

HCV genotype (GT) 1 is the most prevalent genotype in Australia accounting for approximately 55% of infections. The remaining genotype distributions are 5.2% GT2, 36.8% GT3, 1.9% GT4 and 1.6% GT6. In Australia, there is currently no approved therapeutic regimen for treatment of HCV GT4 or GT6 infection that does not require concomitant administration of ribavirin or pegylated interferon. These drugs have poor tolerability and the treatment burden is well documented, resulting in adverse events (AEs), discontinuation of treatment and failure to achieve 'cure'. Zepatier would address this unmet medical need as it offers peginterferon and ribavirin-free dosing in these patients. This application presents clinical data in HCV GT4 and GT6 infected patients.

HCV has a significant adverse effect on the progression of renal disease and outcomes of renal transplants. HCV infection and Chronic Kidney Disease (CKD) results in a burden of mortality that is greater than the sum of morbidity and mortality caused by each condition alone. There is currently no registered treatment for patients with chronic HCV infection with severe renal impairment receiving haemodialysis. The DAAs currently approved for treatment of HCV infection in Australia are not suitable for use in patients with severe renal disease as these agents are either excreted primarily through the renal pathway (Sofosbuvir based regimens or require co-administration of pegylated interferon and/or ribavirin. In addition to their tolerability limitations, ribavirin exacerbates renal-failure related anaemia. The efficacy and safety of GZR/EBR FDC (Zepatier) has been evaluated in a study (P052) in 225 HCV patients with CKD Stage 4 or 5 of whom 76% were receiving haemodialysis.

The proposed FDC of GZR+EBR (100/50 mg) hopes to address the unmet medical needs for subgroups of HCV infected subjects such as those with CKD and other 'hard to cure' patients such as with compensated cirrhosis, HIV co-infection, GT4 and GT6.

Guidance

The sponsor has sought TGA's support in accelerating the review and registration process based on unmet clinical need in Australia for: treatment of Chronic Hepatitis C in patients with severe renal disease, including those receiving haemodialysis, and the limited therapeutic options for patients with HCV genotypes 4 and 6.

Breakthrough Therapy designation was granted on October 18, 2013 for GZR/EBR for the treatment of chronic HCV GT1 infection. This designation was rescinded on April 1, 2015, based on the recent approval of treatment regimens demonstrating SVR12 rates of 94 to 100% with overall favourable safety profiles in this population. Breakthrough Therapy designation was granted on April 1, 2015 for GZR/EBR for the treatment of chronic HCV

GT-1 infection in patients with advanced CKD disease on haemodialysis. Breakthrough Therapy designation was also granted on April 1, 2015 for GZR/EBR for the treatment of patients with chronic HCV GT-4 infection.

Regulatory advice on the Clinical Development Program was obtained from the CHMP via a Scientific Advice Procedure on April 29, 2014. The proposed Phase III trials were judged acceptable in terms of patient population, dose selection/treatment duration, primary efficacy endpoint and time point for assessment, statistical analysis approach and criteria for success. Plans for development of a fixed-dose combination tablet were acceptable.

The TGA had communicated that a Risk Management Plan is a requirement for this submission, and requested the submission of the current EU-RMP with an Australian Specific Annex. This has been provided in this application.

Contents of the clinical dossier

The submission contained the following clinical information:

- Fifty-nine clinical pharmacology studies, including 59 that provided pharmacokinetic data and 4 that provided pharmacodynamic data.
- Two population pharmacokinetic analyses.
- Nine core efficacy/safety studies as listed in Attachment 2.
- Six supportive studies including three dose-finding Phase II studies (P003, P038, P035) and three other supportive studies (P058, P039 and P047).

Comment: P035 was the main Phase II study for determining the dose of EBR, the treatment duration and the patient population to be evaluated in the core Phase II/III studies and this study has been discussed in Attachment 2.

- Two ongoing studies: Study P062 in HCV infected subjects on opiate substitution treatment and Study P065 in HCV-infected subjects with inherited blood disease (IBD). Another ongoing, long-term follow-up study (P017) to evaluate the durability of virologic response and/or viral resistance patterns among subjects with chronic Hepatitis C who have been previously treated with GZR in a prior clinical trials (P035 and P047).
- Pooled analyses, meta-analyses, Integrated Summary of Efficacy, Integrated Summary of Safety.

Paediatric data

The submission did not include paediatric data.

An agreed-upon Paediatric Study Plan (PSP) was submitted on January 21, 2015 to the FDA, and included a deferral of paediatric assessments until after approval of the NDA in adults, and a waiver for paediatric assessments in patients less than 3 years of age.

On December 12, 2014, the Paediatric Committee of the European Medicines Agency granted a positive opinion for the Paediatric Investigation Plan for GZR/EBR, including a waiver for subjects less than 3 years of age and deferral of proposed studies.

Good clinical practice

All the clinical studies were conducted in conformance with Good Clinical Practice (GCP) standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating

in biomedical research. The only exception was the ongoing Phase II study P059 in which some minor GCP non-compliance issues were observed (discussed in Attachment 2).

Pharmacokinetics

Studies providing pharmacokinetic data

Table 7 (below) shows the studies relating to each pharmacokinetic topic.

Table 7: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK	5172-P069	Effect of a high fat meal on the GZR and EBR PKs following a single dose of the FDC tablet
		5172-P055	GZR and EBR PKs following a single dose of FDC2 cf. free combination
		5172-P040	GZR F following ^{14}C-micro-dosing
		8742-P020	F of a single dose of EBR relative to [^{13}C10, ^{15}N2] EBR administered as an IV micro-dose.
		5172-P045	PKs of GZR PMF1 cf. PKs of capsule formulation
		5172-P002v1	PKs of 3 candidate PMFs of GZR relative to the FFP tablet
		5172-P008	PKs of GZR from two different PMF versus the Phase I FFP
		5172-P027	PK profile of 100 mg GZR with and without famotidine
		5172-P001v01	PKs following single-rising oral doses of GZR and food effect. In addition, DDIs b/w single dose ketonazole and single dose of 200 mg GZR
		8742-P005	PK profiles of 100 mg EBR with and without famotidine
		8742-P001v01	PKs of EBR after single and multi oral dose administrations
		8742-P0018	Effect of a high-fat meal on the PKs of EBR PMF2
		8742-P006v01	PKs following 50 mg EBR for 28 consecutive days
		5172-P050	PKs of multiple daily doses of GZR and EBR co-administered to subjects with ESRD on HD days to those obtained on non HD days and in healthy subjects

PK topic	Subtopic	Study ID	*
		5172-P007	Elimination and mass balance of GZR following a single oral dose of [^{14}C]GZR
		8742-P014	Elimination and mass balance of EBR following a single oral dose of [^{14}C]EBR
		045496	popPK model of GZR PKs in healthy subjects and HCV infected patients
		044ZSQ	popPK model of EBR PKs in healthy subjects and HCV infected patients
Target population §	HCV patients	5172-P004v02	PKs and anti-viral activity of GZR administered for 7 consecutive days to HCV-infected male patients
		8742-P002v02	PKs and anti-viral activity of GZR administered for 5 consecutive days to HCV-infected male patients
Special populations	Hepatic impairment	5172-P013	PKs of GZR following 10 days dosing to patients with mild-, moderate- and severe-hepatic insufficiency without hepatitis C and healthy subjects
		8742-P009	PKs of EBR following a single dose to patients with mild-, moderate- and severe-hepatic insufficiency and healthy subjects
	Age	5172-P014	PKs of multi-dose GZR in healthy elderly male and female subjects
		8742-P004	PKs of a single oral dose of EBR in healthy elderly male, healthy elderly female and healthy young male subjects
	Race	5172-P009	PKs of GZR following single and multiple QD oral doses to healthy young Japanese subjects
		7009-P050	PKs of EBR following a single oral dose to healthy Japanese subjects
		5172-P042	PKs of GZR following multiple doses of GZR in healthy Chinese subjects
Interaction Studies	Active components	8742-P008	DDIs between single and multiple doses of GZR and EBR
	CYP3A substrates and strong CYP3A inhibitors	5172-P053	DDI b/w free-combination of GZR FFP and EBR FFP (200 mg/50 mg QD) and rilpivirine
		5172-P029	DDI b/w 200 mg GZR QD and either LPV/RTV (400/100 mg BID), ATV/RTV (300/100 mg BID) or DRV/RTV (600/100 mg BID)

PK topic	Subtopic	Study ID	*
		8742-P017	DDI b/w 50 mg EBR QD and either LPV/RTV (400/100 mg BID), ATV/RTV (300/100 mg BID) or DRV/RTV (600/100 mg BID)
	CYP3A4 substrates	5172-P073	DDIs b/w a single-dose of 400 mg cyclosporine, tacrolimus, MMF and prednisone, and multiple doses of the free-combination of GZR FFP and EBR PMF2 (200 mg/50 mg QD)
		5172-P076	DDIs b/w a single-dose of 10 mg atorvastatin and multiple doses of the free-combination of GZR FFP and EBR PMF2 (200 mg/50 mg QD)
		5172-P030	DDIs b/w multiple doses of 200 mg GZR QD and either methadone or buprenorphine/naloxone
		5172-P032	DDIs b/w multiple doses of 200 mg GZR QD and midazolam (2 mg) or atorvastatin (20 mg) or pitavastatin (1 mg)
		5172-P046	DDIs b/w multiple doses of 200 mg GZR QD and a single-dose of OC (EE 0.03 mg/LNG 0.15 mg)
		5172-P070	DDIs b/w multiple oral doses of 200 mg GZR QD and montelukast (10 mg)
		8742-P010	DDIs b/w multiple doses of 50 mg EBR QD and methadone
		8742-P021	DDIs b/w a single dose buprenorphine/naloxone (8 mg/2 mg) and single oral dose of 50 mg EBR.
		8742-P013	DDIs b/w multiple doses of 50 mg EBR QD and a single dose of OC (0.03 mg EE/0.15 mg LNG)
	Strong CYP3A4 inhibitors	5172-P006v01	DDIs b/w multiple doses of 100 mg RTV BID and a single-dose of 200 mg GZR
		8742-P003	DDIs b/w multiple doses of 400 mg ketoconazole and a single-dose of 50 mg EBR
	CYP3A4 - inducers	5172-P031	DDIs b/w GZR (200 mg QD) and rifampin (600 mg QD or SD) or efavirenz (600 mg QD)
		8742-P011	DDIs b/w a single IV or oral dose of rifampin (600 mg) and a single oral dose of EBR (50 mg)
		8742-P016	DDIs b/w multiple oral doses of EBR (50 mg QD) and multiple doses of efavirenz (600 mg QD)
	HMG CoA reductase inhibitors.	5172-P054	DDIs b/w a single 10 mg dose of rosuvastatin or a single dose of pravastatin and multiple doses of GZR (200 mg QD) alone or with multiple doses of GZR/EBR (200 mg/50 mg QD)

PK topic	Subtopic	Study ID	*
	CYP2C19 – substrate	5172-P072	DDIs b/w multiple oral doses of pantoprazole (40 mg QD) or famotidine (20 mg) and multiple oral doses of a 100 mg GZR/50 mg EBR FDC tablet
	UGT1A1 – substrates	5172-P057	DDIs b/w a single oral 50 mg dose of dolutegravir and multiple oral doses of GZR and EBR (200 mg/50 mg QD).
	BCRP- and P-gp-substrates	5172-P063	DDIs b/w multiple oral doses of GZR and EBR (200 mg/50 mg QD) and a single oral 400 mg dose sofosbuvir
		8742-P023	DDIs b/w multiple oral doses of EBR (50 mg QD) and a single dose of 0.25 mg digoxin
	HIV nucleoside reverse transcriptase inhibitor	5172-P026	DDIs b/w multiple oral doses of GZR (200 mg QD) and tenofovir (300 mg QD)
	Inhibitors of NS5A	5172-P023	DDIs b/w multiple oral doses of GZR (400 mg QD) and GS-5885 (90 mg QD).
		5172-P036	DDIs b/w multiple oral doses of GZR (200 mg QD) and 60 mg daclatasvir
		8408-P004	DDIs b/w multiple oral doses of GZR (200 mg QD) and MK8408 (60 mg QD)
	Inhibitor of NS3/4A	2748-P004	DDIs b/w multiple oral doses of EBR (50 mg QD) and MK-2748 (400 mg QD)
	Inhibitors of NS5B	3682-P007	DDIs following multiple oral doses of GZR/EBR (200 mg QD/50 mg QD) and MK-3682 (300 mg QD)
		3682-P008	DDIS b/w steady state levels of MK-3682 (300 mg QD) and steady state levels of GZR (200 mg QD) and MK-8408 (60 mg QD)
	Phosphate–binder drugs	5172-P056	DDIs b/w a single oral dose of 100 mg GZR and 50 mg EBR and either calcium acetate or sevelamer carbonate

cf. - compared with; b/w – between
* Indicates the primary aim of the study.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

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

Evaluator's conclusions on pharmacokinetics

Zepatier FDC tablets containing 100 mg GZR and 50 mg EBR are intended for oral dosing.

For full details of the evaluator's summary of pharmacokinetics see Attachment 2.

Limitations of the PK studies

- No dedicated PK studies examined bioavailability following multiple doses of the FDC tablet.
- No dedicated PK studies examined the dose proportionality of the FDC tablet.
- No studies specifically examined the volume of distribution following dosing with the FDC.
- The drug-drug interactions (DDIs) studies primarily examined GZR or EBR when given alone or as a free combination. Therefore, in most cases the DDIs with the FDC tablet are unknown.
- A number of DDI studies examined the interaction following only single doses of GZR and/or EBR rather than at steady-state levels.
- Many of the studies which examined the DDIs interaction between GZR and other drugs used a higher dose of GZR (200 mg) than the dose proposed for marketing (100 mg).
- The direct interaction between GZR and ERB was examined using doses that do not correspond (200 mg/20 mg QD) with the proposed dose for marketing (100 mg/50 mg QD).

Pharmacodynamics

Studies providing pharmacodynamic data

Table 8 shows the studies relating to each pharmacodynamic topic.

Comment: Two studies (5172-P004v02 and 8742-P002v02), which provided PK as well as primary and secondary PD data in the target population have been summarised above and IN attachment 2.

Table 8: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Secondary Pharmacology	Effect on QTc	5172-P049	To evaluate effects of a single supratherapeutic oral dose of GZR on QTc interval in healthy subjects
		8742-P015	To evaluate effects of a supra-therapeutic dose of EBR on the QTc interval in healthy subjects

* Indicates the primary aim of the study.

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

Evaluator's conclusions on pharmacodynamics

For full details of the evaluator's summary of pharmacodynamics see Attachment 2.

Limitations of the PD studies

- No dedicated PD studies examined the PD effects of the FDC tablet proposed for marketing.
- No dedicated PD studies examined PD interactions with the FDC tablet or GZR or EBR when administered alone.

Dosage selection for the pivotal studies

The initial Phase II studies provided information that determined the doses of GZR and EBR, the duration of treatment, regimen, i.e., with or without RBV and the patient populations for the pivotal or core studies which are discussed in Section Efficacy below and in Attachment 2.

For full details of the evaluator's summary of dosage selection for the pivotal studies see Attachment 2. The results formed the basis for the selection of the GZR100 mg and the EBR 50 mg doses and the 12 week treatment duration in the pivotal Phase III studies.

Results from the studies also determined the HCV genotypes which were evaluated further in the Phase II/III clinical trials. The Phase III program focused primarily on evaluation of a 12 week regimen of FDC of GZR/EBR, generally administered without RBV. Results of the Phase II studies described supported inclusion of GT1, GT4 and GT6 infected subjects in these Phase III studies as follows:

- **GT1** In Study 035, 127/136 (93.4%) GT1-infected subjects (including mono-infected and HIV co-infected, treatment-naïve or prior PR failures, cirrhotics and noncirrhotics) achieved SVR12. These results provided the rationale for including GT1 infected subjects in Phase III studies.
- **GT2** In Study 047, efficacy of GZR + EBR + RBV was high among subjects whose GT2 infection consists of virions with NS5A L31 variant; efficacy was insufficient among subjects whose GT2 infection consists of virions with NS5A M31 variant. As pre-screening of HCV GT2-infected subjects is impractical, a decision was made not to include evaluations of efficacy of GZR/EBR among GT2-infected subjects in the core Phase III studies.
- **GT3** In Study 035D, 9/20 (45.0%) non-cirrhotic, treatment naïve subjects achieved SVR12 following administration of GZR + EBR + RBV for 12 weeks. Thus, GT3 infected subjects were not included in Phase III studies; however, Protocol 074, a study of GZR/EBR with sofosbuvir (which is active against GT3 infection), was conducted.
- **GT4** In Study 047, 9/10 (90.0%) of treatment-naïve non-cirrhotic, GT4infected subjects (primarily 4a, 4d, and 4-other) achieved SVR12 following administration of GZR + EBR for 12 weeks; no virologic failures were observed. These results provided the rationale for including GT4infected subjects in Phase III studies.
- **GT5** In Study 047, 1/4 (25.0%) of non-cirrhotic, treatment-naïve GT5-infected subjects achieved SVR12 following administration of GZR + EBR for 12 weeks. Although 4/4 subjects who received GZR + EBR + RBV achieved SVR12, as Phase III studies were focused on GZR/EBR (no RBV), GT5-infected subjects were not included in the Phase III studies.
- **GT6** In Study 047, 3/4 (75.0%) of non-cirrhotic, treatment-naïve GT6 infected subjects achieved SVR12 following administration of GZR + EBR for 12 weeks. Hence, GT6-infected subjects were included in the Phase III studies.

Efficacy

Studies providing efficacy data

- Nine core efficacy/safety studies as listed in Attachment 2.
- Six supportive studies including three dose-finding Phase II studies (P003, P038, P035) and three other supportive studies (P058, P039 and P047).
- Two ongoing studies: Study P062 in HCV infected subjects on opiate substitution treatment and Study P065 in HCV-infected subjects with inherited blood disease (IBD). Another ongoing, long-term follow-up study (P017) to evaluate the durability of virologic response and/or viral resistance patterns among subjects with chronic Hepatitis C who have been previously treated with GZR in a prior clinical trials (P035 and P047).

Evaluator's conclusions on efficacy of Zepatier for treatment of chronic hepatitis C infection in adults

All the clinical studies in this submission were well conducted in compliance with the TGA-adopted EU guidelines on the Clinical Evaluation of DAA Intended for Treatment of Chronic HCV[5].

Results of initial Phase II trials supported selection of a broad population for later Phase II and Phase III studies: GT1, 4 and 6; TN and TE (subjects who failed a prior PR or DAA+ PR regimen); mono and HIV/HCV co-infected subjects; cirrhotics and non-cirrhotics; and subjects with CKD Stages 4-5. Phase II studies were conducted to select the dose of each medicine for Phase III (P003 and P038 for GZR, and P035 for EBR), to evaluate the effect of treatment duration on efficacy (P035), and to evaluate the need for ribavirin (RBV) in the regimen (P035 and P047). The effect of treatment duration and the need for RBV were further evaluated in subjects that had failed prior therapy with PR in Phase III (P068). Additional Phase II trials evaluated the efficacy and safety of GZR and EBR in a broader variety of patient populations, including those infected with HCV genotypes other than GT1 (GT3 in P035, and GT2, 4, 5 and 6 in P047), in subjects who had failed prior DAA therapy (P048) and in cirrhotic subjects with moderate hepatic insufficiency (Child-Pugh class B) (P059). In addition, P074 evaluated the triple combination of DAA (Sofosbuvir + GZR/EBR) in GT1 and GT3 HCV infected subjects with and without cirrhosis, with different durations of treatment.

Phase II/III and Phase III studies were designed to confirm the safety and efficacy of GZR with EBR in key populations, including both treatment-naïve (Studies P060, P061 and P052) and PR treatment-experienced (Study P068) subjects, HCV/HIV co-infected subjects (P061 and P068), and HCV-infected subjects with advanced chronic kidney disease (P052). Each of the Phase III studies included subjects with or without compensated cirrhosis. At the time the clinical program for Zepatier commenced, there were no approved interferon-free regimens for treatment of HCV, so an immediate versus deferred treatment (placebo-controlled) study design was adopted in the Phase II/III controlled studies (P060, P052) to overcome the tolerability and feasibility challenges of treating the control arm with peginterferon (administered via injection).

Overall, the comprehensive clinical Phase II and III program for GZR with EBR enrolled and treated 1715 HCV GT1-, GT4, and GT6 infected subjects, along with 82 HCV GT3-infected subjects. These studies enrolled a diverse population of subjects and efficacy was evaluated across the spectrum of HCV infected individuals including approximately:

[5] EMEA/CHMP/EWP/30039/2008, published in 2009

- 54% GT1a, 35% GT1b, 5% GT3- 5%, GT4 and 1% GT6 infected;
- 64% treatment-naïve and 36% treatment-experienced subjects (including 79 subjects that had failed prior therapy with a first generation HCV protease inhibitor + PR);
- 28% subjects with compensated cirrhosis;
- 122 subjects with CKD Stages 4/5, including those on haemodialysis;
- 296 HIV/HCV co-infected subjects;
- Diverse racial/ethnic backgrounds: 15% Black, 8% Asian and 9% were Hispanic.

Each of the Phase II and Phase III efficacy studies of GZR with EBR achieved their primary efficacy endpoint with high and consistent efficacy observed across the populations evaluated.

Efficacy of a 12 week regimen of GZR/EBR ±RBV among GT1, GT4 and GT6 infected treatment naïve subjects:

The 12 week (no RBV) regimen was highly efficacious among GT1a, GT4, and GT6 infected subjects. Overall, 711/752 subjects (94.5%, 95% CI: 92.7 to 96.1%) achieved SVR12 and only 25/752 (3.3% of subjects) experienced virologic failure. Addition of RBV to the regimen did not improve efficacy overall or in any sub-population. Efficacy was high among GT1a, GT1b, and GT4 infected subjects. Activity was also observed among GT6 infected subjects. The main efficacy results in this pool of TN HCV subjects were:

- 399/426 (93.7%; 95% CI: 90.9 to 95.8%) of GT1a infected subjects achieved SVR12; virologic failure occurred among 19/426 (4.5%) of subjects.
- 243/252 (96.4%; 95% CI: 93.3 to 98.4%) of GT1b-infected subjects achieved SVR12; virologic failure occurred among 2/252 (0.8%) of subjects.
- All 3 subjects infected with GT1 subtypes other than GT1a or GT1b achieved SVR12.
- 22/23 (95.7%: 95% CI: 78.1, 99.9%) of GT4a-infected, 28/29 (96.6%, 95% CI: 82.2, 99.9%) of GT4d and 4/4 (100%; 95% CI: 39.8, 100.0%) of GT4. Other-infected subjects achieved SVR12. Overall, 54/56 (96.4%) of treatment naïve GT4infected subjects achieved SVR12; virologic failure occurred in only 1/56 (1.8%) of GT4 infected subjects.
- 5/6 (83.3%; 95% CI: 35.9, 99.6%) of GT6a-infected, 7/9 (77.8%; 95% CI: 40.0, 97.2%) of GT6-Other-infected subjects achieved SVR12. Overall, 12/15 (80%) of GT6 infected subjects achieved SVR12; virologic failure occurred among 3/15 (20.0%) subjects.

Baseline demographics (age, gender, race/ethnicity), presence of HIV co-infection, and geographic region did not substantially impact the efficacy of the 12 week (no RBV) regimen. Efficacy was also comparable among cirrhotics and non-cirrhotics. In particular, SVR12 was achieved in 135/139 (97.8%; 95 CI: 93.8 to 99.4%) of GT1 GT4 and GT6 infected cirrhotics, a population in immediate need for clearance of HCV infection. Only 2/138 (1.4%) cirrhotic subjects experienced virologic failure. Efficacy among GT1a cirrhotics, a traditionally harder-to-cure population was also high: SVR12 was achieved in 73/76 (96.1%) of GT1a cirrhotics; only 2/76 (2.6%) experienced a virologic failure.

Two factors were identified that impacted efficacy of the 12 week (no RBV) among GT1a infected subjects but not among GT1b- or GT4infected subjects:

1. Baseline viral load (VL) with slightly lesser efficacy in GT1a subjects with baseline VL >800,000 IU/mL compared to < 800,000 IU/ml [SVR12: 92.1% (278/302) versus 97.6% (121/124)];

2. The presence of baseline NS5A RAVs that cause a >5-fold shift in the potency of EBR in vitro among GT1a infected subjects was associated with a substantial reduction in efficacy, from an SVR12 of 98.4% to 55.2% in subjects without and with baseline GT1a RAVs, respectively.

Overall, a small subpopulation of subjects with baseline NS5A RAVs with > 5-fold potency shift to EBR and baseline HCV RNA >800,000 IU/mL, representing 26/491 or 5.3% of the population,was the source of 56.5% (13/23) of all GT1a virologic failures. In the remaining GT1a population, 455/465 (97.8%) subjects achieved SVR12. Hence, a 12 week regimen of GZR/EBR (no RBV) may be appropriate for majority of TN GT1a infected subjects.

Among TN, non-cirrhotic GT1b-infected subjects, a 12 week regimen of GZR and EBR (no RBV), SVR12 was achieved in 13/13 (100%) subjects (95% CI 75.3, 100%). Given this high degree of efficacy a shorter duration of therapy was also evaluated. With an 8 week regimen of GZR and EBR, 29/31 (93.5%) subjects (95% CI 78.6, 99.2) achieved SVR12. Virologic failure rates for TN, non-cirrhotic GT1b subjects treated for 8 weeks was comparable to that achieved with 12 weeks of treatment. There was no apparent association of baseline factors that predicted failure. Of note, 3 of the 4 subjects who relapsed in the 8 week treatment arms had no detectable NS3 or NS5A RAVs at the time of failure, suggesting that subjects that fail a shorter regimen may still have multiple options for retreatment. As these results are based on data in very few subjects, it still seems prudent to use the same 12 week treatment regimen in GT1b infected patients.

The observed efficacy of GZR/EBR (no RBV) was lower among GT6 infected subjects compared with GT1- or GT4infected subjects. However, the GZR/EBR regimen was still active in this population. As no all-oral regimen is currently indicated in this population, the availability of a regimen with higher efficacy and better tolerability compared to PR against GT6 infection provides an important option for this population. It is important to note that a relatively small population of GT6 infected subjects enrolled in the program was likely due to the low prevalence of GT6 infection in the North American and European HCV population.

Efficacy of GZR/EBR (±RBV) among GT1, GT4, GT6 infected subjects who failed prior PR-containing regimens

High efficacy was also observed in treatment experienced (TE) subjects, including those that had failed prior treatment with PR and also those who had failed a first generation HCV protease inhibitor + PR (PI+PR) regimen. In TE subjects, the effects of adding RBV to the regimen and extending treatment duration were also evaluated. Overall, efficacy was highest in the 16/18 week (+ RBV) arm. However, high efficacy was observed in the following subgroups of TE subjects receiving the 12 week (no RBV) regimen:

1. a 12 week regimen of GZR/EBR 100 mg/50 mg (no RBV) resulted in SVR12 among 96.5% (55/57) of GT1b/other-infected subjects in the TE-PEP, regardless of the prior response category. Virologic failures occurred among 3.5% of subject,
2. a 12 week regimen of GZR/EBR 100 mg/50 mg (no RBV) resulted in SVR12 among 46/47 (97.9%) of prior-relapser subjects, regardless of genotype. The only failure was a subject who discontinued for administrative reasons. Hence, no prior-relapsers experienced virologic failure with this regimen.

Of note, both of these populations included cirrhotics and non-cirrhotics, subjects with high viral load, subjects with CKD Stages 4/5, subjects with IL-28 TT genotype and HIV co-infected subjects. Thus, this population included subjects with demographic and disease features previously associated with low responsiveness to therapy. Furthermore, presence of baseline NS5A RAVs conferring >5-fold shift in the potency of EBR did not impact the efficacy of 12 week regimen in this population.

GT1a, GT4 or GT6 infected subjects who experienced on-treatment failure during their prior treatment regimen (PR null responders, PR partial responders, PR+DAA non-responders, virologic breakthrough and virologic rebound) were less likely to achieve SVR12 following administration of a 12 week regimen of GZR/EBR (no RBV); however, in these subjects, no virologic failures occurred in the 16/18 week (+ RBV) arm, including subjects with high baseline viral load and/or cirrhosis. These results support a dosing regimen of 16 weeks of GZR/EBR (+ RBV) in GT1a, GT4 or GT6 infected subjects who experienced on-treatment failure during their prior treatment regimen.

Treatment with GZR and EBR had a positive impact on Health-related quality of life (HRQOL), fatigue levels, and impairment while working and performing other daily activities, when assessing mean change from baseline in Patient reported outcomes (PRO) scores within the GZR and EBR (without RBV) groups. Differences in mean change from baseline in PRO scores between GZR and EBR and placebo groups were not apparent (P052 and P060), except with improvements in mental components of general health and overall health among treatment-naïve subjects (P060). As expected, the addition of RBV to GZR and EBR had a negative impact on PROs (P035 and P068). Treatment-experienced subjects treated with GZR/EBR (P068) had better physical and mental components of general health, less fatigue, and less impairment while working and performing other daily activities than subjects treated with GZR/EBR with RBV. However, interpretation of the PROs results in the open-label studies (P035, P068) was limited due to inherent bias of the open-label nature of these studies.

P048/C-Salvage demonstrated the high efficacy of GZR and EBR in subjects who had failed a first generation HCV protease inhibitor + PR (PI+PR) regimen. High rates of SVR12 were achieved regardless of the presence of signature RAVs at baseline overall or among the subjects who had previous virologic failure. Variants in the NS3/4A gene at amino acid loci prone to resistance selection by HCV protease inhibitors were common (44%), but efficacy remained high. This observation is explained by the substantial differences between GZR and earlier PIs with respect to in vitro potency; in particular GZR maintains potency against many of the signature RAVs associated with failure to first generation PIs. Baseline NS3/4A variants associated with a > 5-fold shift in potency to GZR were present in only 4/78 (5.1%) subjects, and 3 of these 4 subjects achieved SVR12. Among GT1a infected subjects, presence of Q80K/R variants did not impact efficacy, again distinguishing GZR from earlier PIs. These results demonstrate that subjects who have failed a prior PI+ Peginterferon alfa + ribavirin (PR) regimen respond similar to those who have failed PR alone, supporting similar dosing recommendations for these subjects.

Efficacy of GZR/EBR (no RBV) among patients with CKD Stage 4/5

Study P052/C-SURFER demonstrated high efficacy of a 12 week regimen of GZR + EBR in CKD 4-5 HCV-infected patients, a population for which there is an unmet medical need for safe and effective anti- HCV therapy. High response rates were observed across several subgroups, including subjects on haemodialysis and not on haemodialysis, GT1a and GT1b-infected subjects, treatment-naïve subjects and those who prior interferon treatment failures and, notably, those with characteristics historically associated with poor response to HCV therapy. In particular, SVR12 was achieved in 100% of GT1a infected subjects, 100% of African American subjects, 98.9% of subjects with the IL28B non-CC genotype, 97.6% of subjects with diabetes and all 6 subjects with cirrhosis. Efficacy was similar in TN and TE subjects.

The sponsors claim that due to the consistency of efficacy of GZR and EBR in GT1, GT4 and GT6 infected subjects observed in various subgroups throughout the clinical development program, it is anticipated that efficacy in GT4 and GT6 infected subjects with advanced CKD would be similar to that in subjects with normal renal function infected with these genotypes. Based on these considerations the recommended RBV-free dosing regimen in

patients with advanced CKD, including those on dialysis, would be 12 weeks of GZR/EBR (100/50 mg QD) in treatment-naive GT1-, GT4 or GT6 infected subjects, all GT1b-infected subjects and GT1a, GT4 and GT6 infected subject who relapsed after a prior interferon-based regimen. Due to lack of an oral, RBV free treatment option in these patients, the above justification provided by the sponsor is acceptable, although efficacy/ safety of GZR+EBR has not actually been evaluated in CKD patients with HCV GT4 or GT6.

Impact of baseline RAVs in TN subjects

There was no evident association between baseline NS3 RAVs and virologic failure in either GT1a or GT1b-infected subjects overall or in key subgroups. The Q80K mutation, which has been associated with decreased efficacy among GT1a infected subjects treated with simeprevir/PR, was detected more than a third GT1a infected TN subjects, but there was no association between the presence of baseline Q80K and treatment response. NS5A RAVs were less prevalent than NS3 RAVs among GT1-infected subjects: approximately 9% of GT1-infected subjects had NS5A RAVs, and approximately 3% of GT1 infected subjects had NS5A RAVs which conferred >5-fold resistance to EBR. This impact was most apparent in GT1a infected subjects with baseline viral loads >800,000 IU/mL, though it should be noted that this subgroup represents only 5.3% of the total cohort of TN subjects with HCV GT1a infection. There was a very modest (and not statistically significant) negative impact of baseline NS5A RAVs on SVR12 in TN GT1b subjects. The impact of NS3 and NS5A RAVs in GT4 and GT6 infected subjects was similar to that observed in GT1 infected subjects.

Impact of baseline RAVs in TE subjects

There was a higher prevalence of baseline NS3 RAVs in GT1a infected subjects than in subjects infected with GT1b, and a slightly lower proportion of GT1a infected subjects who had baseline NS3 RAVs achieved SVR12 compared with GT1b-infected subjects. However, since 9/11 (82%) of GT1-infected patients with baseline NS3 RAVs who experienced virologic failure also had baseline NS5A RAVs, it is not clear that the baseline NS3 RAVs were a critical driver of virologic failure. As in TN subjects, the presence of baseline NS5A RAVs that cause a >5-fold shift in the potency of EBR in vitro among TE GT1a infected subjects was associated with a substantial reduction in efficacy. Subjects with baseline RAVs that confer > 5-fold shift in potency to EBR accounted for only 7.8% (26/334) of GT1a infected subjects, but comprised 76.5% (13/17) of all GT1a virologic failures. The impact of NS3 and NS5A RAVs in GT4 and GT6 infected subjects was similar to that observed in GT1a infected subjects.

Post-baseline RAVs

In both TN and TE subjects, treatment-emergent RAVs in the NS3 and/or NS5A genes were commonly observed in subjects experiencing virologic failure, although there were differences according to genotype. NS3 RAVs conferring >5-fold shift in GZR potency were more commonly observed in GT1a subjects than in GT1b-infected subjects, although the small number of GT1b failures precludes definitive conclusions. NS5A RAVs conferring >5-fold shift in EBR potency were observed in equal proportions in GT1a failures and GT1b failures. Treatment-emergent RAVs were also noted in the GT4 and GT6 infected subjects that experienced virologic failure, though the small number of failures with these genotypes also precludes definitive conclusions.

Durability of efficacy, and long-term impact of virologic failure

At the time of this submission, only limited data are available on the durability of efficacy as SVR24 (secondary efficacy endpoints for many studies) data was not available for

Studies P060, P052 and P068. Furthermore, primary efficacy (SVR12) results for studies P058 in Japanese HCV subjects and study P059 in HCV patients with cirrhosis (CP score 7-9) were also not available and will only be provided in future study reports. The ongoing, long-term follow-up study P017 was designed to evaluate long term development of resistance and so on in over 300 subjects treated with GZR/EBR ± RBV with follow-up for 5 years. Overall, it is not possible to determine the persistence of NS3 and NS5A RAVs that emerge among subjects who fail to achieve SVR following GZR+EBR treatment due to the small number of failures to date and the short follow-up duration.

GZR/EBR + sofosbuvir among treatment-naïve GT3-infected subjects with and without cirrhosis

With other DAA regimens, efficacy for the HCV GT3 infected populations has been less robust than the GT1 infected population and a longer duration of treatment may be necessary for some regimens. Patients with HCV GT3 infection have been well studied in SOF containing regimens. For SOF + RBV high efficacy requires extending duration from 12 to 24 weeks. P074/C-SWIFT was conducted to evaluate the regimen combining 3 different direct acting antiviral with different mechanisms of actions (GZR+EBR+SOF) in GT3-infected subjects. The results of this trial demonstrated that high efficacy was obtained in GT3 TN subjects with and without cirrhosis treated for 8 or 12 weeks; SVR12 was achieved in 14/15 (93.3%) and 14/14 (100%) non-cirrhotic subjects treated for 8 or 12 weeks, respectively, and in 10/12 (83.3%) of cirrhotic subjects treated for 12 weeks. The efficacy was comparable to that observed with the approved regimen of SOF + PR administered for 24 weeks.

There are 3 ongoing trials hoping to provide evidence for efficacy and safety of proposed FDC GZR/EBR 100/ 50 mg in certain patient populations prone to chronic HCV: The Phase II trial (P059) is being conducted in HCV patients with cirrhosis, the Phase III Study P062 is being conducted in HCV patients receiving opiate substitution therapy while Study P065 is being conducted in HCV patients with Inherited blood disorders (IBD). These studies hope to provide important data in these patient subgroups with an unmet medical need who continue to be treated with older HCV PR based regimens despite availability of more effective and tolerable DAA based treatment regimens. However, these trials were ongoing at the time of the submission and efficacy data from these trials are not yet available.

Overall, the comprehensive clinical program provided adequate evidence of efficacy of the FDC GZR/EBR (100/50 mg) for the proposed indication.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

Six Phase III studies evaluated combined therapy with GZR and EBR among 1687 subjects. Of the six Phase III studies, 1 study (P052) administered the study drug as two separate tablets (GZR + EBR in the immediate treatment group) and 5 studies (P060, P061, P062, P065 and P068) administered the study drug as a fixed-dose combination (GZB/EBR). However, Studies P062 and P065 are ongoing with limited safety data provided in the current submission which has been summarised separately. AEs, treatment-related AEs, deaths/ serious AEs (SAEs), discontinuations due to AEs have been evaluated individually for the other 4 Phase III studies. Details of the following studies and the safety data collected for the individually summarised studies/study arms and the 4 main study pools are summarised in Attachment 2:

- Dose-response and non-pivotal efficacy studies
- Protocol 060/ Protocol 061/ Protocol 068 12 Week Safety Pool
- Integrated Safety Pool (ISP)
- Hepatic Safety Pool (HSP)
- PK/' Late ALT/AST Elevation Event' Pool (PKP)

Patient exposure

Safety data was available from 2806 HCV-infected subjects in the Phase II and III studies, as well as from 1234 healthy volunteers, 66 non-HCV-infected patients with liver or kidney dysfunction, and 139 HCV-infected patients in 58 Phase I clinical pharmacology studies.

Phase II and III studies

The extent of GZR[6] exposure for all 1389 subjects who were treated with GZR single entity (SE) in the arms of Studies P003, P035, P038, P039, P047, P048, P052, P058 and P059 which had completed exposure was summarised. The extent of GZR and EBR exposure for all 1097 subjects who were treated with GZR/EBR in the arms of P060, P061, P068 and P074 which had completed exposure was summarised. The extent of EBR exposure for all 944 subjects who were treated with EBR SE in the arms of studies P035, P047, P048, P052, P058 and P059 which had completed exposure was summarised.

The total number of subjects in studies/arms receiving GZR 100 mg with EBR 50 mg in the Phase II and III studies is 1955 (858 SE + 1097 FDC). A summary of the extent of GZR 100 mg and EBR 50 mg exposure for all 858 subjects who were assigned to treatment with GZR 100 mg and EBR 50 mg SE in the arms of P035, P047, P048, P052, P058 and P059 which had completed exposure was given. The mean (range) number of days exposed to study drug for subjects treated with GZR 100 mg + EBR 50 mg was 87.3 days for GZR SE and 87.4 days for EBR SE. The mean (range) number of days for subjects on FDC GZR/EBR was 85.0 days.

Exposure in the 060, 061 and 068 studies 12 week safety population pool

The mean (range) number of days for the 743 subjects on GZR/EBR in this population was 84.6 (4 to 106); 639 subjects were exposed to GZR/EBR without RBV exposure and the remaining 104 subjects in this pool were exposed to RBV in addition to exposure to GZR/EBR. Of the 743 subjects in the P060/ P061/ P068 12-Week Safety Population Pool, 98.9% of subjects completed study medication, and 98.9% completed the trial up to follow-up Week 12. Majority of the 743 treated with GZR/EBR±RBV in this safety pool were male, aged 18-64 years, White with HCV genotype 1a or 1b, baseline HCV RNA > 800,000IU/ml, non-cirrhotic and treatment naïve (all 104 subjects who received GZR/EBR +RBV were treatment experienced).

Integrated safety pool (ISP)

The total number of subjects in the ISP was 1690 (736 SE + 954 FDC). A summary of the extent of GZR and EBR exposure for all 736 subjects in the ISP who were assigned to treatment with GZR and EBR SE was given. The mean duration of any dose was 88.1 days; of the 736 subjects exposed to GZR SE in the ISP, 289 subjects were exposed to GZR and

[6] The total number of subjects in studies/arms with completed exposure who received any dose of GZR in the Phase 2 and 3 studies as of 27-Mar-2015 is 2486 (1389 SE + 1097 FDC). This number includes subjects originally reassigned to GZR, GZR and EBR or GZR/EBR as well as those originally assigned to placebo who later received GZR and EBR or GZR/EBR. This number does not include the active portions of the deferred treatment groups of Protocol 060 and Protocol 052 as these arms had ongoing exposure nor does it include studies P062 and P065, as both studies remained blinded as of 18-Feb-2015

EBR SE without RBV exposure, while the remaining 447 subjects in this pool exposed to GZR SE were also exposed to RBV. A summary of the extent of GZR/EBR exposure for all 954 subjects in the ISP who were assigned to treatment with GZR/EBR was given. The mean duration of any dose of GZR/EBR FDC was 90.3 days; of the 954 subjects exposed to GZR/EBR in the ISP, 744 subjects were exposed to GZR/EBR without RBV exposure, while the remaining 210 subjects in this pool exposed to GZR/EBR were also exposed to RBV.

The rates of completion of study treatment and follow-up at Week 12 was slightly higher among subjects who received GZR/EBR without RBV (95-100%) compared to those who received GZR/EBR with RBV (88-100%). Although the overall frequency of discontinuations due to AE was low, there were numerically more discontinuations observed in the 16 and 18 week arms with RBV with 3.8% (4/106) and 2.3% (2/86), respectively, compared to 0.6% (5/834) in the 12-week no RBV and 0% in both 16- and 18-wk with no RBV arms.

Majority of the subjects in the ISP were male (61.4%), White (75.5%) with median age of 54 years (range 18-82 years) and 11.1% of subjects were >65 years of age. The majority of subjects had GT1 HCV (87.2%), whereas smaller proportions had GT2 (1.8%), GT3 (2.4%), GT4 (6.1%), GT5 (0.5%), and GT6 (1.5%) HCV. 51.2% of subjects had GT1a, and 36.0% had GT1b, and 0.5% had non subtypeable GT1 infection. 25.3% of subjects had baseline HCV RNA ≤ 800,000 IU/mL and approximately half of subjects (49.7%) had baseline HCV RNA ≤ 2,000,000 IU/mL; 27.0% of all subjects had cirrhosis, 38.2% were HCV treatment-experienced and 17.6% of all subjects were co-infected with HIV and HCV. The group of subjects that received placebo for 12 weeks was similar to the group of subjects in the ISP who received GZR with EBR. A slightly lower proportion (53.3%) was male, and a higher proportion (17.1%) was Black. No subjects had GT 2 or GT3 infection. A lower proportion of subjects (37.1%) had HCV RNA <800,000 IU/mL at Baseline. A slightly lower proportion (21.0%) subjects had cirrhosis, no subjects were HCV treatment experienced, and no subjects were co-infected with HIV and HCV.

Hepatic safety pool (HSP)

A summary of the extent of GZR/EBR exposure for all 1016 subjects in the Hepatic Safety Pool who were assigned to treatment with FDC GZR/EBR was given. The total number of subjects who received any dose of GZR in the Hepatic Safety Pool was 2405 (1389 SE+ 1016 FDC). This number includes subjects originally assigned to treatment with GZR without EBR, GZR+EBR, or GZR/EBR as well as those originally randomised to placebo who then received GZR/EBR. The mean (range) number of days for subjects on GZR 100 mg and EBR 50 mg was 82.7 and 86.8, respectively. The mean (range) number of days for subjects on FDC GZR/EBR was 88.8. The disposition of subjects in the Hepatic Safety Pool during the treatment and follow-up phases was summarised. Demographic and baseline disease characteristics were representative of subjects with chronic HCV and were comparable to those of the subjects in the Integrated Safety Population Pool.

PK/'Late ALT/AST elevation event' pool (PKP)

The mean duration of exposure to GZR/EBR for the 1101 subjects in this safety pool was 89.1 days**.** Similar to the HSP, the demographic and baseline characteristics of the PKP were comparable to the characteristics of the subjects in the ISP.

Safety issues with the potential for major regulatory impact

Liver toxicity

Based on the investigation of safety signals observed in Study P003, a program of hepatic safety monitoring was instituted in all subsequent studies that evaluated GZR. This program, developed in consultation with the FDA, included frequent, comprehensive laboratory testing, and defined 3 types of hepatic safety events: Late ALT/AST Elevation

Events: the typical GZR-related hepatic safety signal; Hepatic Events of Clinical Interest (ECI)[7]; and Hepatic Discontinuation Criteria: if a subject met one of these criteria, study therapy would be stopped. This has been discussed in detail in Attachment 2.

An increased rate of Late ALT/AST Elevation Events was associated with doses of GZR above 100 mg administered with PR. The majority of subjects who discontinued study medication for protocol-defined hepatic laboratory discontinuation criteria had Late ALT/AST Elevation Events. No subjects without Late ALT/AST Elevation Events and/or hepatic laboratory ECIs discontinued study medication for protocol-defined hepatic laboratory discontinuation criteria. Overall, Late ALT/AST Elevation Events were not clinically significant and were not accompanied by abnormalities of other tests of hepatic function or by liver-related symptoms. The risk of Late ALT/AST Elevation Events was increased moderately by intrinsic and extrinsic factors which were evaluated using a PK/' Late ALT/AST Elevation Event' analysis, and rates of late ALT/AST elevation events were observed to be higher in females, Asians, the elderly, and those with low body mass index (BMI); however, the rates in each of these subgroups was <2.5%. In a limited number of settings (CP-C cirrhosis, concomitant cyclosporine use) where GZR exposure is increased by >14-fold, the risk of Late ALT/AST Elevation Events is increased to >5%. Of the 25 subjects with Late ALT/AST Elevation Events, 23 subjects had ALT elevations >5x ULN, and 2 subjects just had an AST elevation >5x ULN. The 2 subjects with just an AST elevation >5x ULN likely had increased AST due to skeletal muscle breakdown, rather than hepatic injury,

Hepatic laboratory ECIs, a less-specific measure of GZR related hepatotoxicity, were infrequent, majority of these were transient and not associated with symptoms or other liver-related laboratory abnormalities; these resolved in all subjects, except for 2 CKD subjects with persistent alkaline phosphatase elevations which were likely caused by underlying renal disease. No subject who did not have a Late ALT/AST Elevation Event or a hepatic laboratory ECI discontinued study medication due to hepatic laboratory abnormalities.

Only 1 subject who received GZR 100 mg had concomitant ALT/AST >3x ULN and total bilirubin >2x ULN; this subject was asymptomatic, and the temporal pattern of ALT/AST and total bilirubin elevations was not consistent with hepatocellular injury.

Populations at increased risk of Late ALT/AST Elevation Events have been identified based upon PK data, PK/PD modelling and also analysis of the clinical data. The risk of Late ALT/AST Elevation Events is increased in the presence of intrinsic factors known to increase GZR exposure. Modest increases in GZR exposure are expected in some populations, including females, Asians, cirrhotics and CKD patients who are not on dialysis. The population pharmacokinetic model predicts that GZR steady-state exposures (AUC) are approximately 1.7 fold higher for elderly (67 years old) versus young (31 years old) patients, 1.15 fold higher for low weight (53 kg) versus medium weight (77 kg) patients, 1.4-fold higher for females versus males, 1.6-fold higher for Asians versus Whites, 1.6 fold for CP-A/compensated cirrhotics versus noncirrhotics, and 1. 4 fold higher in non-dialysis-dependent CKD patients compared to patients without CKD. The highest GZR exposures are likely to occur in Asian, female patients with cirrhosis; the population pharmacokinetic model predicts GZR exposures to be approximately 3 fold higher in this patient population. Adding in additional effects of low weight (such as 53 kg) and increased age (for example 67 years) predicts a 4.4-fold increase in GZR for an elderly, low-weight, cirrhotic, Asian, female patient, compared to a young, medium weight, non-cirrhotic White male patient.

[7]Detection of an ECI in a given subject would prompt further monitoring and testing

Comment: The proposed draft Product Information contains adequate information regarding hepatic laboratory testing which should be performed prior to therapy and periodically thereafter.

Haematological toxicity

Haemoglobin decreases were infrequent in the GZR with EBR (no RBV) regimen but were more frequent in the GZR with EBR (+ RBV) regimen, consistent with the well-known side effects of RBV. In the GZR with EBR (no RBV) regimen, no subjects had a Grade 3 or 4 haemoglobin (Hg) decrease; 0.2% (2/1033) had worsening by ≥ 2 grades. In the GZR with EBR (+ RBV) regimen, 2.7% (19/656) had a Grade 3 decrease, and no subjects had a Grade 4 decrease and 11.7% (77/656) had worsening by ≥ 2 grades. The majority of decreases occurred during the first 4 weeks of treatment which overlapped with the time course of bilirubin elevations. Mean haemoglobin levels did not change in the GZR with EBR (no RBV) regimen, but they decreased in the GZR with EBR (+ RBV) regimen. Haemoglobin levels declined approximately 2.4 gm/dL during the first 8 weeks of study treatment in the GZR with EBR (+RBV) 16 week regimen. The magnitude and timing of Hb decrease are consistent with what has been observed with other anti- HCV regimens that utilise RBV.

Evaluator's conclusions on safety

The safety profile of GZR/EBR has been well defined in an extensive clinical development program. In Phase I-III studies, 1234 healthy volunteers, 66 non-HCV-infected persons with liver or kidney impairment and 2704 HCV-infected subjects have been treated with any dose or regimen of GZR and/or EBR.

The ISP pool is the primary pool used for evaluation of AEs and laboratory evaluations and consists of subjects in Phase II/III studies who received at least 8 weeks of therapy with GZR 100 mg with EBR 50 mg. The pool does not include CKD subjects from P052, since these subjects have a distinct safety profile, and the pool does not contain subjects from P074, in which sofosbuvir was co-administered. The ISP includes 1690 HCV-infected subjects who received the doses proposed for marketing (100 mg GZR and 50 mg EBR) for 8 weeks (91 subjects), 12 weeks (939 subjects), 16 weeks (214 subjects), or 18 weeks (149 subjects) and it is therefore the most relevant population for overall safety. Slightly more than one-third (657/1690 [38.9%]) of subjects in the ISP received RBV. The ISP is representative of the overall HCV-infected population, and it included important subsets of HCV-infected individuals. In the ISP, 457/1690 (27.0%) of subjects were cirrhotic and 298/1690 (17.6%) subjects had HCV/HIV co-infection. Additionally, diverse ethnic groups were included in the ISP; the population consisted predominantly of Whites (75.5%), Blacks (12.9%) and Asians (9.8%). This pool provides the most relevant profile for FDC of GZR/EBR at doses and durations proposed for marketing.

The general safety profile of the ISP demonstrated good tolerability of GZR 100 mg with EBR 50 mg. There were few deaths, non-fatal SAEs, or AEs leading to discontinuation; very few of these events were assessed as related to treatment. Few AEs occurred at a rate >10%; the majority were mild, and very few were severe. The most common AEs overall were headache (18.0%) and fatigue (16.2%). The most common drug-related AEs were headache (11.5%) and fatigue (12.0%). Safety profiles were similar in important subpopulations: Cirrhotics and non-cirrhotics had similar AE profiles. HCV/HIV co-infected and HCV mono-infected subjects had similar profiles; HCV mono-infected subjects had a slightly higher incidence of AEs. A RBV-free regimen has a safety advantage, compared to a RBV-containing regimen. The incidence of well-known RBV-related AEs (anaemia, fatigue, dyspnoea, rash, and pruritus) was increased in subjects who received RBV containing regimens. Despite this, GZR with EBR (+ RBV) was generally well-tolerated with few discontinuations. Safety profiles did not meaningfully differ according to the duration of the treatment regimen GZR 100 mg with EBR 50 mg is safe and well-tolerated,

with and without RBV co-administration, for durations of 8, 12, 16, or 18 weeks. GZR 100 mg with EBR 50 mg is safe and well-tolerated, with and without RBV co-administration regardless of the presence of cirrhosis or HCV/HIV co-infection.

AEs were similar in important subpopulations with no differences in AE profiles based on age, gender, or race/ethnicity. Compared to subjects in the ISP (RBV-free treatment regimens), CKD 4-5 subjects in P052 had a higher overall rate of AEs. However, this increased rate was most likely due to underlying renal disease, since AE rates were similar between subjects who received GZR+EBR and placebo; furthermore, compared to subjects in the ISP, CKD subjects had a similar profile of individual AEs. Compared to non-cirrhotics, cirrhotics had a slightly higher, although comparable, incidence of AEs noted in the P060/P061/P068 12 Week Pool, but rates of AEs were similar in the larger ISP. This slightly higher incidence of AEs in the smaller pool was likely reflective of underlying comorbidities related to cirrhosis, rather than due to GZR with EBR. In the Phase III pivotal, placebo-controlled Study P060, once daily fixed-dose oral regimen of GZR/ EBR 100/50 mg for 12 weeks was generally well-tolerated in 421 TN cirrhotic and non-cirrhotic subjects with HCV GT1, GT4, or GT6 infection. Drug-related SAEs and discontinuations for AEs were uncommon. Importantly in P060, no relevant differences were observed between GZR/EBR and placebo (deferred treatment) groups.

Treatment with GZR with EBR does not meaningfully affect the safety profile in subjects with CKD as the rates of AEs, deaths, SAEs, and discontinuations did not meaningfully differ based on renal function. As such, no dosage adjustment of GZR/EBR is warranted in HCV-infected patients with renal impairment regardless of dialysis status.

The safety advantages of a RBV-free regimen were clearly shown in terms of a reduced rate of RBV-related AEs and haemoglobin abnormalities. The rates of common AEs and drug-related AEs were more common with RBV co-administration.

The hepatic safety profile of GZR/EBR has been thoroughly evaluated in the clinical development program. In the GZR development program, dose/exposure-related elevations in ALT/AST were first noted in study P003, predominantly at doses of 400 to 800 mg/day. The Hepatic Safety Pool (HSP) pool consists of 2405 subjects in Phase II/III who received at least 8 weeks of therapy with GZR, regardless of GZR dose and provides the most comprehensive picture of hepatic safety and defines hepatic safety risks associated with higher doses of GZR. In the HSP, 36/2405 (1.5%) subjects had a Late ALT/AST Elevation Event, hepatic laboratory ECI, and/or discontinued study medication due to protocol-specified hepatic laboratory discontinuation criteria. Of these 36 subjects, 25/2405 (1.0%) had a Late ALT/AST Elevation Event, 26/2405 (1.1%) had a hepatic laboratory ECI, and 7 (0.3%) discontinued study medication due to protocol-specified hepatic laboratory abnormality discontinuation criteria. There was an increase in the rate of Late ALT/AST Elevation Events and hepatic laboratory ECIs in subjects who received doses of GZR greater than 100 mg administered with PR. Overall, the most frequent hepatic laboratory criterion fulfilled was 'ALT or AST >3x baseline and >100 IU/L' which occurred in 19/26 subjects who met ECI criteria.

PK/'Late ALT/AST Elevation Event' Pool (PKP), was similar to the HSP and consisted of 2236 subjects. The PKP describes the correlation between GZR exposure and risk of late ALT/AST Elevation Events. Late ALT/AST Elevation Events, a specific measure of GZR-related hepatic safety, occurred in a dose-related manner, and they occurred in <1% of subjects who received the proposed dose of GZR 100 mg. These events generally occurred at or after TW8, and were transient, with most resolving while continuing treatment and the remaining events resolving after discontinuation of treatment. These events were not of clinical concern as they were not accompanied by abnormalities of other tests of hepatic function or by liver related symptoms. The risk of Late ALT/AST Elevation Events was increased moderately by intrinsic and extrinsic factors; GZR exposure is expected to be increased by >12-fold (with geometric mean ratio [90% CIs] of 11.68 [6.10, 22.35] in

patients with Child-Pugh C cirrhosis. The risk of Late ALT/AST Elevation Events is predicted to be >5% in this population, especially in the context of the underlying advanced liver disease. Labelling will address specific patient populations and DDIs that are pertinent to the risk of Late ALT/AST Elevation Events. Increase in ALT is the most specific hepatic laboratory parameter for assessing hepatic safety of GZR with EBR. Periodic monitoring of ALT is recommended in the proposed label.

Among the 2704 subjects in the Phase II/III program, no other obvious laboratory safety concern associated with GZR or GZR with EBR was identified. Moreover, among the 1690 subjects in the Integrated Safety Population Pool (which represents a subset of the protocols and subjects in the from those included in the Phase II/III program, no obvious laboratory safety concern associated with GZR 100 mg with EBR 50 mg was identified. Laboratory abnormalities (in particular, the incidence of ALT/AST, total bilirubin, and haemoglobin abnormalities) were generally similar among subjects treated for 8, 12, 16 or 18 weeks.

Overall, safety of proposed FDC of SZR/EBR (100/50 mg QD) was adequately evaluated with no major safety concerns with the exception of a pattern of ALT/AST elevations associated with GZR administration occurring late in the course of therapy. The rate and severity of these events are dose-dependent. Among subjects who received GZR 100 mg, these late ALT/AST elevation events were infrequent (occurring in <1% of subjects), monitorable (with a consistent timing of initial detection), generally reversible with continued therapy and very infrequently associated with abnormalities associated with liver dysfunction. Other concerns are lack of safety data in HCV patients with severe hepatic insufficiency, liver transplant, HBV/HCV co-infection.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Zepatier in the proposed usage are:

- offers a single tablet, once-daily oral regimen
- provides a simple, well tolerated ribavirin and interferon-free regimen for patients infected with HCV GT 1, 3, 4 and 6
- treats HCV infected patients including hard-to-treat populations such as those with HIV co-infection, Chronic Kidney Disease, and HCV genotype 3, 4 and 6 infection
- Provides a 12 week dosing regimen without ribavirin for most patients (GT 1, 4 and 6 Treatment Naïve and Treatment-Experienced Relapsers, and GT1b Treatment-Experienced On-Treatment-Virologic-Failures (OTVF))
- 8 week regimen may be considered for Treatment Naïve GT1b patients
- 12 week regimen with concomitant administration of sofosbuvir was effective in treating HCV GT3 infected TN patients
- 16 week regimen with concomitant administration of ribavirin is recommended for GT1a, 4 and 6 Treatment-Experienced OTVF
- In GT4 infected (treatment-naïve/treatment experienced, ± HIV co-infection, ± cirrhosis) HCV patients, treatment with GZR+EBR (100/50 mg) for 12 weeks was highly effective (SVR12 up to 96%) and well tolerated. Although only small numbers of GT6 subjects were evaluated in the Phase II/III studies, there was strong data to support use for GT6 (SVR12 of 80%).

- The well-conducted Study P052 demonstrated that 12 weeks of treatment with GZR+EBR (100/50 mg) was well tolerated and highly efficacious (SVR12 of 94%) in 225 advanced CKD patients, including patients on haemodialysis, thus avoiding the need for peginterferon, ribavirin or sofosbuvir in treating these patients and addressing this urgent unmet need.

First round assessment of risks

The risks of Zepatier in the proposed usage are:

- Lack of adequate data to demonstrate durability/maintenance of efficacy; SVR24 results for core Studies P060, P052 and P068 were not available for evaluation in the current submission. Furthermore, the current dossier also does not provide adequate efficacy results from ongoing Studies P058, P059, P017, P062 and P065.
- Development of NS3 and/or NS5A RAVs in subjects with virologic failure has been characterised. NS3 RAVs are likely to revert to wild-type virus and have limited impact on retreatment options. NS5A RAVs are likely to persist for a longer period of time, based on experience with other NS5A inhibitors. The implications on re-treatment have not yet been determined. However, the incidence of virologic failure was generally <4%.
- Increased risk of Late ALT/AST Elevation Events, especially in patients with Child-Pugh C cirrhosis. However, periodic monitoring of ALT is recommended in the proposed label.
- Risk of drug interactions although labelling will address specific patient populations and DDIs that are pertinent to the risk of Late ALT/AST Elevation Events.
- Hyperbilirubinemia has been observed in regimens of GZR with EBR (+ RBV) and reflects the well-known haemolytic effects of RBV.
- Lack of efficacy/ safety data in patients with severe hepatic impairment (CP-C cirrhosis), liver transplant patients and HBV/HCV co-infection.
- Lack of efficacy/ safety data in pregnancy/lactation and paediatric patients.

First round assessment of benefit-risk balance

Chronic hepatitis C virus (HCV) infection is a global public health challenge, affecting up to 170 million people worldwide. Globally, up to 4 million people worldwide, annually, are estimated to have incident HCV infection. Approximately, 55 to 85% of newly infected persons progress to develop chronic infection. Since 2013, other DAAs have become available, and there is now clear evidence that interferon-free regimens, consisting of combinations of DAAs targeting different targets in the HCV life cycle, can be highly effective in clearing chronic HCV infection. While these regimens represent substantial improvements in the therapeutic options for HCV-infected patients, they continue to have important deficits:-

- Some regimens require use of RBV, a medicine that is associated with substantial adverse experiences (even in an interferon-free setting), that is taken twice daily, with food, and that requires close monitoring and strong pregnancy precautions;
- Some regimens have suboptimal efficacy (for example SVR12 below 90%) or require prolonged therapy among important subpopulations, including those at urgent need for therapy (for example, prior PR-null responders with cirrhosis, GT3-infected patients);

- Regimens that include RBV or NIs are not optimal for use in patients with advanced CKD; such patients are particularly impacted by HCV infection, in that HCV infection increases all-cause mortality in patients with advanced CKD relative to absence of HCV infection and HCV-infection substantially worsens outcomes following renal transplant.

The selection of the appropriate regimen and duration of therapy depends on several patient factors including genotype, sub-genotype, mono-infection versus HCV/HIV co-infection, prior treatment experience (such as PR null-responders), advanced liver disease (for example compensated cirrhosis, decompensated cirrhosis), advanced chronic kidney disease (CKD) and presence of liver or kidney transplant. Table 9 lists all oral regimens which are available for treating HCV infection.

Table 9: Summary of HCV all oral regiments by population, durations and need for ribavirin

Regimen	Duration (weeks (w)) /Ribavirin (RBV)	Populations[†]
Sofosbuvir	• 24w +RBV • 12w +RBV • 24w +RBV	• GT1, IFN-ineligible • GT2 • GT3 (Includes HIV/HCV co-infection)
Sofosbuvir/Ledipasvir	• 12w • 24w • 24w +RBV • 24w +RBV	• GT1 or GT4, NC • GT1 or GT4, C • GT1 or GT4, decompensated C or pre/post-LT • GT3, C or prior treatment failures (including HIV/HCV co-infection)
Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir	• 12w • 12w +RBV • 12w +RBV • 24w +RBV	• GT1b NC • GT1b C • GT1a NC • GT1a C
Ombitasvir + Paritaprevir + Ritonavir	• 12w + RBV • 24w + RBV	• GT4, NC • GT4, C
Simeprevir + Sofosbuvir	• 12w +/- RBV	• GT1 or GT4, NC, C, TN, TE (relapsers, non-responders) (including HIV/HCV co-infection)
Daclatasvir + Sofosbuvir (European Union only)	• 12w • 24w • 24w+RBV	• GT1or GT4, NC • GT1 or GT4, C • GT3, TE, C

[†] GT: Genotypes, TN: Treatment-naïve, TE: Treatment Experienced, C: Cirrhotics, NC: Non-cirrhotics, LT: Liver transplant recipients

GZR is a once daily PI with a high potency against GT1, GT2, GT4GT6, with somewhat less potency against GT3; in vitro, it retains high potency against resistance associated variants (RAVs) that are commonly detected among individuals who fail therapies with first generation PIs such as boceprevir, telaprevir and simeprevir. EBR (MK-8742 or EBR) is a once-daily NS5AI with high potency against GT1, GT2a, GT3, GT4, GT5, and GT6; in vitro, it retains potency in the presence of RAVs associated with failure of other NS5A inhibitors such as daclatasvir and ledipasvir. Pre-clinical data suggested that co-administration of GZR with EBR would create a highly potent regimen for HCV GT1 patients, as well as potential utility in GT3 patients. A fixed-dose combination (FDC) of GZR/EBR has been developed, to improve compliance and convenience with a simple daily dosing regimen, low pill burden of one tablet, low potential for medication error and no potential for off-label use of individual components. The efficacy and safety was extensively evaluated in PhaseII, Phase II/III and Phase III clinical trials including a diverse population of GT1 to GT6 infected subjects, including treatment-naïve and treatment-experienced, HCV mono- and HCV/HIV co-infected, and non-cirrhotic and cirrhotic subjects were enrolled in these studies. A distinctive feature of the program was the evaluation of HCV-infected patients

with end-stage renal disease on haemodialysis, a population for which interferon-free treatment options are not available.

The pivotal efficacy studies have consistently demonstrated that Zepatier is efficacious with high SVR 12. Key results include:

- 94 to 96% SVR12 rates in GT1 and GT4 Treatment Naïve subjects.
- 80% SVR12 rates in GT6 Treatment Naïve subjects.
- Potential to reduce treatment duration to 8 weeks in Treatment Naïve GT1b infected subjects who do not have significant fibrosis or cirrhosis.
- 100% SVR12 rates in GT1, 4 and 6 Treatment Experienced relapsers following 12 weeks of treatment with a ribavirin free regimen.
- 96% SVR in GT1a, 4 or 6 Treatment Experienced on-treatment virologic failures when treated for 16 weeks with ribavirin. When infected with GT1b, only 12 weeks of treatment without ribavirin resulted in 100% SVR12 for Treatment Experienced on-treatment virologic failures.
- 93% SVR12 in GT3 Treatment Naïve cirrhotic and non-cirrhotic patients when treated for 12 weeks with sofosbuvir and Zepatier.
- Treatment responses are comparable across subgroups, including cirrhotics, HIV/HCV co-infected and subjects with advance CKD.
- 94% SVR in patients with advanced CKD (including those on haemodialysis), addressed unmet clinical need. The dosing recommendations are comparable to non-CKD subjects (with the exclusion of ribavirin).
- High rates of efficacy persist for at least 24 weeks (94% of Treatment Experienced and 92% of Treatment Naïve subjects achieved SVR 24). At time of submission, longer term follow-up is ongoing.

The safety and tolerability profile of Zepatier has been well defined and found to be generally favourable in an extensive clinical development program. Comparable safety was observed in all subpopulations such as cirrhotics, HIV co-infection and CKD. Importantly, in the placebo controlled studies no relevant differences were observed between the active treatment and placebo (deferred treatment) groups. Also, the safety profiles did not meaningfully differ according to the duration of treatment (12 versus 16 weeks). The most frequent AEs reported (>10%) were headache, asthenia, fatigue and nausea. Notably these AEs occurred at a similar frequency in the active and placebo treatments. There were no deaths assessed as being related to the study drug or were there any CNS or cardiovascular events associated with therapy. Non-fatal serious AEs related to study drug occurred at 0 to 0.5% frequency. These were reported as abdominal pain or overdose (per protocol, overdose for example, taking two tablets daily, was classed as a serious AE regardless of severity).

The safety of GZR/EBR, with or without RBV, has been evaluated in a large and diverse population. GZR/EBR, with or without RBV, has a generally favourable safety profile There were very few deaths, SAEs or discontinuations; in particular, treatment-related events of significance were infrequent and demonstrated no consistent pattern. Common AEs were fatigue, headache and nausea which occurred at a similar frequency on active and placebo treatments. RBV-containing regimens were associated with an expected increase in frequency of drug-related AEs of asthenia, anaemia, pruritus, rash and dyspnoea. Tolerability did not differ substantially according to baseline factors such as age, gender, race/ethnicity, presence of cirrhosis, presence of HCV/HIV co-infection, or the presence of advanced CKD (Stage 4-5). Tolerability was not affected by treatment duration (12 versus 16 weeks).

Late ALT/AST Elevation Events, a specific measure of GZR related hepatic safety, occurred in a dose-related manner, and they occurred in <1% of subjects who received the proposed dose of GZR 100 mg. These events generally occurred at or after TW8, and were transient, not accompanied by abnormalities of other tests of hepatic function, or by liver-related symptoms and most of these events resolved while continuing treatment or after discontinuation of treatment. Among the 2704 subjects in the Phase II/III program, no obvious laboratory safety concern associated with GZR or GZR with EBR was identified. Moreover, among the 1690 subjects in the ISP, no other obvious laboratory safety concerns associated with GZR 100 mg and EBR 50 mg was identified. Laboratory abnormalities (in particular, the incidence of ALT/AST, total bilirubin, and haemoglobin abnormalities) were generally similar among subjects treated for 8, 12, 16 or 18 weeks.

In Australia, there is currently no approved therapeutic regimen for treatment of HCV GT4 or GT6 infection that does not require concomitant administration of ribavirin or pegylated interferon. These drugs have poor tolerability and the treatment burden is well documented, resulting in AEs, discontinuation of treatment and failure to achieve 'cure'. Zepatier would address this unmet medical need as it offers peginterferon and ribavirin-free dosing in these patients. This application presents adequate clinical data to support use in HCV GT4 and GT6 infected patients, although number of patients evaluated was small which was likely related to low incidence of these HCV genotypes.

HCV has a significant adverse effect on the progression of renal disease and outcomes of renal transplants. HCV infection and Chronic Kidney Disease (CKD) results in a burden of mortality that is greater than the sum of morbidity and mortality caused by each condition alone. There is currently no registered treatment for patients with chronic HCV infection with severe renal impairment receiving haemodialysis. The DAAs currently approved for treatment of HCV infection in Australia are not suitable for use in patients with severe renal disease as these agents are either excreted primarily through the renal pathway (sofosbuvir based regimens or require co-administration of pegylated interferon and/or ribavirin). In addition to their tolerability limitations, ribavirin exacerbates renal failure related anaemia. The efficacy and safety of GZR/EBR FDC (Zepatier) has been evaluated in a study (P052) in 225 HCV patients with CKD Stage 4 or 5 of whom 76% were receiving haemodialysis.

The proposed Indication is as follows:

> *'Zepatier is indicated for the treatment of Chronic Hepatitis C infection in adults (see Dosage and Administration and Clinical Trials). (See Clinical Trials for information on HCV genotype-specific activity.)'*

The sponsor contends a non-genotype specific Indication *' for treatment of Hepatitis C'* is justified based on the available data against the background of a rapidly evolving HCV therapeutic landscape.

- This would allow GZR/EBR to be used in combination with emerging therapies and thus not limit treatment options for current and future patients with the greatest unmet need.
- Furthermore a non-genotype specific indication would ensure patients with HCV GT 2 and 5 infection who may have other co-morbidities preventing them receiving existing treatments, have access to a peginterferon/ribavirin free regimen.

The above justification provided by the sponsor seems appropriate considering the proposed indication clearly cross references other sections of the Product Information where detailed information on studied combinations, HCV patient subgroups (genotypes, disease state characteristics, prior treatment history) and recommended treatment durations are located. The long term consequences of CHC infection if left untreated include cirrhosis, liver disease, hepatocellular carcinoma and may result in liver

transplantation. To date, there has been resistance to treatment in some patients due to the poor tolerability of existing interferon and ribavirin based regimens. The advent of interferon free regimens offers patients simple, all-oral therapies, with the potential to halt liver disease progression in less than three or four months of treatment.

The benefit-risk profile of Zepatier given the proposed use is favourable.

First round recommendation regarding authorisation

It is recommended that the application for marketing approval of Zepatier be approved for the proposed indication:

> ' *Zepatier is indicated for the treatment of Chronic Hepatitis C infection in adults (see Dosage and Administration and Clinical Trials). (See Clinical Trials for information on HCV genotype-specific activity).*

However, the approval is subject to incorporation of suggested changes to the proposed Product Information and a satisfactory response to clinical questions below.

Clinical questions

Pharmacokinetics

1. Why were the following drug-drug interactions only examined following a single dose of EBR when it would it have not been more meaningful to examine the interaction with EBR at steady-state:
   - buprenorphine/naloxone (Study 8742-P021)
   - ketoconazole (Study 8742-P003)
   - rifampin (Study 8742-P011); and
   - raltegravir (Study 8742-P016).
2. Why were the following drug-drug interactions only examined following a single dose of GZR when it would it have not been more meaningful to examine the interaction with GZR at steady-state:
   - RTV (Study 5172-P006); and
   - ketoconazole (Study 5172-P001).
3. Why was Study 5172-P045 conducted as a single dose study as the interaction with famotidine should have at least been examined following multiple doses of the FDC?
4. Why do the results of Study 5172-P072 indicating a lack of interaction between the FDC and famotidine differ from the results of Study 5172-P045 which indicate that for EBR at least exposure is increased (35%) in the presence of famotidine?
5. Why was the direct interaction between GZR and ERB examined using doses of 200 mg and 20 mg, respectively, rather than with the proposed dose for marketing (100 mg/50 mg QD)?
6. In Study 5172-P032, why does GZR co-administration have such divergent effects on the exposure of the two CYP3A4 substrates atorvastatin and midazolam?
7. Given that in vitro studies have identified that GZR is primarily metabolised by CYP3A and that rifampin is a potent CYP3A inducer, can the sponsor please clarify the single dose results (Study 5172-P031) in which rifampin co-administration resulted in an increase in GZR exposure? In addition can the sponsor clarify why at steady-state

levels of rifampin and GZR co-administration with rifampin is having little effect on GZR exposure, whereas, co-administration of efavirenz (another CYP3A4 inducer) results in a significant decrease in GZR exposure?

Efficacy

8. The CSR for pivotal Phase III study P060 mentions that the secondary endpoint (SVR24) will be provided later. The CSR for pivotal Phase2/3 study P052 mentions that the following results will be summarised in a later report: SVR24 for the immediate treatment group SVR4, SVR12 and SVR24 for the deferred treatment arm, and for the combined population of the immediate treatment group, the deferred treatment group, and the intensive PK group. Biomarkers for safety signals and impact of HCV treatment on cryoglobulinemia will also be summarised in a later report. In Phase III study P068, the secondary efficacy endpoint of SVR24 will be reported later when final results of study are available as many subjects have not yet reached the Week 24 follow-up visit. In Phase II/3 study P059 in 30 patients with cirrhosis (CP score 7-9), only 4 week data was submitted in current dossier. The primary (SVR12), secondary and exploratory endpoints will be summarised in a future study report. For the ongoing Phase II study P058 in 62 Japanese subjects, only SVR4 rates available (100% results with 50 mg and 100 mg GZR doses in combination with EBR 50 mg).
   - Other ongoing studies include the open-label study P017 with follow-up periods of up to 5 years; study P062 in HCV infected subjects on opiate substitution therapy and study P065 in HCV infected subjects with inherited blood disease (IBD).
   - There is not much evidence on durability/maintenance of efficacy following treatment with Zepatier. On completion of the above-mentioned ongoing studies, the final CSRs should be provided for evaluation.
9. The CSR of study P052 in HCV subjects with CKD did not mention if the study treatments were given without regard to food intake as proposed in the draft Product Information. Could the sponsors please clarify this?
10. The CSR of pivotal Phase III study P060 mentions that RAVs were assessed for any subject with VF and detectable virus above 1000 IU/mL after failure was observed. These subjects were also offered participation in a 3 year long-term follow-up P017, to determine the persistence of RAVs and to determine time course of reversion to wild-type. Viral resistance testing, using population sequencing methodology, focused on the entire NS3/4A and NS5A regions for all subjects at baseline and for those who met the subject virologic failure criteria. However, the CSR for P017 only mentions data on 388 subjects enrolled from Study P035 and P047. Could the sponsors clarify if any of the subjects from Study P060 were actually enrolled in the long-term study P017?

Safety

11. 'Worsening (increased) ALT and/or AST Grade from baseline occurred more frequently in the GZR+EBR immediate treatment group compared to the placebo deferred treatment group. 3/111 (2.7%) and 25/113 (22.1%), respectively, of subjects in the GZR+EBR immediate treatment and placebo deferred treatment groups developed worsened ALT Grade while on treatment; 2/111 (1.8%) and 18/113 (15.9%), respectively, of subjects in the GZR+EBR immediate treatment and placebo deferred treatment groups developed worsened AST Grade while on treatment.'.

Comment: The above statement should read that worsening (increased) ALT and/or AST Grade from baseline occurred ~~more~~ **less** frequently in the GZR+EBR immediate treatment group compared to the placebo deferred treatment group based on the values provided in the subsequent sentences. Could the sponsors please provide clarification?

Comment: Study P059 evaluated GZR 50 mg with EBR 50 mg (not 100 mg as mentioned in the SCS). Could the sponsors provide clarification?

Second round evaluation of clinical data submitted in response to questions

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

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of responses to clinical questions and other information submitted by the sponsors, the benefits of Zepatier in the proposed indication are modified as follows:

The benefits of Zepatier in the proposed usage are:

- Offers a single tablet, once-daily oral regimen.
- Provides a simple, well tolerated ribavirin and interferon-free regimen for patients infected with HCV GT 1, 3, 4 and 6.
- Treats HCV infected patients including hard-to-treat populations such as those with HIV co-infection, Chronic Kidney Disease, and HCV genotype 3, 4 and 6 infection.
- Provides a 12 week dosing regimen - without ribavirin - for most patients (GT 1, 4 and 6 Treatment Naïve and Treatment-Experienced Relapsers and GT1b Treatment-Experienced On-Treatment-Virologic-Failures (OTVF)).
- 8 week regimen may be considered for Treatment Naïve GT1b patients.
- 12 week regimen with concomitant administration of sofosbuvir was effective in treating HCV GT3 infected TN patients.
- 16 week regimen with concomitant administration of ribavirin is recommended for GT1a, 4 and 6 Treatment-Experienced OTVF.
- In GT4 infected (treatment-naïve/treatment experienced, ± HIV co-infection, ± cirrhosis) HCV patients, treatment with GZR+EBR (100/50 mg) for 12 weeks was highly effective (SVR12 up to 96%) and well tolerated. Although only small number of GT6 subjects was evaluated in the Phase II/III studies, there was strong data to support use for GT6 (SVR12 of 80%).
- The well-conducted Study P052 demonstrated that 12 weeks of treatment with GZR+EBR (100/50 mg) was well tolerated and highly efficacious (SVR12 of 94%) in 225 advanced CKD patients, including patients on haemodialysis, thus avoiding the need for peginterferon, ribavirin or sofosbuvir in treating these patients and addressing this urgent unmet need.
- A summary of the SVR24 data from Studies P052, P058, P059, P060, P061 and P068, were provided by the sponsor. Overall, maintenance of efficacy of Zepatier was

demonstrated as SVR24 rates were high, with very few relapses observed between SVR12 and SVR24.

Second round assessment of risks

After consideration of responses to clinical questions and other information submitted by the sponsors, the risks of Zepatier in the proposed indication are modified as follows:-

The risks of Zepatier in the proposed usage are:

- Development of NS3 and/or NS5A RAVs in subjects with virologic failure has been characterised. NS3 RAVs are likely to revert to wild-type virus and have limited impact on retreatment options. NS5A RAVs are likely to persist for a longer period of time, based on experience with other NS5A inhibitors. The implications on re-treatment have not yet been determined. However, the incidence of virologic failure was generally <4%.
- Increased risk of Late ALT/AST Elevation Events, especially in patients with Child-Pugh C cirrhosis. However, periodic monitoring of ALT is recommended in the proposed label.
- Risk of drug interactions although labelling will address specific patient populations and DDIs that are pertinent to the risk of Late ALT/AST Elevation Events.
- Hyperbilirubinemia has been observed in regimens of GZR with EBR (+ RBV) and reflects the well-known haemolytic effects of RBV.
- Lack of efficacy/ safety data in patients with severe hepatic impairment (CP-C cirrhosis), liver transplant patients and HBV/HCV co-infection.
- Lack of efficacy/safety data in pregnancy/ lactation and paediatric patients.

Second round assessment of benefit-risk balance

After consideration of responses to clinical questions and other information submitted by the sponsors, the benefit-risk profile of Zepatier in the proposed indication remains favourable.

Second round recommendation regarding authorisation

It is recommended that Zepatier be approved for the proposed indication of:

> *'Zepatier is indicated for the treatment of Chronic Hepatitis C infection in adults (see Dosage and Administration and Clinical Trials). (See Clinical Trials for information on HCV genotype-specific activity.)*'

Approval is subject to incorporation of some minor changes to the proposed Product Information.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 1.0 (dated 17 June 2015, DLP 27 March 2015) and Australian Specific Annex Version 0.1 (dated August 2015)) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 10.

Table 10: Ongoing safety concerns provided by the sponsor in their RMP submission

Safety specification	Details
Important identified risks	Late ALT elevation Hyperbilirubinaemia Drug resistance development Drug interaction with Moderate or strong CYP3A/P-gp inducers HIV protease inhibitors Atorvastatin, rosuvastatin, lovastatin, simvastatin, fluvastatin St John's wort (Hypercium perforatum)
Important potential risks	None
Missing information	Exposure in pediatric patients Exposure in pregnant lactating women Exposure in patients with Moderate (Child-Pugh ~~C~~)B hepatic impairment Severe (Child-Pugh C) hepatic impairment Exposure in liver transplant patients

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for all safety concerns and additional pharmacovigilance activities for selected safety concerns and missing information items ('Drug resistance development'; 'Exposure in pediatric patients').

Risk minimisation activities

The sponsor proposes only routine risk minimisation activities for all safety concerns and missing information.

Reconciliation of issues outlined in the RMP report

Table 11 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised and the evaluation of the sponsor's responses.

Table 11: Reconciliation of issues outlined in the RMP Evaluation Report

Sponsor's response to Round 1 recommendations with RMP evaluator's comment
TGA recommendation 1.1: Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP
Sponsor's response: The sponsor has agreed to evaluate the relevant impact to the RMP regarding any safety considerations from the nonclinical and clinical evaluators.
RMP Evaluator comment: This is acceptable and the RMP Evaluator notes that no safety concerns were raised in the Clinical and Nonclinical Evaluation Reports.
TGA recommendation 1.2: Unless the sponsor can provide compelling justification against any of the following recommendations, the following should be considered: The sponsor should provide a summary of the data available for the following items, and where data is lacking or sparse add those as missing information: Long-term safety; Australian Indigenous populations; Carcinogenicity data; Effectiveness of hormonal contraception; Patients on opiate substitution therapy; and Patients with severe renal impairment.
Sponsor's response: The sponsor stated that the above items are not required to be included as missing information in the EU RMP v1.2 based on the comments received from the European CHMP. Specific responses to the missing information is as follows: *The sponsor has agreed to submit an interim report of long term safety study P017 (A Long-Term Follow-up Study to Evaluate the Durability of Virologic Response and/or Viral Resistance Patterns of Subjects With Chronic Hepatitis C Who Have Been previously Treated with MK-5172 in a Prior Clinical Trial) to CHMP by 3Q 2016, which will fulfill EMA's requirement of PAMs (Post-Authorisation Measures) for long term safety data. The Final Report due 2Q 2021.* *The sponsor states that it is not an EU requirement to list Australian Indigenous populations as missing information.* *The sponsor advises that in accordance with ICH S1A guidance, carcinogenicity studies were not conducted given that the human use of GZR/EBR is less than 6 months in treatment duration and that there is an absence of a genotoxic signal in the battery of genotoxicity studies and no evidence of a proliferative signal in the chronic toxicity studies.* *The Sponsor considers that the drug-drug interaction (DDI) results of GZR and EBR with Nordette®-28 (Ethinyl Estradiol [EE] 0.03 mg/levonorgesterol [LNG] 0.15 mg) demonstrate a lack of interaction and supports that effectiveness of oral contraceptives will be maintained when coadministered with GZR/EBR.* *The sponsor states that Study MK-5172-062 (C-EDGE CO-STAR, Study of Efficacy and Safety of GZR and EBR in the Treatment of Chronic Hepatitis C Virus Genotype 1, 4 or 6 Infection in Treatment Naïve Participants who are on Opiate Substitution Therapy) was completed in December 2015, therefore this is not missing information. The sponsor intends to submit the CSR describing clinical*

Sponsor's response to Round 1 recommendations with RMP evaluator's comment
data from this study, and consequent labelling updates, to the TGA for review. *The sponsor notes that Study results from Protocol 052 have been submitted to TGA within this application dossier. P052 enrolled only subjects with CKD Stages 4 and 5 (individuals with severe renal impairment), including haemodialysis dependent subjects. CKD stage 4 is defined as estimated Glomerular Filtration Rate (eGFR) of 15-29 mL/min/1.73m².*
RMP Evaluator comment: The sponsor has indicated that data is being collected to address long term safety, and this is considered to support the recommendation to include ' long term safety' as missing information. It is noted that there is no data in Australian Indigenous populations and that this is not an EU RMP requirement, as it is uniquely Australian. Therefore, the appropriate place for the sponsor to include this as missing information would be the ASA. The sponsor's response regarding carcinogenicity is acceptable given the duration of treatment. The sponsor has provided data for the following missing information for d), e) and f), which removes the need to include these safety concerns as missing information.
TGA recommendation 1.3: In the interest of internal consistency, the name of the safety concern/missing information item in the pharmacovigilance plan should exactly match the name of the safety concern/missing information item in the safety specification.
Sponsor's response: The sponsor intends to update the name of the safety concern/missing information item in the pharmacovigilance plan to match the name of the safety concern/missing information item in the safety specification. The sponsor states that the majority of these updates are available in EU RMP version 1.2 and updates will be ongoing. The Australian Specific Annex will be amended to accommodate EU RMP version 1.2 and the TGA RMP Evaluation comments at Milestone 5.
RMP Evaluator comment: The sponsor's response has addressed the evaluators' concerns. The commitment to submit a revised ASA in the pre-ACPM response has been noted.
TGA recommendation 1.4: The sponsor should provide a summary of the evidence relating to the effectiveness of concomitantly administrated oral contraceptives, or in the absence of such data propose relevant additional activities to investigate this.
Sponsor's response: The sponsor states that the effect of GZR or EBR on Nordette®-28 was evaluated in separate studies (8742-P013 and 5172-P046). There was no evidence of decreased plasma concentration of EE or LNG, which demonstrate a lack of interaction. Therefore, the effectiveness of oral contraceptives will be maintained when coadministered with GZR/EBR. The sponsor notes oral contraceptive use was allowed in the Phase II and III program.
RMP Evaluator comment: This is acceptable on the basis of the clinical experience with concomitant medications in the Phase II and III studies (see also the Clinical Evaluation Report).
TGA recommendation 1.5: The following Missing Information item would benefit from additional pharmacovigilance activities in the pharmacovigilance plan: Exposure in patients with HBV/HCV co-infection.
Sponsor's response: Following marketing, pharmacovigilance activities would include a comprehensive review of all patients with HBV/HCV co-infection. *Specifically, the reports would be reviewed individually and in aggregate for trends associated with reported adverse events in HBV/HCV co-infection patients that received Zepatier. The methodology would align with standard reviews of all past medical histories and current medical conditions; identification of those with co-infection with HBV and the adverse event safety profile*

Sponsor's response to Round 1 recommendations with RMP evaluator's comment
would be reviewed for any trends or potential signals.
RMP Evaluator comment: It is noted that the sponsor proposes routine pharmacovigilance activities to monitor patients with HBV/HCV co-infection and does not propose additional pharmacovigilance activities. The sponsor plans to monitor the safety of Zepatier via the Merck Adverse Event Reporting Worldwide Adverse Experience System (MARRS) database. This is acceptable. It is also noted that HBV co-infection is discussed in the proposed Product Information.
TGA recommendation 1.6: It is noted that the sponsor is already conducting or planning to conduct other activities relevant to the pharmacovigilance plan. These additional pharmacovigilance activities should be added to the pharmacovigilance plan.
Sponsor's response: The sponsor noted that the studies listed in Table 4 [not in this AusPAR] are not designed to address the safety concerns or measure the effectiveness of the risk minimization measures, therefore the sponsor respectfully disagrees with including the listed studies in the pharmacovigilance plan in the EU RMP. The sponsor has agreed to update the RMP if new safety findings are observed in these studies.
RMP Evaluator comment: The sponsor's response is noted.
TGA recommendation 1.7: Not all study protocols listed in the pharmacovigilance plan have been attached to the submission. The sponsor should provide the missing protocols, once available.
Sponsor's response: The sponsor states that the protocol for Study P017 'A Long Term Follow Up to Evaluate Durability of Virological Response of Subjects with HCV who have been Treated with MK-5172A in a Prior Trial' has been finalised. The protocol for Study P079 has not yet been finalised. This is a three part combined Phase I PK and Phase III clinical treatment study in paediatric subjects aged 3 to18 years with HCV infection. Once the protocol is available it can be provided to TGA on request.
RMP Evaluator comment: This is acceptable; the sponsor's commitment to submit the protocol when finalised has been noted.
TGA recommendation 1.8: The following studies seem to have been completed: MK-5172-062(C-EDGE CO-STAR); MK-5172-058; and MK-5172-065. The sponsor should use the findings of the above studies to further inform the content of the RMP and make appropriate changes to the RMP and the Product Information document (in particular with regard to adverse events).
Sponsor's response: The sponsor states that there have been no new safety concerns identified for EBR and GZR from the available data from MK-5172-062, MK-5172-058 and MK-5172-065 studies at this time. The sponsor agrees to make appropriate update to the RMP and Product Information upon completion of the final analysis of these data. The RMP will be updated if the studies identify any new safety signals, and the Product Information will be updated in the Clinical Trials and Adverse Events sections reflect the findings of Studies 062 and 065 in their totality.
RMP Evaluator comment: The sponsor's commitment to update the Product Information and RMP with these data is acceptable.
TGA recommendation 1.9: The sponsor should prepare educational materials for to specifically

Sponsor's response to Round 1 recommendations with RMP evaluator's comment
inform prescribers about this medicine, including the indicated HCV genotypes, the most relevant drug-drug interactions, and dosing regimens (including a reiteration of the risks associated with ribavirin). These materials could take the form of a brochure or a Dear Healthcare Professional Letter. The sponsor should make these materials available to the TGA prior to approval.
Sponsor's response: The sponsor states that a Dear Healthcare Professional Letter will be prepared to educate prescribers about this medicine including the indicated HCV genotypes, the most relevant drug-drug interactions, and dosing regimens (including a reiteration of the risks associated with ribavirin). In addition, all educational materials will follow the Australian Medicines Australia Code of Conduct, and so must reflect the content of the approved Product Information. The sponsor contends it would be premature to prepare these documents until the outcome of this application in known and an approved Product Information has been received.
RMP Evaluator comment: This is acceptable. The sponsor should submit these materials to the TGA for approval once they have been drafted, and also include them as an appendix to the ASA.
TGA recommendation 1.10: In the 'Indications' section, the indicated HCV genotypes should be clearly stated rather than solely making reference to the 'Clinical trials' section, which does not clearly indicate for which HCV genotypes Zepatier, is indicated. On this basis, and considering the clinical evaluator's advice, no change to the indications is considered necessary.
Sponsor's response: The sponsor agrees with the clinical evaluator's conclusion that the proposed Indication is appropriate, which refers to the Clinical Trials section for information regarding HCV-genotype-specific activity.
RMP Evaluator comment: The RMP evaluator notes that Harvoni and Viekira Pak specify in the indication they are used for the treatment of HCV Genotype 1, but Sovaldi and Daklinza, which are used to treat multiple genotypes refer to the Clinical Trials section for information regarding genotype. On this basis, and considering the clinical evaluator's advice, no change to the indications is considered necessary
TGA recommendation 1.11: In the 'Contraindications' section, the sponsor should consider including the same contraindications as in the current US FDA product label.
Sponsor's response: The sponsor states that the Australian Product Information now includes the same contraindications as the current FDA label.
RMP Evaluator comment: The changes are noted.
TGA recommendation 1.12: In the 'Precautions' or 'Interactions' section, the sponsor should include expected interactions of Zepatier, as found in the proposed SmPC document.
Sponsor's response: The sponsor states the US format has been adopted over the EU format as this most closely matches the Australian Product Information format, wherein PK data appear in Pharmacology section and clinically meaningful interactions are described in Interactions with Other Medicines in Table 9. The sponsor contends the US/Australian format is concise and easier to read for the end user.
RMP Evaluator comment: The EU table is lengthy and provides information about drugs where dose adjustment is not necessary as well as contraindications. The US version is shorter. However, the table does not include the drugs which are contraindicated such as rifampicin,

Sponsor's response to Round 1 recommendations with RMP evaluator's comment
carbamazepine, phenytoin or ritonavir- these are listed under Contraindications. The US Label has a table which list the drugs which are contraindicated with Zepatier which could be useful, under Contraindications. In addition the US Prescriber Information lists tacrolimus with a drug interaction but the European Summary of Product Characteristics (EU SmPC) (version in Annex 2) does not (no dose adjustment required). The sponsor should: (i) include the CYP3A4 inducers which are contraindicated in Table 9 of the Product Information and (ii) include a table of contraindicated medicines under the ' Contraindications' section of the Product Information, similar to that provided in the US Prescriber Information.
TGA recommendation 1.13: In the 'Precautions' section or in another relevant section, the sponsor should include a statement on management of patients with baseline NS5A polymorphisms.
Sponsor's response: The sponsor states that the prevalence and impact of baseline NS5A polymorphisms on treatment response is addressed in the Microbiology section of the Product Information.
RMP Evaluator comment: This is acceptable as the information is co-located with information on other genetic variants of HCV.
TGA recommendation 1.14: In the 'Precautions' section, the sponsor should provide numerical values of the increase in plasma concentrations in subjects over 65 years of age.
Sponsor's response: Numerical values of the increase in plasma concentration in subjects over 65 years of age are stated in the Pharmacokinetics section of the Product Information. The sponsor noted that there is no requirement for dose adjustment in this population and therefore does not need to be included under Precautions.
RMP Evaluator comment: This is acceptable and the section appropriate.
TGA recommendation 1.15: In the 'Precautions' section, the sponsor should provide numerical values of the increase in plasma concentrations in Asian patients.
Sponsor's response: Numerical values of the increase in plasma concentration in Asian patients are stated in the Pharmacokinetics section of the Product Information. The sponsor noted that there is no requirement for dose adjustment in this population and therefore does not need to be included under Precautions.
RMP Evaluator comment: This is acceptable.
TGA recommendation 1.16: In the 'Precautions' section, the Product Information should include a statement on the potential for ALT/AST elevation in Asian patients.
Sponsor's response: The sponsor has added a statement on the potential for ALT/AST elevation in Asian patients in the Precautions section of the Product Information as follows: ' Higher rates of late ALT elevations occurred in females (2% [11/652]), Asians (2% [4/165]), and subjects aged ≥65 years (2% [3/187])'
RMP Evaluator comment: This is acceptable as the risk of ALT elevation is clearly communicated.
TGA recommendation 1.17: In the 'Adverse events 'section, the Product Information should

Sponsor's response to Round 1 recommendations with RMP evaluator's comment
contain pooled information on adverse events from all relevant studies.
Sponsor's response: The sponsor states that the current presentation of the adverse reaction data in the Product Information is the most informative because it represents the adverse reactions observed in clinical trials that correspond to the proposed posology, and is based on the populations and dosing regimens studied. Two placebo-controlled trials providing insights on the safety profile of Zepatier, one in the treatment naïve population (C-EDGE TN) and the other in the advanced chronic kidney disease population (C-SURFER). The adverse reaction data are presented separately in the Product Information because these studies were conducted in different populations and with different dosing regimens. Table 10 presents adverse reaction data in C-EDGE TN and the pooled data for Zepatier alone for 12 weeks.
RMP Evaluator comment: The sponsor's response appears reasonable. The sponsor should note that the clinical Delegate determines the adequacy of Product Information statements.
TGA recommendation 1.18: In the 'Adverse Events' section, the Product Information should additionally present pooled adverse events in a table that allows easy visualization of the adverse events according to body system and frequency.
Sponsor's response: The sponsor believes Adverse Events section of the Product Information clearly describes the effect of placebo controlled trials for the reasons provided in Response 1.17.
RMP Evaluator comment: See response above (to TGA recommendation 1.17)
TGA recommendation 1.19: In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicines information (CMI) document be revised to accommodate the changes made to the product information document.
Sponsor's response: The CMI has been revised to reflect changes proposed in the clinical evaluation. The CMI may be revised further to accommodate changes made to the Product Information document following the recommendations of the Delegate's Overview and Pre-ACPM Response.
RMP Evaluator comment: This is acceptable and the sponsor's commitment to further update the CMI to reflect any Product Information changes is noted.

Summary of recommendations

It is considered that the sponsor's response to the TGA request for further information has not adequately addressed all of the issues identified in the RMP evaluation report. There are outstanding recommendations (see below)

Outstanding issues

Issues in relation to the RMP

The sponsor has committed to submitting a revised ASA in the pre-ACPM response. Revision of the ASA should address the recommendations made below.

The following outstanding issues should be addressed:

TGA recommendation 1.2: Missing information regarding 'long term safety' and 'safety data in the Australian Indigenous population' should be added to the

revised ASA. Adequate pharmacovigilance and/or risk minimisation activities should also be included in the ASA.

TGA recommendation 1.9: The draft educational materials should be submitted to the TGA when they become available, and should also be included in the revised ASA as an appendix.

TGA recommendation 1.12: Table 9 of the draft Product Information should include interactions with the CYP3A4 inducers listed in the contraindications section of the Product Information. In addition, a table similar to that used in the US Prescriber Information which lists medicines that are contraindicated with Zepatier should be included in the contraindications section of the Australian Product Information (noting any relevant modifications for the Australian context should be made).

In addition, it is noted that the sponsor has made the following commitments in their response:

- Submit a revised ASA in the pre-ACPM response.
- Submit the protocol for Study P017 when it becomes available.
- Update the Product Information and RMP with data from Studies MK-5172-062, MK-5172-058 and MK-5172-065 once the CSR has been finalised.
- Update the CMI to reflect any changes made to the Product Information.

Key changes to the updated RMP

In response to the TGA the sponsor provided an updated RMP (version 1.2, 28 February 2016). Key changes from the version evaluated at Round 1 (version 1.0) are summarised below in Table 12.

Table 12: Summary of key changes between the EU RMP version 1.0 and the EU RMP version1.2

Key changes	
Safety specification	Under Important Identified Risks: HIV protease inhibitors has been replaced with strong OATP1B inhibitors Addition of: Drug Interactions with Fixed Dose Combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate or alafenamide. Removal of Drug Interaction with St John's wort (is included under strong CYP3A inducers) Inclusion of strong inducers of CYP3A as well as moderate. Addition of Drug Interaction with tacrolimus
Pharmacovigilance activities	No additional activities
Risk minimisation activities	Changes to the wording for in the SmPC for the following risks: ALT elevations under Special warnings and precautions for use. Drug Resistance Development Addition of Strong CYP3A inducers Additional wording on contraindication and OATP1B inhibitors

Key changes	
	Change from Drug Interactions with *HIV protease inhibitors* to *Strong OATP1B inhibitors* Drug Interaction with atorvastatin, rosuvastatin, lovastatin, simvastatin, fluvastatin Paediatrics Pregnancy and lactation Liver transplant Exposure in HBV/HCV co-infection Additional risk management plan for: Drug Interactions with Fixed Dose Combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate or alafenamide. Drug Interactions with tacrolimus Exposure in HCV-infected patients with moderate or severe (Child-Pugh B or C) hepatic insufficiency Removal of risk management plan for St John's wort (included under strong CYP3A inducers)
ASA	No update has been provided.

The evaluator has no objection to the above changes as they strengthen the clarity of the summary of safety concerns. It is noted that the sponsor has committed to providing an updated ASA in the pre-ACPM response. The revised version of the ASA should reflect the changes made to the EU-RMP.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise. The suggested wording for the condition of registration will be provided once the revised ASA has been submitted and subsequently evaluated.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There are no pharmaceutical chemistry objections to approval. Finalisation of the submission will be subject to resolution of the outstanding GMP matters and availability of clearance. The submission was not referred to Pharmaceutical Sub Committee (PSC).

Nonclinical

There are no objections to the registration of Zepatier from the nonclinical evaluators. Recommendations for the Product Information have been provided.

Clinical

An extensive clinical development program was undertaken. For details, please refer to the Extract from the clinical evaluation report (CER; Attachment 2).

Pharmacodynamics

Please see CER.

Pharmacokinetics

The data are based on 59 clinical pharmacology studies, including 25 drug-drug interaction studies, in a total of 1240 healthy volunteers, 139 HCV patients, and 66 non-HCV patients with hepatic or renal impairment.

Both GZR and EBR are metabolised by hepatic CYP3A enzyme. The main route of excretion for both drugs is faecal, as parent compounds and as oxidative metabolites. No circulating metabolites of GZR or EBR were detected in human plasma (radiolabelled; Studies 5172-P007 and 8742-P014). The amount of drug excreted in urine is negligible.

Both GZR and EBR are substrates of P-gp. GZR is also a substrate of liver uptake transporters OATP1B1 and OATP1B3. EBR is not a substrate of OATP1B1 or OATP1B3.

GZR has some potential to inhibit CYP3A at the intestinal but not at systemic level. GZR is not anticipated to inhibit any other major CYP enzymes or UGT1A1, carboxylesterase 1 or 2 (CES1 and CES2) or cathepsin A (CatA) and is also unlikely to inhibit most transporters. GZR does not exhibit induction potential for CYP3A4, 1A2 or 2B6.

EBR is not anticipated to inhibit any major CYP enzyme or UGT1A1, CES1, CES2 or CatA. It has some potential to inhibit intestinal P-gp and BCRP and hepatic OATP1B3. EBR does not exhibit induction potential for CYP3A4, CYP1A2 or CYP2B6.

GZR is extensively protein bound (98.8%) in plasma with unbound fraction of 0.012. It does not preferentially distribute to red blood cells (RBCs) (blood to plasma ratio 0.7). EBR is highly protein bound (>99.9%) in plasma with unbound fraction <0.001. It does not preferentially distribute to RBCs (blood to plasma ratio 0.6).

GZR is absorbed with a median peak time to C_{max} (T_{max}) of approximately 2 hours and has an estimated oral Bioavailability (F) of 10 to 40% at 25 mg and 200 mg doses. This could not be determined reliably in the Study 5172-P040. Based on GZR radiolabelled Absorption distribution Metabolism Excretion (ADME) study (Study 5172-P007) the fraction absorbed of GZR is at least 22%.

In the GZR single and multiple ascending dose study (5172-P001), median T_{max} was 2 to 4 hours. The apparent terminal $t_{½}$ ranged from 16.6-42.9 hours after single dose and 16.9-24.7 hours after multiple doses. The GZR AUC_{0-24} increased in a greater than dose proportional manner in the 100 to 1000 mg range. Steady state was generally achieved within 8 days of GZR dosing, with accumulation ratio of 1.5 to 3.5 across doses.

In HCV patients (Study 5172-P004), GZR was absorbed with a median T_{max} of 2 to 4 hours and had mean apparent terminal $t_{½}$ of approximately 25 to 45 hours. GZR exposure increased in a greater than dose-proportional manner across 10 to 800 mg dose range. Steady-state was achieved by approximately5 days. There was accumulation over the 7 days following once daily dosing with accumulation ratio of 2.3 to 4.0 across the tested

dose range. GZR exposure is approximately2 fold higher in HCV patients than in healthy subjects.

EBR is absorbed with a median T_{max} of approximately 3 hours. The estimated PK parameters are absolute Bioavailability (32.4%), Clearance (5.78 L/h), Volume of distribution at steady-state (121 L) and terminal $t_{½}$ (17.15 hours) with the 50 mg dose (study 8742-P020).

EBR has linear and dose proportional pharmacokinetics in the 5 to 100 mg dose range (Study 8742-P001). The mean terminal $t_{½}$ ranged from 14.5 to 19.9 hours after single-dose and 18.8 to 20.6 hours following multiple doses. EBR steady-state is reached within 2 days in healthy subjects at doses of 10-200 mg daily dosing.

In HIV patients (Study 8742-P002), following multiple doses, EBR has a median T_{max} of 2 to 4 hours and mean terminal $t_{½}$ of approximately 20 to 24 hours. EBR exposure increased in an approximately dose-proportional manner over the dose range 5 to 50 mg. Steady-state was achieved by approximately2 to 5 days, with accumulation ratio of 1.5 to 1.9. EBR exposure in HCV patients is similar to that in healthy subjects.

Population pharmacokinetics

The effect of various covariates, on estimate of GZR Clearance (L/h) is shown in Table 13 below.

Table 13: Key GZR population PK parameter values and covariate effects for representative populations

PK Parameters and Baseline Covariates		Baseline Covariate Value	Estimate	Change from Typical (%)	Inter-individual Variability (%)
Typical CL/F, L/hr (100 mg dose, Trt Naïve, White Non-Hispanic Male, HCV GT1a, 50 years old, Weight = 75 kg, eGFR=95 mL/min/1.73 m^2)			**85**	--	**42.1**
Dose	25 mg		186	119	--
	400 mg		39	-54	--
Hepatic Function	Non-cirrhotic, Metavir F3		68	-20	--
	Compensated Cirrhosis (CP-A)		51	-39	--
	Cirrhosis, CP-B		19	-77	--
HCV GT	GT6		107	27	--
Age	5th Percentile	30 years	121	43	--
	95th Percentile	67 years	69	-19	--
Weight	5th Percentile	53 kg	74	-12	--
	95th Percentile	107 kg	97	14	--
Sex	Female		65	-24	--
Race	Black		97	15	--
	Asian		56	-34	--
	Other		109	29	--
Ethnicity	Hispanic		69	-17	--
Use of Peg-IFN			48	-43	--

The effect of various covariates, on estimate of EBR Clearance (L/h) is shown in Table 14 below.

Table 14: Key EBR population PK parameter values and covariate effects

PK Parameters and Baseline Covariates		Baseline Covariate Value	Estimate	Change from Typical (%)	Inter-individual Variability (%)
Typical CL/F, L/hr (Trt Naïve, White Non-Hispanic Male, eGFR=95 mL/min/1.73 m2)			**30.2**	--	**13.4**
Age	5th Percentile	32 years	33.1	9.7	--
	95th Percentile	68 years	29.1	-3.6	--
eGFR	Severe RI	17 mL/min/1.73 m2	25.9	-14.4	--
	Moderate RI	45 mL/min/1.73 m2	28.2	-6.5	--
	Mild RI	75 mL/min/1.73 m2	29.6	-2.1	--
Sex	Female		20.6	-31.8	--
Race	Black		27.8	-8.0	--
	Asian		26.3	-12.9	--
Ethnicity	Hispanic		27.5	-8.8	--
Prior Treatment	Treatment Experienced with Peg-IFN/RBV		28.6	-5.2	--
Use of RBV			33.1	9.6	--
Use of Moderate CYP/Pgp Inhibitors			25.1	-16.9	--
Use of Methadone			23.5	-22.3	--

GZR/EBR interaction

Study 8742-P008 demonstrated lack of GZR/EBR interaction with EBR AUC_{0-24} of 1.01 [90%CI 0.83, 1.24] for EBR+GZR/EBR comparison and GZR AUC_{0-24} of 0.90 [90%CI 0.63, 1.28] for GZR+EBR/GZR comparison.

There was also no evidence of clinically relevant interaction using the FDC formulation (GZR/EBR 100/50) compared to GZR100 mg+EBR 50 mg free combination in a single dose study (GZR AUC_{0-inf} 0.94 [90%CI 0.84, 1.07], GZR C_{max} 0.94 [90%CI 0.78, 1.12]; EBR AUC_{0-inf} 1.15 [90%CI 1.04, 1.26], EBR C_{max} 1.18 [90%CI 1.05, 1.33]).

Food effect

The food study (5172-P069) using the FDC tablet (100 mg/50 mg) in healthy volunteers showed increased GZR exposure (AUC and C_{max} by 1.54 and 2.83 fold respectively) and decreased EBR (AUC and C_{max} by 11% & 15% respectively).

Drug-drug interactions (DDIs)

AUC bounds of (0.4, 5.0) for GZR and, (0.5, 2.0) for EBR were designated by the sponsor as clinically tolerable limits for GZR/EBR (100/50 mg daily) exposure in the presence of various intrinsic and extrinsic factors that affecting bioavailability including drug interactions. A range of DDI studies were carried out for which please see CER.

The directions for use have been detailed in the draft Product Information under Contraindications and Precautions (Interaction with other medicines) sections and are consistent with the supplied data.

Coadministration of GZR/EBR with strong and moderate CYP3A inducers or P-gp inducers decreases GZR and EBR exposure and is contraindicated/not recommended.

Coadministration of GZR/EBR with strong CYP3A inhibitors or P-gp inhibitors increases GZR and EBR exposures but the increases are not considered clinically relevant.

Coadministration of GZR/EBR with drugs that inhibit organic anion transporting polypeptide 1B (OATP1B inhibitors) such as atazanavir, darunavir, lopinavir, saquinavir, tipranavir, or cyclosporine, is contraindicated due to the expected significant increase in GZR exposure and consequent risk of hepatotoxicity. Coadministration with rifampicin is also contraindicated.

Clinical efficacy

All efficacy studies were in adult patients.

Dose selection was examined in three Phase II studies (P003, P038 & 035). The totality of evidence supported the proposed clinical testing of GZR/EBR (100/50) once daily dosing.

Study P003: This was a randomised, double blind, dose ranging study of GZR in treatment-naïve (TN), GT-1, non-cirrhotic patients. A cirrhotic group was subsequently added. Boceprevir (800 mg three times a day (TD)) was used as comparator to GZR (100, 200, 400, 800 mg daily) in a 12 weeks treatment trial. All groups received peginterferon/ribavirin (P/R) response guided therapy (RGT). The patients were randomised into 8 treatment groups (as shown in Table 15 below).

Table 15: Patient treatment groups and patient numbers

	TN Cirr: MK-5172 100 mg qd + Peg-IFN + RBV		TN Non-cirr: MK-5172 100 mg qd + Peg-IFN + RBV		TN Non-cirr: MK-5172 200 mg qd + Peg-IFN + RBV		TN Non-cirr: MK-5172 400 mg qd + Peg-IFN + RBV		TN Non-cirr: MK-5172 800 mg qd + Peg-IFN + RBV	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	36		66		68		24		29	
HCV Genotype										
1a	32	(88.9)	43	(65.2)	41	(60.3)	10	(41.7)	15	(51.7)
1b	4	(11.1)	23	(34.8)	27	(39.7)	13	(54.2)	14	(48.3)
1-Other	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)

	TN Non-cirr: MK-5172 400 mg Down-Dosed to 100 mg qd + Peg-IFN + RBV		TN Non-cirr: MK-5172 800 mg Down-Dosed to 100 mg qd + Peg-IFN + RBV		TN Non-cirr: Boceprevir 800 mg tid + Peg-IFN + RBV		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	43		36		66		368	
HCV Genotype								
1a	27	(62.8)	22	(61.1)	43	(65.2)	233	(63.3)
1b	15	(34.9)	14	(38.9)	23	(34.8)	133	(36.1)
1-Other	1	(2.3)	0	(0.0)	0	(0.0)	2	(0.5)

SVR12 response[8] rates were as shown in Table 16 and showed that 100 mg daily GZR was the highest suitable dose (safety outcome were indicative of increasing incidence and severity of ALT/AST/hepatic effects with the 200 mg dose and above).

Table 16: SVR12 response rates

Treatment	N	n (%)	95% Confidence Interval[†]
TN Cirr: MK-5172 100 mg qd + Peg-IFN + RBV	36	26 (72.2)	(54.8, 85.8)
TN Non-cirr: MK-5172 100 mg qd + Peg-IFN + RBV	66	59 (89.4)	(79.4, 95.6)
TN Non-cirr: MK-5172 200 mg qd + Peg-IFN + RBV	68	62 (91.2)	(81.8, 96.7)
TN Non-cirr: MK-5172 400 mg qd + Peg-IFN + RBV	24	21 (87.5)	(67.6, 97.3)
TN Non-cirr: MK-5172 800 mg qd + Peg-IFN + RBV	29	23 (79.3)	(60.3, 92.0)
TN Non-cirr: MK-5172 400 mg Down-Dosed to 100 mg qd + Peg-IF	43	40 (93.0)	(80.9, 98.5)
TN Non-cirr: MK-5172 800 mg Down-Dosed to 100 mg qd + Peg-IF	36	33 (91.7)	(77.5, 98.2)
TN Non-cirr: Boceprevir 800 mg tid + Peg-IFN + RBV	66	40 (60.6)	(47.8, 72.4)

[†]Based on Clopper-Pearson method.
N = Number of subjects included in the analysis.
n (%) = Number of subjects with undetectable (TND) HCV RNA at the 12 Week Follow-Up visit and the percentage calculated as (n/N)*100.

Study P038: This was a randomised, double blind, dose ranging study of GZR (25, 50 or 100 mg daily) with P/R by RGT, in treatment-naïve, GT-1, non-cirrhotic patients for 12 weeks. The patients were randomised into the treatment groups shown in Table 17.

[8] Plasma HCV RNA <25 IU/mL at 12 weeks after the end of study treatment, after becoming undetectable at the end of treatment, indicative of sustained response.

Table 17: Treatment groups

	MK-5172 25 mg + Peg-IFN + RBV for 12 Weeks		MK-5172 50 mg + Peg-IFN + RBV for 12 Weeks		MK-5172 100 mg + Peg-IFN + RBV for 12 Weeks		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	29		28		30		87	
HCV Genotype								
1a	24	(82.8)	25	(89.3)	22	(73.3)	71	(81.6)
1b	4	(13.8)	3	(10.7)	8	(26.7)	15	(17.2)
1	1	(3.4)	0	(0.0)	0	(0.0)	1	(1.1)

SVR12 response rates were indicative of similar effect with the 50 mg and 100 mg GZR dose administered with P/R.

Table 18: SVR12 response rates

Treatment	N	m	n (%)	95% Confidence Interval[†]
MK-5172 25 mg + Peg-IFN + RBV for 12 Weeks	24	24	13 (54.2)	(32.8, 74.4)
MK-5172 50 mg + Peg-IFN + RBV for 12 Weeks	25	25	21 (84.0)	(63.9, 95.5)
MK-5172 100 mg + Peg-IFN + RBV for 12 Weeks	26	26	23 (88.5)	(69.8, 97.6)

[†]Based on Clopper-Pearson method.
N = Number of subjects included in the analysis.
m = Number of subjects with an HCV RNA result at the Follow-Up Week 12 visit.
n (%) = Number of subjects with undetectable (TND) or unquantifiable (TD(u)) HCV RNA at the Follow-Up Week 12 visit and the percentage calculated as (n/N)*100.

Study P035 (C-WORTHY): This was the pivotal dose selection study with combined GZR+EBR administration and was conducted in 4 groups with diverse patient populations (Table 19).

Table 19: Treatment groups

Group A Randomised, Double Blind, Treatment Naïve (TN), GT1, Noncirrhotic patients.	Group B Open label, TN or Previous Null Responders (NR), GT1, ±Cirrhosis, ±HIV patients.
Group C Open label, Treatment Naïve, GT-1b, Noncirrhotic patients.	Group D Open label, Treatment Naïve, GT-3, Noncirrhotic patients.

Within each group, the respective patients were randomised resulting in total of 20 treatment groups (A1 to A3, B1 to B13, C1 to C2 and D1 to D2) involving treatment with GZR (100 mg based on the previous studies) and EBR (20 mg or 50 mg) with or without RBV for a duration of 8, 12 or 18 weeks. The SVR12 response rates were reported as shown in Table 20.

Table 20A: SVR12 response rates

Treatment	N	n (%)	95% Confidence Interval[†]
A1: TN NC: MK-5172 100 mg + MK-8742 20 mg + RBV for 12 Weeks	22	22 (100.0)	(84.6, 100.0)
A2: TN NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	24	23 (95.8)	(78.9, 99.9)
A3: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	12	12 (100.0)	(73.5, 100.0)
B1: TN NC/GT1a: MK-5172 100 mg + MK-8742 50 mg + RBV for 8 Weeks	29	24 (82.8)	(64.2, 94.2)
B2: TN NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	29	29 (100.0)	(88.1, 100.0)
B3: TN NC/GT1a: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	31	30 (96.8)	(83.3, 99.9)
B4: TN C: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	30	27 (90.0)	(73.5, 97.9)
B5: TN C: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	29	28 (96.6)	(82.2, 99.9)
B6: TN C: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks	31	31 (100.0)	(88.8, 100.0)
B7: TN C: MK-5172 100 mg + MK-8742 50 mg for 18 Weeks	31	29 (93.5)	(78.6, 99.2)
B8: NR: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	30	30 (100.0)	(88.4, 100.0)
B9: NR: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	33	30 (90.9)	(75.7, 98.1)
B10: NR: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks	33	33 (100.0)	(89.4, 100.0)
B11: NR: MK-5172 100 mg + MK-8742 50 mg for 18 Weeks	32	31 (96.9)	(83.8, 99.9)
B12: TN HIV NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	29	28 (96.6)	(82.2, 99.9)
B13: TN HIV NC: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	28	26 (92.9)	(76.5, 99.1)
C1: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg + RBV for 8 Weeks	29	27 (93.1)	(77.2, 99.2)
C2: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg for 8 Weeks	31	29 (93.5)	(78.6, 99.2)

Table 20B: SVR12 response rates in GT-3 patients:

D1: TN NC/GT3: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	19	9 (47.4)	(24.4, 71.1)
D2: TN NC/GT3: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks	18	11 (61.1)	(35.7, 82.7)

[†]Based on Clopper-Pearson method.
N = Number of subjects included in the analysis.
n (%) = Number of subjects with undetectable (TND) or unquantifiable (TD(u)) HCV RNA at the Follow-Up Week 12 visit and the percentage calculated as (n/N)*100.

The study provided substantive evidence for dose selecting GZR/EBR (100/50 daily for 12 weeks without RBV) for subsequent testing in Phase III studies in the primary population of TN, GT-1 patients. Clinically usefully information on shorter treatment in GT-1b patients and in treatment-experienced patients was also obtained.

Suboptimal response with GZR/EBR plus P/R was clearly demonstrated in the treatment of GT-3 patients consistent with the known lower in vitro antiviral activity of GZR and EBR against GT-3.

Study P047 (C-SCAPE): This was an additional Phase II study in TN, non-cirrhotic patients with less common Genotypes 2, 4, 5 and 6 for treatment with GZR 100 mg daily with or without EBR 50 mg daily and with or without RBV for 12 weeks. The patients were randomised into treatment groups as shown in Table 21.

Table 21: Randomised treatment groups

	GT2: MK-5172 100 mg + MK-8742 50 mg + RBV (Arm A1)		GT2: MK-5172 100 mg + RBV (Arm B1)		GT4,5,6: MK-5172 100 mg + MK-8742 50 mg + RBV (Arm B2)		GT4,5,6: MK-5172 100 mg + MK-8742 50 mg (Arm B3)		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	30		30		19		19		98	
HCV Genotype (Variant)										
1	0	(0.0)	4	(13.3)	1	(5.3)	1	(5.3)	6	(6.1)
2(31L/M)[†]	1	(3.3)	1	(3.3)	0	(0.0)	0	(0.0)	2	(2.0)
2(31M)	15	(50.0)	12	(40.0)	0	(0.0)	0	(0.0)	27	(27.6)
2(31L)	14	(46.7)	11	(36.7)	0	(0.0)	0	(0.0)	25	(25.5)
2(unknown)	0	(0.0)	2	(6.7)	0	(0.0)	0	(0.0)	2	(2.0)
4	0	(0.0)	0	(0.0)	10	(52.6)	10	(52.6)	20	(20.4)
5	0	(0.0)	0	(0.0)	4	(21.1)	4	(21.1)	8	(8.2)
6	0	(0.0)	0	(0.0)	4	(21.1)	4	(21.1)	8	(8.2)

SVR12 response rates were reported as in Table 22 below.

Table 22: SVR12 response rates

Treatment	N	n (%)	95% Confidence Interval[†]
GT2: MK-5172 100 mg + MK-8742 50 mg + RBV (Arm A1)	30	24 (80.0)	(61.4, 92.3)
GT2: MK-5172 100 mg + RBV (Arm B1)	30	20 (66.7)	(47.2, 82.7)
GT4,5,6: MK-5172 100 mg + MK-8742 50 mg + RBV (Arm B2)	19	18 (94.7)	(74.0, 99.9)
GT4: MK-5172 100 mg + MK-8742 50 mg + RBV (Arm B2)	10	10 (100.0)	(69.2, 100.0)
GT5: MK-5172 100 mg + MK-8742 50 mg + RBV (Arm B2)	4	4 (100.0)	(39.8, 100.0)
GT6: MK-5172 100 mg + MK-8742 50 mg + RBV (Arm B2)	4	3 (75.0)	(19.4, 99.4)
Other: MK-5172 100 mg + MK-8742 50 mg + RBV (Arm B2)[‡]	1	1 (100.0)	(2.5, 100.0)
GT4,5,6: MK-5172 100 mg + MK-8742 50 mg (Arm B3)	19	14 (73.7)	(48.8, 90.9)
GT4: MK-5172 100 mg + MK-8742 50 mg (Arm B3)	10	9 (90.0)	(55.5, 99.7)
GT5: MK-5172 100 mg + MK-8742 50 mg (Arm B3)	4	1 (25.0)	(0.6, 80.6)
GT6: MK-5172 100 mg + MK-8742 50 mg (Arm B3)	4	3 (75.0)	(19.4, 99.4)
Other: MK-5172 100 mg + MK-8742 50 mg (Arm B3)[‡]	1	1 (100.0)	(2.5, 100.0)

[†]Based on Clopper-Pearson method.
[‡]Six subjects (4 in Arm B1, 1 in Arm B2 and 1 in arm B3) were identified as GT1 subjects post-randomization. They were included in FAS analysis and excluded from PP analysis.
N = Number of subjects included in the analysis.
n (%) = Number of subjects with undetectable (TND) or unquantifiable (TD(u)) HCV RNA at the Follow-Up Week 12 visit and the percentage calculated as (n/N)*100.

Based on the results in this trial a decision was taken to pick HCV GT 4 & 6 patients for inclusion in Phase III trials along with the primary population of GT-1 patients. The patients with GT-2 and GT-5 infection were not included in subsequent pivotal efficacy trials.

Pivotal efficacy studies

Study 060 (C-EDGE-TN): This was a Phase III randomised, double blind, study in treatment-naïve (TN), HCV GT-1, 4 or 6 patients with or without cirrhosis for treatment with GZR/EBR (100/50 mg daily without RBV) for 12 weeks (Immediate and Deferred Treatment Arms). The trial provides pivotal efficacy data in TN patients with HCV GT 1, 4 and 6 infection. The patients were randomised to the treatment groups as described below (Table 23).

Table 23: Treatment groups

	Immediate treatment arm: GZR/EBR for 12 Weeks		Deferred treatment arm: GZR Placebo/EBR Placebo for 12 Weeks		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	316		105		421	
HCV Genotype						
1a	157	(49.7)	54	(51.4)	211	(50.1)
1b	131	(41.5)	40	(38.1)	171	(40.6)
4	18	(5.7)	8	(7.6)	26	(6.2)
6	10	(3.2)	3	(2.9)	13	(3.1)

SVR12 response rates were reported in the Immediate Treatment Arm and shown in Table 24 below (Full Analysis Set).

Table 24: SVR12 response rates

Treatment	N	n (%)	95% Confidence Interval[†]	p-Value[‡]
Immediate treatment arm: GZR/EBR for 12 Weeks	316	299 (94.6)	(91.5, 96.8)	<.001

[†]Based on Clopper-Pearson method.
[‡]Based on a one-sided exact test for a binomial proportion. A one-sided p-value<0.025 supports a conclusion that the true SVR12 is >73%.
N = Number of subjects included in the analysis.
n (%) = Number of subjects who achieved SVR12 and the percentage calculated as (n/N)*100.
LLoQ is 15 IU/mL.

SVR12 response was generally consistent across various subgroups.

Study 068 (C-EDGE-TE): This was a Phase III randomised, open-label trial in treatment-experienced (TE), HCV GT 1, 4 or 6 patients with prior treatment failure on P/R, for treatment with GZR/EBR (100/50 mg daily with or without RBV) for 12 or 16 weeks. The patients could be with or without cirrhosis and with or without HIV co-infection. The randomisation was stratified by baseline cirrhosis and prior P/R treatment response (relapse or partial or null responders). The trial provides pivotal efficacy data in TE patients with HCV GT 1, 4 and 6 infection. The patients were randomised to the treatment groups Table 25.

Table 25: treatment groups

	GZR/EBR for 12 Weeks		GZR/EBR + RBV for 12 Weeks		GZR/EBR for 16 Weeks		GZR/EBR + RBV for 16 Weeks		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
HCV Genotype										
1a	61	(58.1)	60	(57.7)	48	(45.7)	58	(54.7)	227	(54.0)
1b	34	(32.4)	29	(27.9)	48	(45.7)	36	(34.0)	147	(35.0)
1-other	1	(1.0)	0	(0.0)	0	(0.0)	2	(1.9)	3	(0.7)
4	9	(8.6)	15	(14.4)	5	(4.8)	8	(7.5)	37	(8.8)
6	0	(0.0)	0	(0.0)	4	(3.8)	2	(1.9)	6	(1.4)

SVR12 response rates were as shown in Table 26 (Full Analysis Set).

Table 26: SVR12 response rates

Treatment	N	n (%)	95% Confidence Interval[†]	p-Value[‡]
GZR/EBR for 12 Weeks	105	97 (92.4)	(85.5, 96.7)	<.001
GZR/EBR + RBV for 12 Weeks	104	98 (94.2)	(87.9, 97.9)	<.001
GZR/EBR for 16 Weeks	105	97 (92.4)	(85.5, 96.7)	<.001
GZR/EBR + RBV for 16 Weeks	106	103 (97.2)	(92.0, 99.4)	<.001

[†]Based on Clopper-Pearson method.
[‡]Based on a one-sided Exact Test for a binomial proportion. A one-sided p-value<0.0125 supports a conclusion that the true SVR_{12} is >58%.
N = Number of subjects included in the analysis.
n (%) = Number of subjects who achieved SVR_{12} and the percentage calculated as (n/N)*100.

SVR12 response was generally consistent across various subgroups.

Study 061 (C-EDGE COINFXN): This was a Phase III, open-label, single arm, trial in TN patients with HCV GT 1, 4 or 6 patients with or without cirrhosis, for treatment with GZR/EBR (100/50 mg daily without RBV) for 12 weeks. All patients had HIV co-infection.

A total of 218 patients were distributed across various genotypes as shown in Table 27.

Table 27: Patient distribution across genotypes

	GZR/EBR for 12 Weeks	
	n	(%)
Subjects in population	218	
HCV Genotype		
1a	144	(66.1)
1b	44	(20.2)
1-other	1	(0.5)
4	28	(12.8)
6	1	(0.5)

SVR12 response rates are shown in Table 28 (Full Analysis Set).

Table 28: SVR12 response rates

Treatment	N	n (%)	95% Confidence Interval[†]	p-Value[‡]
GZR/EBR for 12 Weeks	218	207 (95.0)	(91.2, 97.5)	<.001

[†]Based on Clopper-Pearson method.

[‡]Based on a one-sided exact test for a binomial proportion. A one-sided p-value<0.025 supports a conclusion that the true SVR_{12} is >70%.

N = Number of subjects included in the analysis.

n (%) = Number of subjects who achieved SVR_{12} and the percentage calculated as (n/N)*100.

LLoQ is 15 IU/mL.

SVR12 response by Genotype is shown in Table 29.

Table 29: SVR12 response rates by genotype

	GZR/EBR for 12 Weeks		
	N	n (%)	95% Confidence Interval[†]
Genotype			
1a	144	136 (94.4)	(89.3, 97.6)
1b	44	42 (95.5)	(84.5, 99.4)
1-other	1	1 (100.0)	(2.5, 100.0)
4	28	27 (96.4)	(81.7, 99.9)
6	1	1 (100.0)	(2.5, 100.0)

SVR12 response was consistent across various other subgroups.

Study 052 (C-SURFER): This was a Phase II/III, randomised, double blind study in TN and TE HCV GT-1 patients with or without cirrhosis who had chronic kidney disease (CKD) Stage 4 or 5, including patients on Haemodialysis (HD). At baseline, a total of 35% and 41% patients had diabetes mellitus and cardiovascular disease respectively. The treatment regimen was GZR/EBR (100/50 mg daily without RBV) for 12 weeks. The patients were randomised into treatment groups as shown in Table 30.

Table 30: Treatment groups

	Intensive PK arm: GZR 100mg + EBR 50mg for 12 Weeks		Immediate treatment arm: GZR 100mg + EBR 50mg for 12 Weeks		Deferred treatment arm: GZR Placebo + EBR Placebo for 12 Weeks		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	11		111		113		235	
HCV Genotype								
1a	10	(90.9)	53	(47.7)	59	(52.2)	122	(51.9)
1b	1	(9.1)	58	(52.3)	53	(46.9)	112	(47.7)
1-other	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.4)
Dialysis status								
On Dialysis	6	(54.5)	86	(77.5)	87	(77.0)	179	(76.2)
Not On Dialysis	5	(45.5)	25	(22.5)	26	(23.0)	56	(23.8)
CKD stages								
Stage 4	4	(36.4)	18	(16.2)	22	(19.5)	44	(18.7)
Stage 5	7	(63.6)	93	(83.8)	91	(80.5)	191	(81.3)

SVR12 response rate in the Immediate and Intensive PK group was reported as shown in Table 31.

Table 31: SVR12 response rates

Treatment Arm	N	n (%)	95% Confidence Interval†	p-Value‡
Immediate + Intensive PK arms: GZR 100mg + EBR 50mg for 12 Weeks	116	115 (99.1)	(95.3, 100.0)	<.001

†Based on Clopper-Pearson method.
‡Based on a one-sided exact test for a binomial proportion. A one-sided p-value <0.025 supports a conclusion that the true SVR_{12} is >45%.
N = Number of subjects included in the analysis.
n (%) = Number of subjects who achieved SVR_{12} and the percentage calculated as (n/N)*100.
LLoQ is 15 IU/mL

At Week 4, the pharmacokinetic parameters of GZR in HD and non-HD patients in the intensive PK arm were as shown in Table 32.

Table 32: Week 4 pharmacokinetic parameters of GZR in HD and non-HD patients in the intensive PK arm

PK	Hemodialysis Patients from Intensive PK Arm†					Non-Dialysis Patients from Intensive PK Arm†					(Hemodialysis / Non-Dialysis)		
Parameter	N	Range	GM‡,§	95% CI‡	GCV	N	Range	GM‡,§	95% CI‡	GCV	GMR‡	90% CI‡	rMSE‖
AUC0-24 (uM*hr)¶	6	1.79 - 3.89	2.22	(1.29, 3.82)	29.1	5	1.58 - 11.18	2.85	(1.57, 5.16)	98.2	0.78	(0.41, 1.50)	0.587
Cmax (uM)	6	0.11 - 0.95	0.29	(0.15, 0.57)	97.2	5	0.20 - 1.06	0.43	(0.21, 0.92)	70.0	0.67	(0.29, 1.52)	0.739
C2hr (uM)	6	0.04 - 0.34	0.13	(0.06, 0.30)	80.0	5	0.02 - 0.35	0.16	(0.07, 0.40)	152.2	0.81	(0.30, 2.19)	0.899
C4hr (uM)	6	0.11 - 0.53	0.18	(0.09, 0.35)	62.6	5	0.08 - 0.58	0.21	(0.10, 0.43)	100.3	0.85	(0.39, 1.86)	0.702
C24hr (nM)	6	17.86 - 53.20	34.62	(18.18, 65.94)	40.6	5	13.17 - 151.01	30.10	(14.86, 60.95)	121.2	1.15	(0.53, 2.49)	0.698
Tmax (hr)	6	1.15 - 7.98	3.01			5	1.02 - 8.00	4.02					

†Intensive PK Arm: GZR 100mg + EBR 50 mg QD for 12 weeks (open label) - 24 hr PK sampling collected on Week 4 following PM dose.
‡Back-transformed least squares mean (or mean difference) and confidence interval from linear fixed effects model performed on natural log-transformed values.
§Median reported for Tmax.
‖rMSE: Square root of mean square error from the linear model. rMSE*100% approximates the between-subject %CV on the raw scale.
¶One hemodialysis patient had Week 4 Predose sample collected with a Time Since Last Dose (TSLD) of 16.25 hr, which is deviated from the TSLD of 18-30 hr for Ctrough collection.
GM: Geometric Mean, GMR: Geometric Mean Ratio, CI: Confidence Interval GCV: Percent Geometric Coefficient of Variation

The HD/non-HD AUC GMR for GZR was 0.78 indicative of minor role of kidneys and dialysis in the excretion of GZR.

At Week 4, the pharmacokinetic parameters of EBR in HD and non-HD patients in the intensive PK arm were as shown in Table 33.

Table 33: Week 4 pharmacokinetic parameters of GZR in HD and non-HD patients in the intensive PK arm

PK	Hemodialysis Patients from Intensive PK Arm†					Non-Dialysis Patients from Intensive PK Arm†					(Hemodialysis / Non-Dialysis)		
Parameter	N	Range	GM‡ ¶	95% CI‡	GCV	N	Range	GM‡ ¶	95% CI‡	GCV	GMR‡	90% CI‡	rMSE‖
AUC0-24 (uM*hr)¶	6	1.78 - 5.30	3.20	(2.14, 4.78)	36.5	5	1.55 - 5.17	2.24	(1.44, 3.48)	55.8	1.43	(0.88, 2.32)	0.436
Cmax (uM)	6	0.16 - 0.32	0.22	(0.16, 0.31)	28.9	5	0.10 - 0.28	0.16	(0.11, 0.22)	40.7	1.44	(0.99, 2.10)	0.336
C2hr (uM)	6	0.09 - 0.28	0.17	(0.10, 0.28)	42.8	5	0.03 - 0.18	0.11	(0.06, 0.18)	78.2	1.58	(0.86, 2.93)	0.552
C4hr (uM)	6	0.12 - 0.31	0.20	(0.13, 0.31)	39.3	5	0.05 - 0.24	0.12	(0.07, 0.19)	59.7	1.67	(1.00, 2.79)	0.464
C24hr (nM)	6	34.69 - 181.40	86.24	(45.76, 162.54)	56.9	5	17.57 - 172.57	54.36	(27.15, 108.83)	101.5	1.59	(0.74, 3.40)	0.686
Tmax (hr)	6	2.00 - 6.00	3.04			5	1.98 - 8.00	6.00					

† Intensive PK Arm: GZR 100mg + EBR 50 mg QD for 12 weeks (open label) - 24 hr PK sampling collected on Week 4 following PM dose.
‡ Back-transformed least squares mean (or mean difference) and confidence interval from linear fixed effects model performed on natural log-transformed values.
¶ Median reported for Tmax.
‖ rMSE: Square root of mean square error from the linear model. rMSE*100% approximates the between-subject %CV on the raw scale.
¶ One hemodialysis patient had Week 4 Predose sample collected with a Time Since Last Dose (TSLD) of 16.25 hr, which is deviated from the TSLD of 18-30 hr for Ctrough collection.
GM: Geometric Mean, GMR: Geometric Mean Ratio, CI: Confidence Interval GCV: Percent Geometric Coefficient of Variation

The HD/non-HD AUC GMR for EBR was 1.43 was indicative of minor role of kidneys and dialysis in the excretion of GZR.

The proposed use in renal impairment is based on this study and the Study 050 in which patients with severe renal insufficiency were compared with Healthy Matched Controls. The results for GZR in Study 050 are shown below.

Table 34: GZR results in renally insufficient patients

	Severe Renal Insufficiency			Healthy Matched Control			Severe Renal Insufficiency/ Healthy Matched Control			
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE†	Total SD†
AUC_{0-24}‡ (µM•hr)	8	1.88	(1.23, 2.86)	8	1.14	(0.843, 1.54)	1.65	(1.09, 2.49)	0.119	0.405
C_{max}‡ (µM)	8	0.255	(0.152, 0.429)	8	0.154	(0.106, 0.224)	1.66	(0.99, 2.77)	0.253	0.505
C_{24}‡ (nM)	8	23.3	(15.4, 35.2)	8	14.5	(10.7, 19.6)	1.60	(1.06, 2.42)	0.204	0.405
C_2‡ (µM)	8	0.152	(0.0816, 0.281)	8	0.0961	(0.0610, 0.151)	1.58	(0.85, 2.92)	0.448	0.613
CL/F‡, ¶ (L/hr)	8	69.4	(45.6, 106)	8	114	(84.5, 155)	0.61	(0.40, 0.92)	0.119	0.405
Vz/F‡ (L)	8	3490	(2320, 5260)	8	5760	(4180, 7930)	0.61	(0.39, 0.94)	0.428	
T_{max}§ (hr)	8	3.00	(0.50, 6.00)	8	2.50	(1.00, 6.00)				
Apparent terminal $t_{½}$‖ (hr)	8	36.30	30.53	8	35.18	19.64				

The results for EBR in Study 050 are shown in Table 35.

Table 35: EBR results in renally insufficient patients

	Severe Renal Insufficiency			Healthy Matched Control			Severe Renal Insufficiency/ Healthy Matched Control			
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE†	Total SD†
AUC_{0-24}‡ (µM•hr)	8	4.07	(3.01, 5.52)	8	2.19	(1.76, 2.72)	1.86	(1.38, 2.51)	0.057	0.291
C_{max}‡ (µM)	8	0.271	(0.196, 0.373)	8	0.163	(0.129, 0.206)	1.66	(1.21, 2.28)	0.120	0.311
C_{24}‡ (nM)	8	126	(88.6, 179)	8	60.9	(47.3, 78.5)	2.07	(1.46, 2.93)	0.064	0.338
C_2‡ (µM)	8	0.196	(0.140, 0.274)	8	0.117	(0.0915, 0.149)	1.68	(1.20, 2.34)	0.215	0.328
CL/F‡, ¶ (L/hr)	8	13.9	(10.3, 18.9)	8	25.9	(20.8, 32.2)	0.54	(0.40, 0.72)	0.057	0.291
Vz/F‡ (L)	8	569	(420, 772)	7††	901	(699, 1160)	0.63	(0.45, 0.89)	0.315	
T_{max}§ (hr)	8	4.00	(4.00, 6.00)	8	4.00	(2.00, 4.00)				
Apparent terminal $t_{½}$‖ (hr)	8	28.97	18.26	7††	25.02	19.08				

Based on these results, it is proposed that dose adjustment is not needed in patients with renal impairment including those on haemodialysis. Note this recommendation does not apply to the use of GZR/EBR with sofosbuvir.

Study 059 (Part A): This was a Phase II/III, open label study in TN and TE, HCV GT-1 patients with Child-Pugh Class B (hepatic insufficiency score 7-9) for treatment with GZR 50 mg plus EBR 50 mg daily without RBV for 12 weeks. The patients were randomised as shown in Table 36.

Table 36: Patient treatment groups

	CP-B: GZR 50 mg + EBR 50 mg for 12 Weeks		Non-cirrhotic: GZR 100 mg + EBR 50 mg for 12 Weeks		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	30		10		40	
HCV Genotype						
1a	27	(90.0)	6	(60.0)	33	(82.5)
1b	3	(10.0)	4	(40.0)	7	(17.5)
Prior Treatment Status						
Naive	19	(63.3)	6	(60.0)	25	(62.5)
Null responder	6	(20.0)	2	(20.0)	8	(20.0)
Partial responder	0	(0.0)	1	(10.0)	1	(2.5)
Relapser	5	(16.7)	1	(10.0)	6	(15.0)

Only SVR4 response rate was reported and was achieved by 28/30 (93.3%) patients (95%CI 84.4%, 100.0%).

One death was reported in the follow-up phase after completion of treatment. A non-cirrhotic group (GZR/EBR 100/50) had also been enrolled for comparison of PK data. The PK results for GZR and for EBR are as shown in Tables 37 and 38.

Table 37: PK results for GZR

PK	Non-Cirrhotic Patients					CP-B Patients					(CP-B/Non-Cirrhotic)		
Parameter[†]	N	Range	GM[‡,†]	95% CI[‡]	GCV	N	Range	GM[‡,†]	95% CI[‡]	GCV	GMR[‡]	90% CI[‡]	rMSE[‖]
AUC0-24 (uM*hr)	10	1.03 - 6.61	1.83	(1.13, 2.98)	54.9	9	0.35 - 6.65	2.29	(1.37, 3.83)	115	1.25	(0.70, 2.24)	0.731
Cmax (uM)	10	0.15 - 1.24	0.32	(0.18, 0.57)	64.2	9	0.03 - 1.14	0.37	(0.20, 0.67)	151	1.15	(0.58, 2.28)	0.861
C2hr (uM)	10	0.09 - 0.44	0.21	(0.12, 0.38)	47.1	9	0.03 - 0.70	0.22	(0.12, 0.41)	169	1.06	(0.53, 2.11)	0.862
C4hr (uM)	10	0.06 - 0.93	0.18	(0.10, 0.31)	81.6	9	0.03 - 0.63	0.16	(0.09, 0.29)	118	0.9	(0.46, 1.74)	0.825
C24hr (nM)	10	7.48 - 54.11	19.89	(11.38, 34.76)	56.8	9	5.62 - 235.33	33.95	(18.85, 61.14)	149	1.71	(0.87, 3.33)	0.836
Tmax (hr)	10	0.50 - 3.03	2.02			9	1.00 - 8.00	2.00					

[†] PK parameters represent the D28 intensive PK data for each patient.
[‡] Back-transformed least squares mean and confidence interval from linear fixed effects model performed on natural log-transformed values.
[†] Median reported for Tmax.
[‖] rMSE: Square root of mean square error from the linear model. rMSE*100% approximates the between-patient %CV on the raw scale.
GM: Geometric Mean, GMR: Geometric Mean Ratio, CI: Confidence interval, GCV: Percent Geometric Coefficient of Variation

Table 38: PK results for EBR

PK	Non-Cirrhotic Patients					CP-B Patients					(CP-B/Non-Cirrhotic)		
Parameter[†]	N	Range	GM[‡,†]	95% CI[‡]	GCV	N	Range	GM[‡,†]	95% CI[‡]	GCV	GMR[‡]	90% CI[‡]	rMSE[‖]
AUC0-24 (uM*hr)	10	1.12 - 3.84	1.91	(1.41, 2.58)	36.7	9	0.76 - 4.46	1.72	(1.25, 2.36)	58.3	0.9	(0.63, 1.29)	0.452
Cmax (uM)	10	0.10 - 0.26	0.15	(0.12, 0.20)	34.3	9	0.06 - 0.24	0.12	(0.09, 0.16)	45.5	0.8	(0.59, 1.09)	0.384
C2hr (uM)	10	0.05 - 0.20	0.11	(0.08, 0.15)	47.6	9	0.04 - 0.17	0.10	(0.07, 0.14)	49	0.93	(0.64, 1.33)	0.457
C4hr (uM)	10	0.09 - 0.22	0.13	(0.10, 0.17)	31.4	9	0.04 - 0.23	0.10	(0.07, 0.13)	52.5	0.73	(0.53, 1.01)	0.405
C24hr (nM)	10	23.00 - 105.66	48.01	(33.48, 68.85)	43.2	9	17.04 - 157.38	49.74	(34.02, 72.73)	73.1	1.04	(0.67, 1.60)	0.54
Tmax (hr)	10	2.93 - 6.03	3.01			9	2.00 - 8.00	2.02					

[†] PK parameters represent the D28 intensive PK data for each patient.
[‡] Back-transformed least squares mean and confidence interval from linear fixed effects model performed on natural log-transformed values.
[†] Median reported for Tmax.
[‖] rMSE: Square root of mean square error from the linear model. rMSE*100% approximates the between-subject %CV on the raw scale.
GM: Geometric Mean, GMR: Geometric Mean ratio, CI: Confidence interval, GCV: Percent Geometric Coefficient of Variation

Based on this study as well as GZR Study 013 and EBR Study 009, it is proposed that GZR/EBR dose adjustment is not needed in mild hepatic impairment. The GZR/EBR combination is contraindicated in HCV patients in the presence of moderate or severe hepatic impairment.

Study 074 (C-SWIFT): This was a Phase II open label, study in TN, HCV GT-1 and TN HCV GT-3 patients with or without cirrhosis for treatment with GZR/EBR (100/50 mg daily) plus Sofosbuvir (400 mg daily).

GT1 patients (cirrhotic [C] or non-cirrhotic [NC]) were to be treated for 4, 6 or 8 weeks and were randomised as shown in Table 39. SVR12 response rates are shown in Table 40.

Table 39: GT1 patient treatment groups

	GT1 NC: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 4 Weeks		GT1 NC: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 6 Weeks		GT1 C: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 6 Weeks		GT1 C: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 8 Weeks		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
HCV Genotype										
1a	26	(83.9)	26	(86.7)	16	(80.0)	16	(76.2)	84	(82.4)
1b	5	(16.1)	4	(13.3)	4	(20.0)	5	(23.8)	18	(17.6)

Table 40: SVR12 response rates in GT-1 patients (Full Analysis Set)

Treatment	N	n (%)	95% Confidence Interval[†]
GT1 NC: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 4 Weeks	31	10 (32.3)	(16.7, 51.4)
GT1 NC: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 6 Weeks	30	26 (86.7)	(69.3, 96.2)
GT1 C: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 6 Weeks	20	16 (80.0)	(56.3, 94.3)
GT1 C: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 8 Weeks	21	17 (81.0)	(58.1, 94.6)

[†]Based on Clopper-Pearson method.
N = Number of subjects included in the analysis.
n (%) = Number of subjects with undetectable (TND) or unquantifiable (TD(u)) HCV RNA at the Follow-Up Week 12 visit and the percentage calculated as (n/N)*100. A missing HCV RNA result is imputed to TND or TD(u) if TND or TD(u) at both preceding and subsequent visits.

Thus the SVR12 response was not advantageous compared to treatment with GZR/EBR (100/50 mg) for 12 weeks without sofosbuvir as seen in the pivotal TN study P060.

GT3 patients (cirrhotic [C] or non-cirrhotic [NC]) were to be treated with 8 or 12 weeks and were randomised as shown in Table 41 and the SVR12 response rates are shown in Table 42.

Table 41: GT3 patients and treatment groups

	GT3 NC: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 8 Weeks		GT3 NC: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 12 Weeks		GT3 C: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 12 Weeks		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	15		14		12		41	
HCV Genotype								
3	15	(100.0)	14	(100.0)	12	(100.0)	41	(100.0)

Table 42: SVR12 response rates in GT3 patients (Full Analysis Set)

Treatment	N	n (%)	95% Confidence Interval[†]
GT3 NC: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 8 Weeks	15	14 (93.3)	(68.1, 99.8)
GT3 NC: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 12 Weeks	14	14 (100.0)	(76.8, 100.0)
GT3 C: GZR 100 mg + EBR 50 mg + Sofosbuvir 400 mg for 12 Weeks	12	10 (83.3)	(51.6, 97.9)

[†]Based on Clopper-Pearson method.
N = Number of subjects included in the analysis.
n (%) = Number of subjects with undetectable (TND) or unquantifiable (TD(u)) HCV RNA at the Follow-Up Week 12 visit and the percentage calculated as (n/N)*100. A missing HCV RNA result is imputed to TND or TD(u) if TND or TD(u) at both preceding and subsequent visits.

Study 048 (C-SALVAGE): This was a Phase II open label study in HCV GT-1 patients with or without cirrhosis who were prior failures on Direct Acting Antiviral agents (DAAs) administered concomitantly with P/R. The study treatment was GZR/EBR (100/50 mg daily) plus RBV for 12 weeks. The patients were distributed as shown in Table 43 and SVR12 response rates and SVR12 response rates by genotype or Prior DAA are shown in Tables 44-46.

Table 43: Patient distribution

	GZR 100 mg + EBR 50 mg + RBV for 12 Weeks n	(%)
Subjects in population	79	
HCV Genotype		
1a	30	(38.0)
1b	49	(62.0)
Prior DAA		
Boceprevir	28	(35.4)
Telaprevir	43	(54.4)
Simeprevir	8	(10.1)

Table 44: SVR12 response rates

Treatment	N	n (%)	95% Confidence Interval†
GZR 100 mg + EBR 50 mg + RBV for 12 Weeks	79	76 (96.2)	(89.3, 99.2)

†Based on Clopper-Pearson method.
N = Number of subjects included in the analysis.
n (%) = Number of subjects who achieved SVR_{12} and the percentage calculated as (n/N)*100.

Table 45: SVR12 response by genotype

	GZR 100 mg + EBR 50 mg + RBV for 12 Weeks		
	N	n (%)	95% Confidence Interval†
Genotype			
1a	24	23 (95.8)	(78.9, 99.9)
1b	46	45 (97.8)	(88.5, 99.9)

Table 46: SVR12 by Prior DAA was as follows (PP population)

	GZR 100 mg + EBR 50 mg + RBV for 12 Weeks		
	N	n (%)	95% Confidence Interval†
Prior DAA			
Boceprevir	25	24 (96.0)	(79.6, 99.9)
With Signature Baseline RAVs	9	8 (88.9)	(51.8, 99.7)
Without Signature Baseline RAVs	16	16 (100.0)	(79.4, 100.0)
Telaprevir	40	39 (97.5)	(86.8, 99.9)
With Signature Baseline RAVs	18	17 (94.4)	(72.7, 99.9)
Without Signature Baseline RAVs	22	22 (100.0)	(84.6, 100.0)
Simeprevir	5	5 (100.0)	(47.8, 100.0)
With Signature Baseline RAVs	4	4 (100.0)	(39.8, 100.0)
Without Signature Baseline RAVs	1	1 (100.0)	(2.5, 100.0)

Virologic failures

In Treatment Naïve patients (Studies 060, 061, 052, 035 & 047), On-treatment Virologic Failure occurred in 4/752 (0.5%) patients, and relapse occurred in 21/752 (2.8%) patients following 12 weeks of GZR/EBR treatment without RBV.

In Treatment Experienced patients (Studies 068, 052 & 035), On-treatment virologic failure occurred in 0/159 (0.0%) patients, and relapse occurred in 10/159 (6.3%) patients following 12 weeks of treatment with GZR/EBR without RBV.

Resistance associated variants (RAVs)

The impact of RAVs at baseline on the efficacy of GZR/EBR and association between treatment-emergent RAVs and virological failure was assessed in the clinical trials program.

Baseline RAVs: treatment naïve (TN)

Presence of NS3 RAVs at baseline did not impact the efficacy of GZR/EBR regimen in GT-1 patients. The Q80K mutation, which has been associated with lower efficacy in GT-1a patients treated with simeprevir/P/R, was detected in more than one third GT-1a TN patients but an association with response to GZR/EBR was not evident.

Presence of NS5A RAVs at baseline conferring a >5 fold shift in in vitro potency of EBR had an impact on the efficacy of GZR/EBR regimen in GT-1a patients. Approximately 9% GT-1 patients had NS5A RAVs, and approximately 3% had NS5A RAVs which conferred >5 fold resistance to EBR. This impact was most apparent in GT-1a patients with baseline viral load above 800,000 IU/mL. There was a very modest negative impact of baseline NS5A RAVs on SVR12 response in TN GT-1b patients.

Far less data are available in GT 4, 6 and 3 patients. *The sponsor is requested to provide updated summary in its pre-ACPM response.*

Baseline RAVs: treatment experienced (TE)

There was a higher prevalence of baseline NS3 RAVs in GT-1a patients than in GT-1b patients, and a slightly lower proportion of GT-1a patients with baseline NS3 RAVs achieved SVR12 compared with GT-1b patients. However, since 9/11 (82%) GT-1 patients with baseline NS3 RAVs who experienced virologic failure also had baseline NS5A RAVs, the role baseline NS3 RAVs is not clear.

As in TN patients, the presence of baseline NS5A RAVs conferring a >5 fold shift in in vitro potency of EBR in TE GT-1a patients was associated with a substantial reduction in efficacy. Patients with baseline RAVs conferring > 5 fold shift in potency to EBR accounted for 7.8% (26/334) of GT-1a patients but comprised 76.5% (13/17) of all GT-1a patients with virologic failure.

Far less data are available in GT 4, 6 and 3 patients. *The sponsor is requested to provide updated summary in its pre-ACPM response.*

Post-baseline RAVs

Virologic failure was often accompanied by emergence of NS3 and/or NS5A mutations not detected prior to therapy in both TN and TE patients. The NS3 RAVs conferring >5 fold shift in GZR potency were more commonly observed in GT-1a patients than in GT-1b patients. The NS5A RAVs conferring >5 fold shift in EBR potency were observed in equal proportion in GT-1a and GT-1b virologic failure patients.

Following administration of GZR, treatment-emergent substitutions in NS3/4A sequence at amino acids 168, 156, 56 and 155 were observed in > 10% patients. NS3 RAVs are likely to revert to wild-type virus within a few months of virologic failure.

Following administration of EBR, treatment-emergent substitutions in NS5A sequence at amino acids 28, 30, 31, and 93 were observed in > 10% of patients. NS5A RAVs are likely to persist for longer duration. These were generally more persistent among GT-1a patients and became undetectable at follow-up Week 12 in only 5% patients. Similar persistence of NS5A RAVs was observed in GT-1b infected virologic failures.

Treatment-emergent RAVs were also noted in the GT 4, 6 and 3 patients with virologic failure but the data are currently very limited. *The sponsor is requested to provide updated summary in its pre-ACPM response.*

Overall, the dataset on virologic failure is currently very small and follow-up is short. The implications on re-treatment have not yet been determined.

Clinical safety

The overall safety database included 4143 participants consisting of 1439 subjects in Phase I studies and 2704 HCV patients in Phase II and III trials.

The Integrated Safety Population (ISP) consisted of HCV patients in Phase II/III studies who received at least 8 weeks of therapy with clinical doses of GZR/EBR (100/50 mg). This is the primary dataset for adverse effects profiling. This dataset consisted of 1690 patients and included patients who received GZR/EBR (100/50) for 8 weeks (n=91), 12 weeks (n=939), 16 weeks (n=214) or 18 weeks (n=149). A total of 657/1690 (38.9%) patients also received concomitant RBV. The mean duration of treatment was 88 days for the single-entity GZR-EBR given together and 90 days the fixed dose GZR/EBR formulation. An overall summary of safety from treatment phase and first 14 days of follow up is shown below.

Table 47: Overall safety summary from treatment phase and first 14 days of follow up

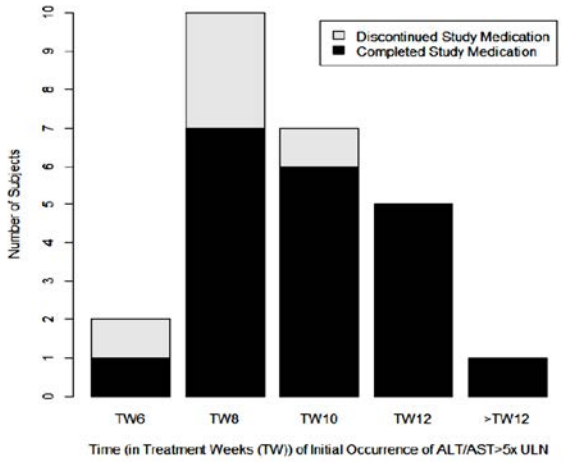
	GZR 100 mg with EBR 50 mg		GZR 100 mg with EBR 50 mg + RBV		All GZR 100 mg with EBR 50 mg +/- RBV		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1,033		657		1,690		105	
with one or more adverse events	738	(71.4)	549	(83.6)	1,287	(76.2)	72	(68.6)
with no adverse event	295	(28.6)	108	(16.4)	403	(23.8)	33	(31.4)
with drug-related† adverse events	414	(40.1)	444	(67.6)	858	(50.8)	41	(39.0)
with serious adverse events	25	(2.4)	17	(2.6)	42	(2.5)	3	(2.9)
with serious drug-related adverse events	1	(0.1)	3	(0.5)	4	(0.2)	0	(0.0)
who died	2	(0.2)	1	(0.2)	3	(0.2)	0	(0.0)
discontinued‡ due to an adverse event	5	(0.5)	11	(1.7)	16	(0.9)	1	(1.0)
discontinued due to a drug-related adverse event	3	(0.3)	5	(0.8)	8	(0.5)	1	(1.0)
discontinued due to a serious adverse event	1	(0.1)	2	(0.3)	3	(0.2)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Overall, the most common AEs were headache (18.0%) and fatigue (16.2%). These were also the most common ADRs (headache 11.5% and fatigue 12.0%). The AE profile in various subpopulations was comparable or could be reasonably attributed to the demographic/clinical/therapeutic (for example, RBV) features of the subpopulation. Three deaths were reported as noted above in the table and were assessed as unlikely to be related to the study drugs.

The Hepatic Safety Pool (HSP) consisted of 2405 patients in Phase II/III studies who received at least 8 weeks of therapy with GZR, regardless of GZR dose. This is the primary dataset for assessment of hepatic safety. In the HSP, 36/2405 (1.5%) patients had a Late ALT/AST Elevation Event, hepatic laboratory Event of Clinical Interest (ECI) and/or discontinued study medication due to protocol-specified hepatic laboratory abnormality discontinuation criteria. Of these 36 patients, 25/2405 (1.0%) had a Late ALT/AST Elevation Event, 26/2405 (1.1%) had a hepatic laboratory ECI and 7/2405 (0.3%) discontinued study medication as specified. The most frequent hepatic laboratory criterion fulfilled was 'ALT or AST >3x baseline and >100 IU/L' which occurred in 19/26 patients who met the ECI criteria.

Time course of development of Late ALT/AST Elevation Events (>5xULN) by Treatment Weeks in the HSP dataset are shown in Figure 3 below.

Figure 3: Time course of development of Late ALT/AST Elevation Events (>5xULN) by Treatment Weeks in the HSP dataset



The dataset in the studies pooled for 'PK/'ALT/AST Late Elevation Event' Pool' (PKP) was similar to the HSP and consisted of 2279 patients. The PKP was used to describe the correlation between GZR exposure and risk of late ALT/AST Elevation Events. Late ALT/AST Elevation Events, a specific measure of GZR-related hepatic safety, occurred in 7/769 (0.9%) patients who received the proposed dose of GZR 100 mg. At this dose, these were generally not accompanied by raised bilirubin. At this dose, the predicted rate is 0.8% (95%CI 0.5%, 1.2%). The dose relationship of Late ALT/AST Elevation Events with the GZR exposure is shown in Table 48 below.

Table 48: The dose relationship of Late ALT/AST Elevation Events with the GZR exposure

Dose / Population	GZR AUC0-24hr Values in Patients with PK Data			Observed Rate in Patients with Safety Data			Predicted Rate (%, 95% CI)
	N (PK)[†]	GM AUC0-24 (nM·hr)	GMR[‡]	N (Event)[§]	N (Safety)[¶]	Rate (%, 95% CI)	
25 mg	29	242	0.14	0	28	0.0 (0.0, 12.3)	0.1 (0.0, 0.2)
50 mg	89	1303	0.76	0	88	0.0 (0.0, 4.1)	0.4 (0.2, 0.7)
100 mg Reference	1270	1721	1.00	7	1273	0.5 (0.2, 1.1)	0.5 (0.3, 0.8)
100 mg Other	770	2818	1.64	7	769	0.9 (0.4, 1.9)	0.8 (0.5, 1.2)
200 mg	39	8498	4.94	1	65	1.5 (0.0, 8.3)	2.1 (1.2, 3.1)
400 mg	42	31062	18.05	4	64	6.3 (1.7, 15.2)	6.2 (3.4, 9.9)
800 mg	40	113645	66.05	6	58	10.3 (3.9, 21.2)	16.6 (8.3, 27.8)

[†] N (PK): Number of patients with available PK data.

[‡] GMR = geometric mean ratio of PK relative to the reference population at 100 mg.

[§] N (Event): Number of patients with occurrence of the Late ALT/AST Elevation Event.

[¶] N (Safety): Number of patients with available safety information for the evaluation of Late ALT/AST Elevation Event.

The reference population included non-cirrhotic, non-severe CKD, non-Asian HCV-infected patients in the 100 mg dosing arms of the Phase 2 and 3 studies/arms included in this analysis.

The risk of Late ALT/AST Elevation Events is expected to be higher in the presence of interacting intrinsic and extrinsic factors such as hepatic impairment and co-administration with other drugs. It can also be expected to be higher in the post-market phase when the product is used in large number of less well selected patients.

Only very limited data from Study 073 (C-SWIFT) are available for HCV GT-3 patients (n=41) which required the use of triple combination of GZR/EBR/SOF 100/50/400 mg daily for 12 weeks. This is considered a major deficiency in this submission with respect to the risk of drug induced hepatotoxicity in the context of a higher prevalence of HCV GT-3 in Australian population.

In active controlled, Thorough QT studies, single supra-therapeutic doses of GZR (1600 mg) and EBR (700 mg) did not show clinically relevant prolongation in QT interval.

Risk management plan

EU-RMP Version 1.2 (dated 28 February 2016) and Australian Specific Annex Version 0.1 (dated August 2015) apply to this submission. Further changes to RMP make occur following sponsor's response to the Second round RMP report. The submission was not referred to the Advisory Committee on Safety of Medicines (ACSOM).

Risk-benefit analysis

Delegate's considerations

Summary of issues

- Baseline NS5A testing in HCV Genotype 1a patients.
- Limited Phase II data in HCV Genotype 3.

Proposed action

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

Request for ACPM advice

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

1. Does the ACPM support the proposed instructions for Dosage & Administration in HCV genotypes 1, 4 and 6 patients, including no requirement for baseline NS5A testing in GT-1a patients?
2. Does the ACPM support the proposed use of triple DAA therapy (with sofosbuvir) in HCV genotype 3 patients based on preliminary evidence from a Phase II trial (N=41)?
3. Does the ACPM propose any additional efficacy data or post market surveillance activities?
4. 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 Australian government has taken the initiative to offer parity of access to the new oral Hepatitis C treatments regardless of a patient's disease status or economic background. By enabling general practitioner (GP) prescribing of DAA HCV therapies, the Pharmaceutical Benefits Access Committee (PBAC) has provided Australians with access to treatment regardless of geographic location and without the need for a Specialist visit. With the availability of oral DAA regimens, Australia can lead the way towards the WHO goal of elimination of HCV infection and the associated burden of liver disease.

New information - Change to dosage and administration: Removal of genotype 6

The sponsor acknowledges the Delegate's support of Zepatier treatment in patients with HCV Genotype (GT) 6. Currently, an unmet clinical need exists in Australia for interferon-free treatment regimens of GT6. However, as summarised in Table 5 of the proposed Product Information, efficacy of Zepatier was lower in GT6 infected subjects (SVR 80%, 12/16) compared to the efficacy in GT1- and GT4infected subjects (GT1a: SVR 94% 399/426; GT1b: 96% SVR, 246/255; GT4 SVR 96%, 54/56).

Emerging clinical data suggests SVR rates in GT6 may be lower than suggested by the data presented in this application. SVR rates of 63% were observed in 35 GT6 infected patients in an ongoing study. In addition, MSD notes that a pan-genotypic sofosbuvir/velpatasvir regimen has been registered in the US and recommended for registration in Europe which, if registered in Australia, would provide a more effective treatment option (100% SVR in ASTRAL-1 study, n=41) for patients with GT6[9]. For these reasons, the sponsor proposes to withdraw the dosing instructions in GT6 patients from the Australian Product Information.

The sponsor provides the following comments, on issues raised by the Delegate, for the ACPM's consideration:

Does the ACPM support the proposed instructions for Dosage and Administration in HCV genotypes 1, 4 and 6 patients, including no requirement for baseline NS5A testing in GT1a patients?

The sponsor supports the proposed instructions for Dosage and Administration in HCV GT1 and 4. As noted above, the sponsor proposes to withdraw the Dosage and Administration guidance in GT6 patients from the Australian Product Information based on emerging clinical data.

The sponsor proposes that there should be *no requirement for baseline NS5A testing* in GT1a patients. The Australian Liver Association (ALA) has published local clinical best practice guidelines[10] for HCV treatment. These clearly state that baseline testing is not required in the majority of patients given the very high SVRs achieved with the currently approved DAAs:

> ***Direct-acting antivirals and drug resistance:*** *Resistance-associated variants (RAVs) have been identified for all of the approved DAAs. However, given the high SVR rates observed with combination therapy, there is currently no role for baseline HCV resistance testing in treatment-naive people or prior non-responders to pegIFN-based therapy. Resistance testing for NS3, NS5B and NS5A RAVs should be considered following DAA treatment failure, to guide salvage therapy. Resistance testing involves direct sequencing of the HCV genome and is available through specialised laboratories*.'[11]

As mentioned above, RAVs have been identified for all approved NS5a inhibitors and impact efficacy among HCV GT1a patients receiving NS5a inhibitors[12,13]. The ALA guidelines suggest baseline RAV testing is unnecessary due to the high SVR rates (>90%) observed with DAAs registered in Australia. Reported SVRs are 96% for sofosbuvir/ledipasvir [HARVONI] in GT1a and 100% for daclatasvir + sofosbuvir [Daklinza + Sovaldi] in GT1. Pre-treatment RAV testing is not recommended in the Australian labels of other approved NS5a inhibitors (ledipasvir [Harvoni], daclatasvir [Daklinza] and ombitasvir [Viekira]). Zepatier reports a comparable SVR of 92% in GT1a patients and so by this rationale baseline RAV testing would not be warranted.

Moreover, RAV testing is not readily available in Australia and is used only for academic purposes and so would be difficult to implement in a clinical setting. By contrast in the US, commercial RAV testing is available and thus it was more practical to implement testing of patients with HCV genotype 1a infection for the presence of virus with NS5A RAVs prior to initiation of treatment with Zepatier to determine dosage regimen and duration.

[9]US EPCLUSA sofosbuvir/velpatasvir Product Information
[10]Gastroenterological Society of Australia ' Australian recommendations for the management of hepatitis C infection: a consensus statement 2016' March 2016
[11]Thompson ' Australian recommendations for the management of hepatitis C infection: a consensus statement' MJA 204 (7), 18-Apr-2016
[12]Australian HARVONI sofosbuvir/ledipasvir Product Information
[13] Australian DAKLINZA daclatasvir Product Information

The proposed product labelling for Zepatier uses clinical parameters (genotype and prior treatment status) to select the appropriate regimen for specific patient populations. This approach is supported by the data presented in this application, and using this approach, high efficacy is expected across the proposed patient populations. The use of clinical parameters to guide selection of appropriate dosing regimens is an approach very familiar to hepatologists and gastroenterologists and can be readily implemented in Australia.

In conclusion, the sponsor defers to the ALA guidelines and contends that these provide the appropriate guidance for baseline NS5A testing. Therefore, the sponsor concurs with the Delegate's conclusion that the effects of NS5a polymorphisms on SVR rates are appropriately described in the draft Product Information. Given the lack of widespread availability of screening tests for NS5a RAVs in Australia, a recommendation for screening should not be included in the Product Information.

The sponsor is requested to provide an updated summary of data on baseline (TN and TE) and treatment emergent RAVs in GT 3, 4 and 6 patients.

Genotype 3 – RAV data in patients with GT 3 in the C-SWIFT trial are summarised in the Zepatier registration dossier. In brief, only 1 failure was observed in the 12 week arm of the C-SWIFT study (n=25). NS5A RAVs were detected in 4/40 (10.0%) of GT3 subjects at baseline. All of these subjects achieved SVR12. No further data on RAVs in patients with HCV GT 3 are available to date.

Genotype 4 - In clinical studies, SVR12 was observed in 93% (38/41) of GT4 patients with NS5a RAVs. Additional GT4 baseline RAV data will be available from two ongoing studies:

In the ongoing P062 CO-STAR study in subjects receiving opiate substitution therapy, 3 of the 11 GT4infected subjects enrolled in the immediate treatment arm had baseline RAVs; all 11 GT4infected subjects achieved SVR12.

In the deferred treatment arm of P060, there were 3 GT-4 infected subjects with baseline RAVs; all 3 achieved SVR12.

Treatment-emergent RAVs were seen in genotypes GT4infected subject studied in the pivotal trials. Treatment emergent RAVs for the treatment naïve (TN) and treatment experienced (TE) populations were summarised in the submission and in Table 1 of the proposed Product Information. No additional data on treatment emergent RAVs are available to date as all of the GT4 subjects in the ongoing studies achieved SVR.

The long term follow up study Protocol 017 will assess presence of antiviral resistance to GZR (NS3 inhibitor) and EBR (NS5A inhibitor) to determine if there is a reversion to a wild type during long term follow-up. However this study is not due to report until 2022.

Genotype 6 - As advised above, the sponsor proposes to withdraw the dosing instructions in GT6 patients. This is not attributed to any impact of RAVs on efficacy in subjects with GT6.

Does the ACPM support the proposed use of triple DAA therapy (with sofosbuvir) in HCV genotype 3 patients based on preliminary evidence from a Phase II trial (N=41)?

HCV GT3 causes a more aggressive form of chronic liver disease with a faster progression to cirrhosis compared to other HCV genotypes. GT3 constitutes almost 40% of the Australian HCV patient population. The sponsor concurs with the Delegate that the proposed use of triple DAA therapy (Zepatier with sofosbuvir) in GT3 patients is justified on the basis of high clinical need in these patients and positive data submitted in the dossier.

The sponsor acknowledges there are limited safety data available in patients with GT3 infection due to the small size of the dataset (total of 41 GT3-infected subjects received sofosbuvir + EBR/GZR in C-SWIFT, including 15 treated for 8 weeks and 26 treated for 12 weeks). The Delegate considers this to be a concern with respect to the need for triple

therapy with sofosbuvir [SOF] and the risk of drug induced hepatotoxicity with GZR. However, the general safety profile and the hepatic safety profile of EBR/GZR + SOF should be similar to the safety profile of EBR/GZR with the exception of limitations for the use of SOF-containing regimens in subjects with renal impairment.

In broad terms, general safety in GT3 infected subjects in the C-SWIFT (P074) study was similar to other EBR/GZR clinical trials. The most common AEs were headache, fatigue and nausea. No subject discontinued the study medication due to an AE and no subject had an SAE.

The risk of hepatotoxicity is not expected to be increased in GT3 patients who will receive EBR/GZR + SOF. The sponsor contends the rate of occurrence of hepatotoxicity in GT3-infected subjects would not be materially different compared with GT1 or GT4infected subjects. In C-SWIFT, 0/41 subjects had Late ALT/AST elevations, defined as increases in ALT to >5X ULN, following at least 1 normal value between treatment Weeks 2 to 4. Referencing a much larger safety data base, 13/1690 subjects (0.8%) in the Integrated Safety Population who received 50 mg EBR/100 mg GZR had Late ALT/AST elevations. The frequency of Late ALT/AST elevations was clearly correlated with GZR exposure. GZR pharmacokinetic [PK] exposure is not affected by HCV GT3 as compared to GT1 based on the GZR population PK model[14] and is not anticipated to be impacted by sofosbuvir or GS-33107 based on their known metabolic pathways[15]. Based on a DDI study, (5172-P063) co-administration of multiple doses of GZR+EBR with a single dose of sofosbuvir increased expsosure of sofosbuvir (AUC 2.4–fold) but not GS-33107. The AUC increase in sofosbuvir exposure was lower than that observed for sofosbuvir when co-administered with cyclosporine (4.5-fold)[15] and no dose adjustments is required for sofosbuvir when co-administered with cyclosporine. Additionally, as described above, concomitant use of GZR/EBR and sofosbuvir was generally well-tolerated in C-SWIFT and therefore no dose adjustment is required for sofosbuvir and GZR/EBR. Finally, sofosbuvir is not associated with a risk of hepatotoxicity regardless of Child- Pugh class.[16]

The safety of EBR/GZR in clinical practice will be directed by the approved Product Information. With regards to hepatic safety, the proposed Product Information notes elevated ALT and the need for monitoring during treatment (Precautions) and contraindicates use in Child-Pugh B/C due to GZR increased levels. These instructions will apply to administration of EBR/GZR + SOF as well as administration of EBR/GZR.

The sponsor accepts the Delegate's suggestion to add a comment to the Product Information that usage in GT3 is based on early evidence in a limited number of patients. The suggested revision to the Clinical Trials Clinical Trials in Treatment Naïve Subjects with Genotype 3 Chronic Hepatitis C Infection section is as follows:

> *Zepatier usage in patients with genotype 3 infection is based on evidence in a limited number of patients.*

The Delegate has requested the Sponsor indicate whether confirmation of use in HCV GT3 patients in a larger trial is underway.

One trial in GT3-infected patients is underway, Protocol P083 'C-ISLE'. Supported by the data obtained in PN074, 100 compensated cirrhotic HCV GT3 subjects were randomised to one of 5 treatment arms in C-ISLE. Of these, 47 subjects were treatment-naive and randomised 1:1 to EBR/GZR + SOF + ribavirin [RBV] for 8 weeks or EBR/GZR + SOF for 12 weeks. 53 subjects were treatment-experienced and randomised 1:1:1 to EBR/GZR + SOF ± RBV for 12 weeks or EBR/GZR + SOF + RBV for 16 weeks. In total, 59 subjects have been

[14] Modeling and simulation report
[15] U.S. Prescribing Information: SOVALDI (sofosbuvir) Tablets: 2013.
[16] Australian SOVALDI sofosbuvir Product Information

randomised to 12 week treatment duration. A Clinical Study Report for this study is currently targeted for third quarter of 2017.

Does the ACPM propose any additional efficacy data or post market surveillance activities?

The sponsor welcomes the Delegate's commentary regarding the safety profile of Zepatier, and the clinical evaluator's opinion that the risk-benefit balance of Zepatier is favourable given the proposed usage. The sponsor considers the efficacy data and analyses presented in the dossier are sufficient to support the proposed registration.

As mentioned above, Study P083 is ongoing to confirm activity in GT3 patients.

The sponsor is requested to provide an update on longer term durability.

Durability of effect is supported by SVR24 of 94% in TE and 92% in TN patients. The Delegate has noted that longer term durability is unknown although additional follow up is underway in the ongoing P017 study.

No further long term durability data are available beyond those previously provided to TGA. As mentioned in the sponsor's response, final CSRs with SVR24 data from P052, P058 and P060 are available. SVR24 persistence data from Studies P052 and P060 have been presented to TGA in the sponsor's responses. In summary, these studies confirm SVR24 rates over 90% in TN and TE patients.

Durability will be assessed in the Long Term Follow Up study P017 'Durability of Virologic Response and / or Viral Resistance Patterns in Participants with Chronic Hepatitis C Who Have been previously treated with GZR'. Its primary objectives are to:

- evaluate durability of SVR in subjects who received a GZR containing regimen and remained virologically controlled through the follow up period
- evaluate the presence of antiviral resistance to GZR and/or EBR in subjects who were virologic failures, and determine if there is a reversion to wild type virus within the 3 or 5 year follow up period
- evaluate long term safety of GZR.

All subjects have received GZR and a subset has received EBR/GZR. This study is currently enrolling with over 2300 subjects enrolled to date. No durability data from this study have yet been reported. The Final study report is due in the first quarter of 2022.

Furthermore, the sponsor does not recommend any post-market surveillance activities beyond those described in the RMP/ASA. The sponsor considers the current RMP and ASA to be sufficiently robust in addressing the identified and potential safety issues as well as missing information through routine pharmacovigilance and the data to be gathered in Protocol 017. The sponsor considers version 1.3 of the EU RMP (dated April 2016) and accompanying ASA v0.2 (dated July 2016) to be sufficient. (An updated version of the ASA, addressing matters raised by the RMP evaluator, is provided in parallel to this response. Further administrative revisions will be made to the EU RMP and Australian ASA once the final approved EU and Australian labels are received.)

Other matters

Zepatier has been approved in the USA and Canada and has received a positive opinion from the European CHMP. The Canadian and Swiss Health Authorities have approved Zepatier for use in GT3 (without any associated conditions of registration) based on the same dataset as presented in the Australian application. The CHMP positive opinion is for approval of the same Indications as sought in Australia, although the European SmPC does not recommend use in GT3 due to the low numbers of GT3 subjects in clinical trials. In New Zealand, an application for registration (de novo evaluation) is under review by Medsafe. The clinical aspects of the application and proposed Data Sheet have been accepted by Medsafe.

Advisory committee considerations

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

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Zepatier tablet containing 50/100 mg fixed dose combination of EBR / GZR to have an overall positive benefit–risk profile for the Delegate's amended indication**;**

> *Zepatier is indicated for the treatment of Chronic Hepatitis C genotype 1 and 4 infection in adults (see DOSAGE AND ADMINISTRATION and CLINICAL TRIALS).*

In making this recommendation the ACPM

- noted that the most prevalent HCV in Australia were genotypes 1 and 3 with small populations with genotype 2, 4 and 6.
- noted that Zepatier is effective in treatment naive and treatment experienced patients, both with and without cirrhosis.
- noted that the optional 8 weeks duration of treatment in genotype 1b patients was not based on the data from pivotal studies and requires further substantive evidence prior to inclusion in dosage and administration.
- noted the safety profile of Zepatier and the advantage it may provide in patients with renal impairment.
- expressed concern that the number of patients with HCV genotype 3 was very limited in the clinical studies included in the dossier and would require larger dataset to support approval.
- noted that the proposed use in genotype 6 had been withdrawn by the sponsor due to lower efficacy.

Proposed conditions of registration

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

Proposed Product Information/Consumer Medicine Information (CMI) amendments

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

- Amendment of the Dosage and Administration section of the Product Information and relevant section of the CMI that Zepatier is indicated in HCV genotypes 1 and 4 only.
- Removal of statement from the Dosage and Administration that proposed optional 8 weeks treatment in genotype 1b naïve patients.

Specific advice

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

1. Does the ACPM support the proposed instructions for Dosage and Administration in HCV genotypes 1, 4 and 6 patients, including no requirement for baseline NS5A testing in GT-1a patients?

Yes, ACPM supports the proposed instructions for Dosage and Administration in HCV genotypes 1 and 4 patients. The ACPM supported the inclusion of information on baseline NS5A under Pharmacodynamics/Resistance section of the Product Information rather than as an inclusion in the Indication or the Dosage and Administration sections.

2. Does the ACPM support the proposed use of triple DAA therapy (with sofosbuvir) in HCV genotype 3 patients based on preliminary evidence from a Phase II trial (N=41)?

This is based on an early very small study. The ACPM noted the ongoing clinical trial in HCV genotype 3 patients identified by the sponsor in its pre-ACPM response and recommended that a separate future submission based on larger dataset will be appropriate to assess the use of Zepatier in HCV genotype 3 infection.

3. Does the ACPM propose any additional efficacy data or post market surveillance activities?

Yes, this would be particularly important for GT4 subjects of whom numbers were small.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Zepatier EBR/GZR 50/100 mg for oral administration, indicated for:

> *Zepatier is indicated for the treatment of Chronic Hepatitis C genotype 1 or 4 infection in adults (see Dosage and Administration and Clinical Trials).*

Specific conditions of registration applying to these goods

Risk Management Plan for the Zepatier (EBR/ GZR 50 mg /100 mg) tablet: RMP (version 1.3, dated 13 April 2016, data lock point of 26 November 2015) with Australian Specific Annex (version 0.2, dated July 2016), which were submitted with application PM-2015-02428-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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