Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Glecaprevir / pibrentasvir

Proprietary Product Name: Maviret

Sponsor: AbbVie Pty Ltd

First round: June 2017

Second round: October 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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ADME	Absorption, Distribution, Metabolism and Excretion
2-DAA	Two component DAA therapy
AE	Adverse event
AFP	Alpha fetoprotein
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ART	Anti-retroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
AUC_{inf}	Area under the plasma concentration-time curve from time zero to infinity
AUC_t	Area under the plasma concentration-time curve from time zero to time of last measurable concentration
B/P	Blood to plasma ratio
BCRP	Breast cancer resistance protein
BID	Twice daily
BMI	Body mass index
BSA	Body surface area
CBZE	Carbamazepine-10, 11-epoxide
CI	Confidence interval
CKD	Chronic kidney disease
CL/F	Apparent oral clearance
C_{max}	Maximum observed plasma concentration
COC	Combined oral contraceptive
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Meaning
CYP	Cytochrome P450 enzymes
DAA	Direct-acting antiviral agent
DCV	Daclatasvir
DDI	Drug-drug interaction
DDQ	Desire for Drugs Questionnaire
DF	Disoproxil fumarate
DNA	Deoxyribonucleic acid
DSV	Dasabuvir
ECG	Electrocardiogram
EE	Ethinyl estradiol
eGFR	Estimated glomerular filtration rate
EOTR	End of treatment response
ESRD	End-stage renal disease
F	Bioavailability
FDC	Fixed-dose-combination
FIH	First-in-human
FMO	Flavin monooxygenases
f_u	Unbound fraction
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLE	Glecaprevir/ABT-493/A-1282576
GLE/PIB	GLE 100 mg/PIB 40 mg as a FDC tablet
GT1	Genotype 1
GT1a	Genotype 1a
GT1b	Genotype 1b
HBsAg	Hepatitis B surface antigen

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

Abbreviation	Meaning
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger RNA
NET	Norethindrone
NG	Norgestrel
NGM	Norgestimate
NGMN	Norelgestromin
NS3	Non-structural protein 3
NS4A	Non-structural protein 4A
NS5A	Non-structural 5A inhibitor
NS5B	Non-structural protein 5B
OATP1B1	Organic anion transporting polypeptide 1B1
OATP1B3	Organic anion transporting polypeptide 1B3
OBV	Ombitasvir
OCT	Organic cation transporters
PCS	Potentially clinically significant
PCS	Potentially clinically significant
PD	Pharmacodynamic
pegIFN	Pegylated interferon
P-gp	P-glycoprotein
PI	Protease inhibitors
PIB	Pibrentasvir/ABT-530/A-1325912
PIB	Pibrentasvir
PK	Pharmacokinetic
POP	Progestin only pill
PP	Per protocol

Abbreviation	Meaning
PR	PegIFN + RBV
PT	Preferred term
PT	Post-treatment
PTV	Paritaprevir
PVF	Primary virologic failure
QD	Once-daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's correction formula
R	Ritonavir
RBV	Ribavirin
RNA	Ribonucleic acid
RVR	Rapid virologic response
SAD	Single-ascending dose
SAE	Serious adverse event
SAF	Safety population
SmPC	Summary of Product Characteristics
SMV	Simeprevir
SOC	System Organ Class
SOF	Sofosbuvir
SOWS	Short Opiate Withdrawal Scale
StD	Standard deviation
SVR	Sustained virologic response
SVR12	Percentage of subjects achieving sustained virologic response 12 weeks following treatment, defined as HCV RNA < LLOQ
SVR24	Sustained virologic response 24 weeks post-dosing
SVR4	Sustained virologic response 4 weeks post-dosing
$t_{1/2}$	Terminal phase elimination half-life

Abbreviation	Meaning
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum observed plasma concentration
UGT	UDP-glucuronosyltransferases
ULN	Upper limit of normal
USP	U.S. Pharmacopeia Convention
V2 or Vc	Volume of distribution of the central compartment
V2/F or Vc/F	Apparent volume of distribution of the central compartment
V3 or Vp	Volume of distribution of the peripheral compartment
V3/F or Vp/F	Apparent volume of distribution of the peripheral compartment
VAS	Visual analogue scale
WBC	White blood cell
β	Apparent terminal phase elimination rate-constant
ΔΔQTcF	time-matched drug-placebo difference in QTcF interval, baseline-adjusted

Definition of terms:

- Plasma HCV RNA levels were measured by a central laboratory using the Roche COBAS Taqman PCR assay. The LLOD is 15 IU/mL with results reported as 'not detected'. The LLOQ is 25 IU/mL with results reported as '<25 IU/mL HCV RNA detected'.
- On-treatment quantifiable HCV RNA: Any two consecutive HCV RNA values ≥LLOQ during treatment, or at the final treatment measurement and the next consecutive post-treatment measurement.
- Post-treatment quantifiable HCV RNA: Any two consecutive post-treatment HCV RNA measurements ≥LLOQ.
- On-treatment virologic failure: Confirmed HCV RNA ≥LLOQ after HCV RNA <LLOQ during treatment, or confirmed increase from nadir in HCV RNA (two consecutive HCV RNA values > 1 log10 IU/mL above nadir) at any time point during treatment or HCV RNA ≥LLOQ persistently during treatment with at least 6 weeks treatment.
- Rebound: Confirmed HCV RNA ≥LLOQ after HCV RNA <LLOQ during treatment, or confirmed increase from nadir in HCV RNA (two consecutive HCV RNA values > 1 log10 IU/mL above nadir) at any time during treatment.
- Relapse: Confirmed HCV RNA ≥LLOQ between the end of treatment and 12 weeks after the last dose of study drugs in patients completing treatment and with HCV RNA <LLOQ at the end of treatment.
- RVR: Rapid virologic response (HCV RNA <LLOQ at the Week 4 measurement).
- EOTR: End of treatment response (HCV RNA <LLOQ at the Week 12 measurement).

- SVR4: HCV RNA <LLOQ measured 4 weeks after the last actual dose of study drug without any confirmed quantifiable (≥LLOQ) post-treatment value before or during that SVR window.
- SVR12: HCV RNA <LLOQ measured 12 weeks after the last actual dose of study drug without any confirmed quantifiable (≥LLOQ) post-treatment value before or during that SVR window.
- SVR24: HCV RNA <LLOQ measured 24 weeks after the last actual dose of study drug without any confirmed quantifiable (≥LLOQ) post-treatment value before or during that SVR window.

1. Submission details

1.1. Submission type

This is an application to register glecaprevir/pibrentasvir as a fixed dose combination.

1.2. Drug class and therapeutic indication

Maviret is a fixed dose combination tablet containing 2-DAA used for the treatment of patients with chronic HCV infection of any genotype. The tablet contains glecaprevir (a NS3/4A protease inhibitor) and pibrentasvir (a NS5A inhibitor), which together target multiple steps in the HCV lifecycle.

The proposed indication is:

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

1.3. Dosage forms and strengths

Maviret is a bilayer, film-coated tablet containing glecaprevir 100 mg and pibrentasvir 40 mg. The formulation proposed for marketing is identical to the formulation used in the Phase III registration studies.

1.4. Dosage and administration

The recommended dosage of Maviret is three 100 mg/40 mg tablets to be taken orally once daily with food, irrespective of fat or calorie content. For treatment-naïve patients with GT1-GT6 infection, the recommended treatment duration is 8 weeks for non-cirrhotic patients and 12 weeks for patients with compensated cirrhosis. For treatment-experienced, NS5A inhibitor-naïve patients with GT1, GT2, GT4-GT6 infection, the recommended treatment duration is 8 weeks for non-cirrhotic patients and 12 weeks for patients with compensated cirrhosis. For treatment-experienced, NS5A inhibitor-experienced patients with GT1, GT2, GT4-GT6 infection and any treatment-experienced patient with GT3 infection, the recommended treatment duration is 16 weeks for non-cirrhotic and compensated cirrhotic patients.

2. Background

2.1. Information on the condition being treated

Up to 200 million people worldwide are infected with HCV with 2 to 4 million new infections annually. Approximately 80% of infections are related to IV drug use, with lesser numbers attributed to sexual transmission, blood transfusions and tattoos. Approximately 300,000 Australians were infected with HCV in 2011. Acute infections become chronic in 70% to 90% of cases and this leads commonly to cirrhosis, chronic liver failure, hepatocellular carcinoma, liver transplantation and death. After 20 years of infection, 20-30% of patients will have progressed to cirrhosis, 5-10% will have developed end-stage liver disease and 4-8% will have died of liver-related causes. HCV has six genotypes (GT) and multiple subtypes with genotypes 1 to 3 distributed worldwide. Genotypes 1a and 1b account for 60% of global HCV infections. In Australia, the most common genotypes are 1a and 1b (54% prevalence) and 3a (37% prevalence). The incidence of HCV GT4 infection is low in the US (~1%) and in Europe (~5% on

average). However, in North Africa and the Middle East, it has a prevalence of ~50% (up to 90% in Egypt). It is spreading to Europe and the rest of the world through immigration and IV drug use.

2.2. Current treatment options

Until recently, the standard of care treatment for chronic HCV infection was the combination of pegylated interferon and ribavirin (pegIFN/RBV) for 48 weeks. The response to this treatment varies according to HCV genotype and host IL28B genotypic subtypes (CC, CT and TT). Patients with the IL28B CC genotype are able to mount stronger immune responses to the HCV virus and spontaneous viral clearance rates and responsiveness to antiviral therapy are enhanced. In patients with HCV GT1 infection, sustained viral response (SVR) rates following pegIFN/RBV therapy are only 45% in treatment-naïve patients and significantly lower in prior relapsers and non-responders. Moreover, the side effect profile of pegIFN/RBV is unfavourable with a high incidence of lethargy, fatigue, depression and anaemia. PegIFN/RBV therapy has now been superseded and replaced by DAA combinations with or without RBV.

The NS3/4A protease inhibitors boceprevir, telaprevir, sofosbuvir and simeprevir used singly in combination with pegIFN/RBV have improved SVR rates in treatment-naïve and treatment-experienced patients and shortened treatment duration to 24 weeks in many patients with HCV GT1 infection. The combinations of sofosbuvir and RBV and simeprevir and RBV, with or without pegIFN, have shown promise in patients with HCV GT4 infection. However, these 1-DAA combinations are associated with increased rates and severity of AEs, including rash, in addition to the common side effects of pegIFN/RBV. Simeprevir is well tolerated and has the advantage of once daily dosing. However, telaprevir and boceprevir both require TID therapy.

More recently, VIEKIRA PAK has been approved for the treatment of patients with HCV GT1. It is a combination product of three DAAs with different mechanisms of action and which all have potent activity against HCV GT1. They have non-overlapping viral resistance profiles and they also appear to have non-overlapping toxicity with RBV. Paritaprevir, ombitasvir and dasabuvir are potent DAAs; however, resistance develops to each agent when used as monotherapy. The 3-DAA regimen used in VIEKIRA PAK obviates the need for concomitant pegIFN/RBV therapy; increases SVR rates compared with 1-DAA + pegIFN/RBV combination therapy; shortens treatment duration from 24 to 12 weeks; and improves safety and tolerability. Dasabuvir has no activity against HCV GT4 but paritaprevir and ombitasvir have potent activity. For this reason, TECHNIVIE was developed as a fixed dose 2-DAA combination of paritaprevir and ombitasvir plus ritonavir which is otherwise identical to that used in VIEKIRA PAK. This 2-DAA combination has value for the treatment of patients with HCV GT4 infection.

HARVONI (lepidasvir and sofosbuvir) is well tolerated and effective in HCV GT1 infection; and sofosbuvir with RBV is effective in HCV GT2 and GT3 infections. It is also approved for use in GT4 GT5, or GT6-infected patients who are not suitable for pegIFN treatment. In the EU, HARVONI with RBV for 24 weeks is approved for the treatment of GT1 and GT4 infection in patients with decompensated cirrhosis, who are either awaiting liver transplantation or during the post-transplant period. Velpatasvir is a novel HCV NS5A inhibitor with potent antiviral activity *in vitro* against GT1-6 replicons. Velpatasvir and sofosbuvir have been formulated in a FDC tablet as EPCLUSA for once daily use. EPCLUSA is a well-tolerated, once daily, single dose, 12 week treatment for patients with HCV infection of any genotype, in non-cirrhotic patients and in those with compensated or decompensated cirrhosis (in combination with RBV).

2.3. Clinical rationale

Successful clearance of HCV reduces liver-related morbidity and mortality with a reduction in the incidence of HCC. SVR rates of 95% to 100% can now be achieved with DAA combinations in

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

2.4. Formulation

2.4.1. Formulation development

2.4.1.1. Development of GLE formulations

A number of GLE formulations were investigated as part of Phase I and II. GLE tablets were formulated at five dose strengths (2.5 mg, 25 mg, 50 mg, 100 mg and 200 mg); however, the examination of two of the formulations (GLE 50 mg prototype Phase IIb Tablet B and 200 mg prototype Phase IIb Tablet A) was limited as a result of poor bioavailability.

The 2.5 mg and 25 mg tablets evaluated as part of the first–in-human (FIH) study (M13-356) utilised amorphous solid dispersion which was blended with additional excipients (that is, microcrystalline cellulose) and compressed into tablets of the selected dosage strength. Phase IIa and Phase IIb Tablets: GLE Phase IIa tablets were formulated based on the FIH at 100 mg dose strength by increasing loading in the tablet and removing microcrystalline cellulose to reduce pill count at higher dose levels. GLE Phase IIb tablet contains the same composition as the Phase IIa tablet. The different name was used mainly to identify the clinical development stage of the formulation.

2.4.1.2. Development of PIB formulations

PIB formulations were also evaluated as part of Phase I and II studies. PIB tablets were formulated at five dose strengths of 1.5 mg, 15 mg, 25 mg, 40 mg and 100 mg; however due to poor bioavailability, the PIB 25 mg test formulation tablet strength and 100 mg test formulation were only used in formulation development bioavailability Study M13-581.

The 1.5 mg and 15 mg tablets examined as part of the FIH study (M13-355) utilised an amorphous solid dispersion which was blended with additional excipients (that is, microcrystalline cellulose) and compressed into tablet of the selected dosage strength. Following on from the FIH tablets, both the Phase IIa and IIb formulations were amorphous solid dispersions but the excipient composition was slightly different between the two formulations.

Additional PIB formulations were evaluated in parallel to FIH, Phase IIa and Phase IIb formulations in Phase I studies but were not developed further due to lower bioavailability compared to FIH, Phase IIa or Phase IIb tablets. Depending upon the clinical stage of development, FIH, Phase IIa or Phase IIb tablets were used as reference for the additional formulations that were evaluated. In addition, the formulation was evaluated only in a Phase I bioavailability, Absorption, Distribution, Metabolism and Excretion (ADME) study.

2.4.1.3. Development of phase III formulation

Phase I and Phase II studies were undertaken using separate tablet formulations of GLE and PIB. Therefore, to reduce pill count and improve compliance, AbbVie developed and investigated multiple pilot co-formulations of GLE/PIB with different compositions and dose strengths in Phase I bioavailability studies. Most of these co-formulations had lower bioavailability relative to the reference Phase IIa or Phase IIb tablets and further development was not undertaken.

The Phase III formulation is fixed-dose co-formulated film-coated bilayer tablet of GLE/PIB (100 mg/40 mg tablets). Three tablets are to be taken as a single dose (300 mg/120 mg) once daily, administered with food.

2.4.1.4. Development of Co-formulated bilayer tablets

Development of co-formulated GLE/PIB consisted of manufacturing two intermediates each for GLE and PIB. The process resulted in formation of a uniform amorphous solid dispersion in a matrix. The bilayer tablets are prepared by milling each intermediate individually followed by blending with the excipients to form two separate drug/excipient blends.

The earlier bilayer tablets were manufactured as uncoated GLE/PIB bilayer tablets and were evaluated in Phase I studies.

2.4.1.5. Phase III formulation

The tablet core composition for the Phase III formulation was the same as bilayer tablet with an additional non-functional film-coating. The film-coated bilayer tablet was manufactured and used in registrational studies. It contains GLE 100 mg and PIB 40 mg per tablet and is to be administered as 3 tablets at the target dose of GLE/PIB 300 mg/120 mg QD. The Phase III formulation (Bulk Lot Number: RD-15-001 and manufactured in Ireland) was compared to the Phase IIb tablet in Study M14-714.

For the Phase III studies, the film-coated bilayer tablets were administered with food.

2.4.1.6. Proposed commercial' formulation

The 'proposed commercial' formulation of GLE/PIB is the same as the Phase III formulation used in the registrational studies. All batches of the 'proposed commercial' formulation are manufactured using the same equipment, manufacturing process and manufacturing site and are exactly the same composition as the Phase III formulation. The quantitative compositions of the proposed commercial formulation of GLE/PIB and the tablet film coating are presented.

2.4.1.7. Additional GLE/PIB Co-formulations not further developed

Additional GLE/PIB co-formulations were evaluated in Phase I bioavailability studies; however, most of these formulations demonstrated lower bioavailability relative to the reference Phase IIa or Phase IIb tablets and no further development was undertaken.

2.5. Excipients

The tablets contain copovidone, tocopherol, colloidal silicon dioxide, propylene glycol monocaprylate, croscarmellose sodium, sodium stearyl fumarate and Opadry II 32F240023 pink (hypromellose 2910, lactose monohydrate, titanium dioxide, macrogol 3350 and iron oxide red). The tablets do not contain gluten, but they do contain lactose.

Comment: Update the text in Description section of proposed PI to state ‘tablets’ rather than ‘tablet’.

2.6. Guidance

A pre-submission meeting with the TGA was held and the submission complies with the outcomes of that meeting. The clinical development plan, proposed indication, treatment duration and justifications for a fixed dose combination were reviewed. The development program was conducted in accordance with the relevant US[1] and CHMP[2] guidelines. Specific

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

scientific advice from the FDA and CHMP was obtained at the end of Phase I and the end of Phase II. Both bodies approved the Phase III dose and duration selection, including the assessment of 8, 12 and 16 weeks regimens.

2.7. Evaluator's commentary on the background information

The background information provided by the Sponsor is satisfactory.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contains new clinical studies as follows:

- Clinical Pharmacology Studies
  - 43 PK studies; Two of these studies also contain PD data related to the QTc effects of therapeutic and supra-therapeutic doses of GLE + PIB.
  - a single study (R&D/16/0234) examines the population PKs of both GLE and PIB in HCV-infected subjects and examines the relevance of a range of factors that may contribute to PK variability.
- Pivotal Efficacy/Safety Studies
  - Two randomised, controlled studies (M15-464 and M13-594).
  - Seven uncontrolled Phase II/3 efficacy and safety studies, M13-583, M13-590, M15-462, M15-410, M14-867, M14-868 and M14-172.
- Other Efficacy/Safety Study
  - One pilot Phase II study M14-213.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

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

3.4. Evaluator's commentary on the clinical dossier

Overall, the clinical dossier is satisfactory. With the exception of study M14-213, all the studies submitted may be considered pivotal despite the inclusion of uncontrolled Phase II studies. The uncontrolled Phase II studies were in part exploratory; however, the confirmatory arms underpinned important data supporting the proposed PI. The studies presented assessed efficacy in patients with all HCV genotypes, in treatment-naïve and treatment-experienced patients (including failed DAA therapies), in patients without cirrhosis or with compensated cirrhosis, in patients with severe renal impairment, and patients with HCV/HIV-1 co-infection. Different treatment durations were explored over 8, 12 and 16 weeks based on baseline disease characteristics.

4. Pharmacokinetics

Comment: As the formulation of GLE/PIB proposed for marketing represents a fixed-dose combination of 100 mg/40 mg film-coated tablets, which is identical to the Phase III formulation, where possible the following discussion on the PKs of GLE/PIB will primarily focus on this Phase III formulation.

4.1. Studies providing pharmacokinetic information

See table below.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK – Relative BA	M14-714	Relative BA and food effect of FDC GLE/PIB film-coated bilayer tablets relative to the reference Phase IIb formulation
		M13-601	Relative BA of the GLE Phase IIa and Phase IIb test formulation A and PIB Phase IIb test formulation A and the FIH formulations
		M14-214	Relative BA of the GLE Phase IIb test formulation and the Phase IIa and FIH formulations
		M14-711	Relative BA of four experimental GLE/PIB formulations and reference Phase IIb formulations
		M13-581	Relative BA of the PIB Tablets –test formulations and FIH formulation
		M13-580	Relative BA of co-formulated GLE/PIB test formulation and the reference Phase IIa formulations
		M14-611	Relative BA of the co-formulated GLE/PIB test formulations and the reference Phase IIa formulations
		M14-719	Relative BA of three different co-formulated GLE/PIB formulations and the reference Phase IIb formulations
		M14-725	Relative BA and food effect on blended GLE/PIB film-coated tablets and the reference co-formulated uncoated bilayer tablet formulation
		M14-717	Relative BA and food effect on experimental GLE/PIB uncoated, bilayer tablets and reference Phase IIb formulations

PK topic	Subtopic	Study ID	*
	ADME	M13-890	ADME of [^{14}C]-GLE and [^{14}C]-PIB in healthy males
	Escalating doses	M15-543	Potential for QTc prolongation following combination administration of GLE and PIB
		M14-716	PKs, safety and tolerability of GLE and PIB when given in combination
		M13-356	Safety, tolerability and PKs of single and multiple escalating doses of GLE
		M13-355	Safety, tolerability and PKs of single and multiple escalating doses of PIB
PK in special populations	Target population	M13-595	Safety, tolerability, PKs, and antiviral activity of multiple dose levels of GLE and PIB administered as monotherapy for 3 days in treatment-naïve adults with chronic HCV GT1 infection
		M14-868	PKs of ABT-493, ABT-530 and RBV and the emergence and persistence of viral variants in patients with HCV
		M15-410	PKs of ABT-493, ABT-530, and RBV, and to evaluate the role of RBV in patients with HCV infection
		M14-867	PKs of GLE, PIB, and RBV, and the emergence and persistence of viral variants with this treatment regimen
	Hepatic impairment	M13-604	PKs and safety of single-dose GLE and/or PIB in subjects with normal hepatic function and stable chronic hepatic impairment
	Renal Impairment	M13-600	PKs and safety of a single dose of GLE and PIB in subjects with normal renal function, mild, moderate and severe renal impairment and in subjects with ESRD
	Race	M15-432	PKs and safety of multiple doses of GLE and PIB given alone and in combination in healthy Han Chinese, Japanese and Caucasian adults
		M14-066	PKs and safety of multiple oral doses of GLE and PIB given alone and in combination in healthy Han Chinese, Japanese, and Caucasian adults
PK interactions	GLE and PIB	M13-586	PKs and safety of multiple oral doses of GLE and PIB given in combination under non-

PK topic	Subtopic	Study ID	*
			fasting conditions in healthy adults
	CYP Substrates	M13-605	DDI between GLE + PIB at steady state and caffeine, midazolam, tolbutamide, omeprazole, dextromethorphan and cyclosporine
		M14-380	Effect of GLE + PIB on the PKs and safety of caffeine, tolbutamide, omeprazole, midazolam and dextromethorphan
		M13-578	DDI between GLE + PIB at steady state and felodipine or amlodipine administered as a single dose
		M13-584	PK interaction following administration of a single 100 mg dose of cyclosporine
		M13-599	*PK interaction with single doses of two angiotensin receptor blockers*
		M14-721	DDI between GLE + PIB and simvastatin or lovastatin
		M14-715	PK interaction with multiple doses of 20 mg to 40 mg of omeprazole
	CYP and P-gp inducers	M14-724	DDI with carbamazepine
		M14-723	DDI between rifampin administered as a single dose and at steady state and GLE + PIB
	Anti-HIV medication	M13-603	DDI between GLE and PIB at steady-state and atazanavir and ritonavir at steady-state
		M13-597	DDI between multiple doses of Atripla and multiple doses of GLE + PIB in HIV-mono-infected subjects
		M15-584	DDI between multiple doses of GLE + PIB and multiple doses of Genvoya or Triumeq
	P-gp substrate	M13-582	DDI between GLE + PIB at steady state and a single dose of digoxin
		M14-532	DDI between sofosbuvir and GLE + PIB
		M13-585	DDI between a single 150 mg dose of dabigatran and GLE 300 mg QD + PIB 120 mg QD.
	OATP-substrates	M13-579	DDI between GLE + PIB and pravastatin, rosuvastatin or atorvastatin

PK topic	Subtopic	Study ID	*
	Other interactions	M14-213	PKs of ABT-450, ritonavir, PIB, and RBV in patients with chronic HCV infection
		M13-598	Effect of GLE and PIB on the PKs of oral contraceptives
		M13-602	Effect of GLE 300 mg QD + PIB 120 mg QD on the PKs of methadone or buprenorphine/naloxone
Population PK analyses	Target population	R&D/16/0234	To characterise the popPKs of GLE and PIB and identify to identify covariates

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

4.2. Summary of pharmacokinetics

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Analytical methods for detecting GLE/PIB in plasma

Plasma concentrations of GLE and PIB were determined using validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) methods. Across the studies the lower limit of quantitation (LLOQ) for GLE ranged from 0.0282 ng/mL to 0.200 ng/mL and for PIB ranged from 0.0198 ng/mL to 0.197 ng/mL.

4.2.1.2. Absorption

Sites and mechanism of absorption

The formulation of GLE/PIB proposed for marketing represents a fixed-dose combination (FDC) of 100 mg/40 mg film-coated tablet, which is to be taken orally with food. Following the recommended dose of 300 mg/120 mg (3 x 100/40 mg tablets) in healthy adults and a moderate-fat breakfast the C_{max}, T_{max} and $t_{1/2}$ values for the GLE component were 937 ng/mL, 4 h and 6.0 h, respectively, and for the PIB component were 221 ng/mL, 5 h and 13 h, respectively, whereas, following a high-fat breakfast the values for GLE were 633 ng/ml, 5.0 h and 6.3 h, respectively, and for PLE were 237 ng/mL, 5 h and 13.5 h, respectively. PopPK modelling based on the data of patients with chronic HCV provided predictions for the absorption rate constant (Ka) of 8.63 /day and 6.13/day for GLE and PIB, respectively.

4.2.1.3. Bioavailability

Absolute bioavailability

The absolute bioavailability of GLE and PIB has not been determined. Although not specifically stated, this is most likely due to the poor solubility of both GLE and PIB in water.

4.2.1.4. Bioavailability relative to an oral solution or micronised suspension

The relative bioavailability of GLE and PIB compared to either an oral solution or micronised suspension has not been determined.

4.2.1.5. Bioequivalence of clinical trial and market formulations

GLE/PIB formulations

The to-be-marketed FDC formulation of GLE/PIB is identical to the Phase III formulation and the relative bioavailability of this form of the FDC was compared to the reference Phase IIb formulation, which comprised a free combination of 100 mg GLE and 40 mg PIB tablets, under fasted conditions in 23 healthy subjects as part of Study M14-714. Following a 300 mg/120 mg dose of GLE/PIB, the results indicated that under fasting conditions, the AUC values for GLE and PIB were 56% and 36% lower, respectively, following administration of the FDC tablets of GLE/PIB than following the free-combination of Phase IIb tablets.

GLE formulations

During the Phase I and II sections of the clinical development program the principal formulations of GLE used were the 25 mg strength tablets used in the FIH study (M13-356) and the 100 mg Phase IIa and Phase IIb tablets, which were compositionally identical. The relative bioavailability of the 100 mg Phase IIa formulation, the 50 mg and 200 mg Phase IIb test formulations and the 25 mg FIH formulation was examined in two studies M13-601 and M14-214. Study M13-601 is the most relevant to the current discussion as it examined GLE exposure in healthy subjects following administration of a single, consistent dose (400 mg) of the Phase IIa formulation (4 x 100 mg) and FIH formulation (16 x 25 mg) approximately 30 minutes after the start of a moderate fat breakfast. The results indicated that following administration of four 100 mg GLE Phase IIa tablets, GLE C_{max} and AUC values were 83% and 76% higher than following administration of the sixteen 25 mg FIH tablets.

PIB formulations

During the Phase I and II sections of the clinical development program the principal formulations of PIB used were the 15 mg strength tablets used in the FIH study (M13-355) and the 40 mg Phase IIa and Phase IIb tablets, which unlike the corresponding GLE formulations, differed slightly in excipient composition. Unfortunately, bioequivalence of the principal formulations of PIB used in the Phase I and II trials does not appear to have been established.

Question: Can the sponsor please justify why the bioequivalence of the FIH PIB formulation and the 40 mg Phase IIa and 2b PIB formulations have not been examined?

An extensive range of formulations of GLE, PIB and co-formulations GLE/PIB were also developed and investigated as part of the clinical development process; however, due to poor or lower bioavailability than the to-be-marketed (Phase III) formulation in humans they were not developed further. Therefore, although the relevant studies are summarised, in most cases they will not be discussed in detail as part of the current evaluation.

4.2.1.6. Bioequivalence of different dosage forms and strengths

A single dosage strength (100 mg/40 mg) and formulation (film-coated FDC) of GLE/PIB tablets is proposed for marketing.

4.2.1.7. Bioequivalence to relevant registered products

Not applicable.

4.2.1.8. Influence of food

Study M14-714 also examined the effects of a moderate- and high-fat breakfast on the PKs of the Phase III formulation. Following a 300 mg/120 mg dose of GLE/PIB FDC, food increased the exposure to the GLE component by 1.8- to 3.2-fold compared to fasted conditions and exposure to the PIB component by 1.4- to 2.1-fold. Moreover, following administration of the FDC tablet, GLE and PIB exposure under fed conditions was similar to the levels of GLE and PIB exposure attained following administration of the free combination of the Phase IIb tablet formulation under fasted conditions.

Comment: No studies have directly examined the relative bioavailability of the reference Phase IIb formulation under fasted and fed conditions. Thus it is difficult to accurately compare the PKs of FDC Phase III formulation and the Phase IIb formulations under fed conditions. However, if we compared the GLE and PIB exposure under fasted (results from Study M14-714) and fed (results from Study M14-724) conditions following a single dose of the free combination of 300 mg GLE + PIB to healthy subjects we can see that exposure to the GLE component is increased by ~1.3- to 1.40-fold and for the PIB component is increased by ~1.4- to 1.7-fold under fed conditions compared to when the subjects were fasted. Although this comparison is far from ideal as the study has not been undertaken in the same population, it clearly identifies that food may significantly effect GLE and PIB exposure when given as the free combination, and perhaps calls into question the results of studies, such as M14-868 or M15-410, in which patients have been administered the free combination without instruction regarding whether tablets should be taken with food or not.

4.2.1.9. Dose proportionality

GLE + PIB

Two studies (M15-543 and M14-716) examined GLE and PIB exposure following administration of 2 doses of the free combination of GLE + PIB in healthy subjects. The primary objective of the first of these studies, M15-543, was to assess the potential for QTc prolongation following combination administration of GLE and PIB; however, it also investigated the PKs of GLE and PIB following single doses of the free combination at dose strengths of 600 mg + 240 mg and 400 mg + 120 mg. The point estimates for the ratios comparing GLE C_{max} and AUC_{inf} following doses of GLE 600 mg + PIB 240 mg vs. GLE 400 mg + PIB 120 mg were 3.6-fold and 3.9-fold, respectively, and for PIB C_{max} and AUC_{inf} were 1.8- and 2.1-fold, respectively. Similarly, in Study M14-716 the ratio of the point estimates for GLE C_{max} and AUC_{inf} values following doses of 800 mg + 240 mg of the free combination of GLE + PIB vs. 400 mg + 120 mg of GLE + PIB were 8-fold and 13-fold, respectively, and for PIB were 2.2-fold and 3.0-fold, respectively.

Overall, these results suggest that following administration of increasing doses of GLE + PIB to healthy subjects increases in GLE are greater than dose proportional, whereas, the results for PIB are equivocal.

GLE

Study M13-356 examined GLE PKs following a single administration of GLE at a range of doses (25 mg to 800 mg) in 45 healthy subjects. GLE exhibited non-linear PKs with greater than dose proportional increases in exposure following single GLE doses of 25 mg to 800 mg. For instance, following a 200 mg dose of GLE the C_{max}/dose and AUC_{inf}/dose were 0.60 (ng/ml)/mg and 2.71 (ng.h/ml)/mg, respectively, whereas, following a 800 mg dose they were 15.4 (ng/ml)/mg and 43.7 (ng.h/ml)/mg, respectively.

PIB

Study M13-355 examined PIB PKs following single escalating doses of 1.5 mg to 600 mg PIB. Over the dose range 1.5 mg to 120 mg PIB exposure increased in a greater than dose proportional manner, whereas, they were linear across the 120 mg to 600 mg dose range.

4.2.1.10. Bioavailability during multiple-dosing

GLE

Study M13-356 also examined the PKs of GLE following administration of multiple escalating doses of 200 mg to 800 mg QD for 10 days. Similar to the PKs of GLE following single doses, GLE also exhibited non-linear PKs with greater than dose proportional increases in exposure following multiple doses with mean C_{max}/dose and AUC_{0-24}/dose values increasing from 0.74

(ng/mL)/mg and 2.83 (ng.h/ml)/mg, respectively, following GLE 200 mg QD to 21.5 (ng/mL)/mg and 100(ng.h/mL)/mg, respectively following GLE 800 mg QD. Steady state was attained following 10 days of dosing and median accumulation ratios for C_{max}, Ctrough and AUC_{0-24} values ranged from 0.8 to 2.4 over the 200 to 800 mg dose range. Following both the 200 mg QD and 400 mg QD doses there was minimal accumulation of GLE by Day 10, whereas, following the 800 mg QD dose, the GLE exposures on Study Day 10 were approximately 81% to 142% higher than those on Study Day 1.

PIB

Sub-study 2 of Study M13-355 examined PIB PKs following administration of multiple escalating doses of 30 mg to 600 mg QD for 10 days. Following multiple doses of PIB, C_{max} and AUC_{0-24} values increased in a greater than dose proportional manner between doses ranging from 30 mg to 180 mg and were then approximately linear following the 180 mg and 600 mg doses. In addition, the mean PIB C_{max} and AUC_{0-24} values were 4% to 53% higher at steady state on Study Day 10 compared to Study Day 1, suggesting minimal accumulation.

4.2.1.11. Effect of administration timing

Not applicable.

4.2.2. Distribution

4.2.2.1. Volume of distribution

The PopPK report, R&D/16/0234, identified that a two-compartment model with first-order absorption and elimination adequately described the GLE and PIB plasma concentration-time data. The estimated values for the apparent volume of distribution of the central (Vc/F) and peripheral (Vp/F) compartments for GLE were 130 L and 39.6 L, respectively, and for PIB were 1380 L and 2250 L, respectively.

4.2.2.2. Plasma protein binding

In vitro studies (R&D/16/0374 and R&D/16/0372) were undertaken to determine the unbound fractions (f_u) of GLE and PIB in human and animal plasma, human liver microsomes, and liver homogenate. Human whole blood-to-plasma ratios (B/P) indicated that there was no concentration dependence in plasma binding for either GLE or PIB when tested at concentrations ranging from 0.1 to 30 µM.

For GLE, the mean unbound fraction at 1 µM in human plasma was 0.025, respectively, whereas, for PIB, the mean unbound fraction in human plasma was 0.000057.

No preferential partitioning into red blood cells was observed for GLE or PIB in any of the species tested. GLE had average B/Ps of 0.64, 0.60, 0.55, 0.75 and 0.57 in mouse, rat, dog, monkey and human, respectively, whereas, PIB had B/Ps of 0.59, 0.57, 0.66, 0.60 and 0.62 in mouse, rat, dog, monkey and human, respectively.

4.2.2.3. Erythrocyte and tissue distribution

Please see the preceding sections of this report entitled volume of distribution and plasma binding for further information.

4.2.3. Metabolism

4.2.3.1. Interconversion between enantiomers

Not applicable.

4.2.3.2. Sites of metabolism and mechanisms / enzyme systems involved

The ADME Study, M13-890, identified that following oral administration, both [^{14}C]-GLE and [^{14}C]-PIB were primarily cleared via the biliary-faecal route; however, CYP3A metabolism played a secondary role in the metabolism of [^{14}C]-GLE.

4.2.3.3. Non-renal clearance

Following a 400 mg dose of [^{14}C]-GLE the mean recovery of administered radioactivity was 92.8%; with nearly the entire dose (92.1%) recovered in faeces, whereas, the remaining radioactivity (0.661%) was recovered in urine. Following a 120 mg dose of [^{14}C]-PIB, the mean recovery of administered radioactivity was 96.6%, which was entirely contained in the faeces; as no measurable radioactivity could be detected in urine.

4.2.3.4. Metabolites identified in humans: active and other

No metabolites for GLE or PIB were identified in human plasma.

4.2.3.5. Pharmacokinetics of metabolites

Not applicable.

4.2.3.6. Consequences of genetic polymorphism

Not applicable.

4.2.4. Excretion

4.2.4.1. Routes and mechanisms of excretion

As stated previously, both GLE and PIB were primarily cleared via the biliary-faecal route.

4.2.4.2. Mass balance studies

Following administration of 400 mg [^{14}C]-GLE, although no GLE metabolites were identified in human plasma, in pooled faeces samples, unchanged GLE accounted for 22.6% of the radioactive dose and seven GLE metabolites were identified. By contrast, following administration of 120 mg [^{14}C]-PIB, unchanged PIB was the only radiochemical component of drug related materials detected in faeces.

4.2.4.3. Renal clearance

As stated previously, only 0.661% of radioactivity was recovered in the urine following a 400 mg dose of [^{14}C]-GLE, whereas, no radioactivity was detected in the urine following a 120 mg dose of [^{14}C]-PIB.

4.2.4.4. Intra and inter individual variability of pharmacokinetics

The PopPK analysis, R&D/16/0234, provided estimates for the inter-individual variability on apparent oral clearance (CL/F) and bioavailability (F) of GLE of 0.874 and 1.84, respectively. For PIB, the estimated inter-individual variability values for CL/F, apparent volume of distribution of the central compartment (V2/F) and F were 0.084, 0.334 and 0.198, respectively. The estimated residual variability for GLE was 0.562, whereas, for PIB it was 0.252.

4.2.5. Pharmacokinetics in the target population

4.2.5.1. Bioequivalence

Two studies (M14-868 and M15-410) examined the relative exposure to GLE and PIB following administration of the free combination of the Phase II formulation of 300 mg GLE + 120 mg PIB *with or without* food and the Phase III FDC *with* food in patients with HCV. The results of both studies indicated that GLE and PIB exposures were comparable following administration of either the free combination or FDC formulation.

Comment: It is very difficult to interpret these findings as the results compare fed exposures for the FDC to a combination of fed and unfed exposures for the free combination.

4.2.5.2. Dose proportionality

The primary aim of Study M13-595, which was the first study to be undertaken in the target population, was to assess the safety, tolerability, PKs and antiviral activity of multiple doses

levels of GLE and PIB administered as monotherapy for 3 days in treatment-naïve adults with chronic HCV GT1 infection with and without compensated cirrhosis. In subjects with HCV-infection, increase in GLE exposure was more than dose-proportional over the 100 mg to 700 mg range. Similarly, the increase in PIB exposure was more than dose-proportional over the 15 mg to 120 mg range; however, between the 120 mg and 400 mg doses the increase in PIB exposure was less than dose proportional.

4.2.6. Pharmacokinetics in special populations

4.2.6.1. Pharmacokinetics in subjects with impaired hepatic function

Study M13-604 examined the PKs of a single-dose of GLE and/or PIB under non-fasting conditions in subjects with normal hepatic function and in subjects with mild, moderate and severe hepatic impairment as assessed by the Child-Pugh score. Following the PI recommended dose of the free combination of GLE 300 mg + PIB 120 mg, GLE AUC values were 33% and 100% higher in subjects with mild and moderate hepatic impairment, respectively, and increased by 10-fold in subjects with severe hepatic impairment compared to the subjects with normal hepatic function. For GLE C_{max} values, there was little difference (≤ 1%) between subjects with normal hepatic function and subjects with mild hepatic impairment, whereas, GLE C_{max} values were increased by 38% and 3.8-fold in subjects with moderate and severe hepatic impairment. PIB AUC and C_{max} values in subjects with mild hepatic impairment were similar (≤ 20% difference), whereas, in subjects with moderate hepatic impairment they were 26% higher, compared to the subjects with normal hepatic function. In subjects with severe hepatic impairment PIB C_{max} was 41% lower and PIB AUC was increased by 114% compared to the subjects with normal hepatic function. This study also examined GLE and PIB protein binding in and indicated that the fraction unbound GLE in subjects with mild or moderate impairment and of PIB in all hepatic impairment groups was not significantly different from normal subjects ($p > 0.05$), but was significantly higher for GLE in subjects with severe hepatic impairment ($p < 0.05$).

4.2.6.2. Cirrhotic subjects

As part of Study M13-595, GLE and PIB exposure was also assessed in members of the target population who had and did not have cirrhosis. GLE exposures in cirrhotic subjects following 200 mg QD dosing were between the exposure of 200 mg QD and 300 mg QD in non-cirrhotic subjects, whereas, PIB exposures were similar in both non-cirrhotic and cirrhotic subjects. Similar findings were also observed in Study M14-867.

Adding further support for these findings the PopPK analysis, R&D/16/0234 identified that cirrhosis was a covariate for both GLE F and CL/F and the estimated GLE exposure in subjects with compensated cirrhosis were 120% higher than in subjects without cirrhosis, whereas, for PIB there was only a 7% difference in exposure between subjects with compensated cirrhosis and those without cirrhosis.

4.2.7. Pharmacokinetics in subjects with impaired renal function

Study M13-600 assessed the PKs following a single dose of the free combination of GLE 300 mg + PIB 120 mg under non-fasting conditions in subjects with normal renal function, in subjects with mild, moderate and severe renal impairment and in subjects with end-stage renal disease (ESRD), as assessed by the estimating glomerular filtration rate (eGFR). In addition the study also examined the impact of haemodialysis in subjects with ESRD requiring dialysis. The results indicated that as eGFR decreased there was a trend towards increasing GLE and PIB AUC_{inf} values, with maximum predicted increases of 56% and 46%, respectively, in subjects with ESRD not on dialysis compared to normal subjects. By contrast, C_{max} values were similar (≤ 25% difference) in all groups regardless of renal function. In addition, GLE and PIB exposures were similar (≤ 18% difference) in subjects with ESRD requiring dialysis prior to haemodialysis and on a non-dialysis day and there was no significant difference in GLE and PIB protein binding between the functional groups, nor was protein binding affected by haemodialysis.

Providing further support for the results of Study M13-600, the PopPK analysis, R&D/16/0234 estimated that GLE exposure was 55% higher in subjects with moderate or severe renal impairment and 86% higher exposure in subjects with end stage renal disease compared to subjects with normal renal function. For the PIB component, exposure was 13% higher in subjects with moderate or severe renal impairment and 54% higher exposure in subjects with end stage renal disease compared to subjects with normal renal function.

4.2.8. Pharmacokinetics according to age

The PopPK analysis, R&D/16/0234, identified that age was a significant covariate for GLE and PIB CL/F such that a 10-year increase in age (65 years versus 55 years) is associated with 32% higher GLE exposure and 13% higher PIB exposure.

4.2.9. Pharmacokinetics related to genetic factors

Not examined.

4.2.10. Pharmacokinetics in other special population / with other population characteristic

4.2.10.1. Gender

The PopPK analysis, R&D/16/0234, also identified that the subject's gender affected GLE and PIB exposure as GLE exposure was 39% higher in females than in males and PIB was 37% higher in females compared to males.

4.2.10.2. Race

Two studies, M15-432 and M14-066 compared the PKs under non-fasting conditions in healthy Han Chinese, Japanese and Caucasian adult subjects following multiple oral doses of GLE and PIB given alone and in combination. In Study M15-432 following the recommended dose of 300 mg GLE and 120 mg PIB QD for 7 days steady-state GLE and PIB exposures in Japanese and Han Chinese were comparable to Caucasians with point estimates for the ratio of central values for GLE AUC_{24} of 0.81 and 0.87 for Han Chinese and Japanese subjects, respectively, and for PIB AUC_{24} of 0.76 and 0.99, respectively. Additionally, a range of GLE doses (100 mg, 200 mg and 300 mg) were administered in combination with either 80 mg or 120 mg PIB and the results identified that the non-linear dose-exposure relationships for GLE and PIB were similar for the three racial groups. The second study, M14-066 compared the PKs following multiple doses of the free combination of GLE 700 mg + PIB 160 mg QD in the three racial groups. However, given the higher than recommended dose and the non-linear nature of the dose exposure relationships for both GLE and PIB, these results will not be discussed.

Adding further support for Study M15-432 the PopPK analysis, R&D/16/0234 identified that Race was a covariate of PIB CL/F and provided estimates that PIB exposure was 26% higher in Asian subjects than in Caucasians. By contrast, Race was not identified as a covariate of GLE exposure.

4.3. Population pharmacokinetics

4.3.1. PopPK analysis ID

As discussed previously in this report a PopPK analysis, R&D/16/0234, was undertaken to characterise the popPKs of GLE and PIB when administered alone and in combination in HCV-infected subjects and identify demographic, pathophysiologic and treatment factors that may contribute to the variability in the PKs of GLE and PIB. The data set included results from a total of 2710 subjects who were administered GLE and 2704 subjects who received PIB enrolled in four Phase II studies (Studies M13-595, M14-867, M14-868 and M15-410) and six Phase III studies (Studies M13-583, M13-590, M13-594, M14-172, M15-462 and M15-464). The analysis

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

For GLE, bodyweight, body mass index (BMI), body surface area (BSA), race, genotype, dialysis, prior HCV treatment history and co-administration with ribavirin (RBV) did not significant impact on GLE exposure. By contrast, a 10-year increase in age (65 years versus 55 years) was associated with 32% higher GLE exposure; GLE exposure was 39% higher in females than in males; GLE exposures in subjects with compensated cirrhosis were increased by 2.2-fold when compared to subjects without cirrhosis; and GLE exposure was 55% higher in subjects with moderate or severe renal impairment and 86% higher exposure in subjects with end stage renal disease than in subjects with normal renal function. In regards to co-administered medication: GLE exposure was 5% lower in subjects who took high dose proton pump inhibitors (PPIs, e.g. omeprazole 40 mg QD equivalent or higher) and 16% higher exposure in subjects who took opioid medications.

The geometric mean of individual-estimated GLE $AUC_{24,ss}$ were 4800 ng.h/mL and 10500 ng · h/mL in HCV-infected subjects with and without cirrhosis, respectively. In Phase I Studies, the estimated GLE $AUC_{24,ss}$ in healthy subjects who received GLE/PIB 300 mg/120 mg QD dose is 4380 ng.h/mL which is comparable to the GLE $AUC_{24,ss}$ in HCV-infected subjects without cirrhosis (that is, 4800 ng.h/mL).

For PIB, dialysis, genotype, prior HCV treatment history and co-administration with RBV had no significant impact on PLE exposure, whereas, PIB exposure was higher by: 13% in subjects aged 65 compared to 55 (that is, 10-year increase); 37% in females than in males; 26% in Asian subjects compared to other races; 7% in subjects with compensated cirrhosis compared to subjects without cirrhosis; 13% in subjects with moderate or severe renal impairment and 54% higher exposure in subjects with end stage renal disease compared to subjects with normal renal function; and 27% in subjects who took breast cancer resistance protein (BCRP) inhibitors. By contrast, a 10-kg increase in bodyweight (90 kg versus 80 kg) decreased exposure by approximately 3%.

The geometric mean of individual-estimated PIB $AUC_{24,ss}$ was 1430 ng.h/mL in HCV-infected subjects. No significant difference in PIB exposures was observed between HCV-infected subjects with or without cirrhosis. In Phase I Studies, the estimated PIB $AUC_{24,ss}$ in healthy subjects who received GLE/PIB 300 mg/120 mg QD was 2170 ng.h/mL, which is an increase of approximately 50% compared to the PIB $AUC_{24,ss}$ reported for HCV-infected subjects.

4.4. Pharmacokinetic interactions

4.4.1. GLE and PIB

Part of Study M15-432 examined the effect of multiple doses of 120 mg PIB QD on GLE PKs following multiple doses of 300 mg GLE QD and the effects of multiple doses of 300 mg GLE QD on PIB PKs. The ratios (GLE + PIB/GLE) of the central values for GLE C_{max} and AUC_{24} were close to 1.0 (approximately 1.17), whereas, for PIB, the ratios (GLE + PIB/PIB) of the central values for C_{max} and AUC_{24} were 2.86 and 3.14, respectively.

Study M13-586 assessed the PKs and safety following multiple oral doses of the free combination of GLE (ranging from 100 mg QD to 1200 mg QD) and PIB under non-fasting conditions in healthy adult subjects. PIB at doses of 120 or 160 mg QD significantly increased GLE exposure. For instance, GLE steady-state C_{max} and AUC_{0-24} values were 41% to 72% and 45% to 83% higher, respectively, following co-administration with PIB compared to when GLE was administered alone. In the presence of PIB, GLE dose-dependently increased the exposures of PIB. Co-administration with GLE 400 mg QD increased 120 mg QD PIB exposures (C_{max} and AUC_{0-24}) by 2- to 2.5-fold and 40 mg QD PIB exposures (C_{max} and AUC_{0-24}) by 5-fold. In contrast, 100 mg QD GLE increased 40 mg QD PIB exposures (C_{max} and AUC_{0-24}) by 50%.

Overall these results indicate that at the recommended dose of the free combination, 300 mg GLE QD and 120 mg PIB QD, co-administration of GLE with PIB has little effect on GLE exposure compared to when GLE is administered alone, whereas, for PIB, co-administration with GLE increases PIB exposure by >3-fold compared to when PIB is administered alone.

4.4.2. CYP substrates

Two studies, M13-605 and M14-380, examined the interactions between steady-state GLE + PIB and a single dose of a range of CYP substrates administered as a cocktail, which included 100 mg caffeine (CYP1A2), 1 mg midazolam (CYP3A), 500 mg tolbutamide (CYP2C9), 20 mg omeprazole (CYP2C19) and 30 mg dextromethorphan (CYP2D6) given as a drug cocktail. The first of these studies, M13-605, examined the PKs of the substrates following the recommended dose of the free combination (that is, 300 mg GLE QD and 120 mg PIB QD) and the results indicated that although co-administration of GLE + PIB had little to no effect on the PKs of tolbutamide (2C9), the AUC_{inf} values for caffeine (1A2) and midazolam (3A) were increased by 35% and 27%, respectively, whereas, the AUC_t values for omeprazole (2C19) and dextromethorphan (2D6) were decreased by 21% and 25%, respectively. In addition, this study examined the interaction between steady-state GLE + PIB and a single dose of 400 mg cyclosporine, another drug that is extensively metabolised by CYP3A. Although co-administration of GLE + PIB QD had little effect on cyclosporine PKs, steady-state GLE and PIB exposure was significantly increased by 5.08- and 1.93-fold, respectively, in the presence of cyclosporine.

The second study, M14-380 examined the PKs of the CYP cocktail following multiple administrations of a higher than recommended dose of GLE + PIB (that is, 700 mg + 160 mg). Overall the results of this study confirmed the findings observed in Study M13-605, in regards to tolbutamide (2C9), caffeine (1A2), midazolam (3A) and dextromethorphan (2D6); however, unlike the previous study, the higher dose of GLE + PIB had no effect on the PKs of omeprazole (2C19).

Question: Can the sponsor please comment on a possible mechanism for the adverse DDI identified between cyclosporine and GLE + PIB identified in Study M13-605?

Study M13-578 examined the potential interaction between steady state GLE + PIB (300 mg + 120 mg QD) and a single dose of two CYP3A4 substrates felodipine (2.5 mg) and amlodipine (5 mg). The results indicate that GLE and PIB C_{max}, AUC_{24}, and C24 values were similar (≤ 25% difference) when administered alone or with a single dose of felodipine or amlodipine. By contrast, felodipine C_{max} and AUC_{inf} values increased 31% when felodipine was co-administered with GLE and PIB compared to when felodipine was administered alone, whereas, amlodipine C_{max} and AUC_{inf} values were similar (≤ 22% difference) in the presence or absence of GLE + PIB.

Study M13-584 also examined the PK interaction following administration of a single dose of cyclosporine (a CYP3A4-substrate and an inhibitor of CYP3A4, P-gp, BCRP, OATP1B1, and OATP1B3) and steady state GLE 300 mg QD + PIB 120 mg QD; however, in this study cyclosporine was administered at a lower dose of 100 mg and not 400 mg as in Study M13-605. Following co-administration of 100 mg cyclosporine with GLE + PIB the GLE C_{max}, AUC_{24} and C24 values were only modestly increased (30%, 37% and 34%, respectively) as were the corresponding values for PIB (11%, 22%, and 26%, respectively). As in the earlier study, cyclosporine C_{max} and AUC_{inf} were minimally affected by co-administration of single or steady-state doses of GLE and PIB (≤ 14% increase).

Comment: At low doses (that is, 100 mg) of cyclosporine the effect on the PKs of GLE + PIB is relatively minor; however, given that in many cases, e.g. organ transplantation, nephrotic syndrome and rheumatoid arthritis, the recommended doses range from 3 mg/kg to 10 mg/kg, in general in adults a much higher dose of cyclosporine would be required than a 100 mg dose and the likelihood of an adverse drug interaction between cyclosporine and GLE + PIB would increase.

Study M13-599 examined the interaction between steady-state GLE 300 mg QD+ PIB 120 mg QD and single doses of two angiotensin receptor blockers, one of which, losartan, is a substrate for CYP2C9 and CYP3A. The results indicated that steady-state GLE + PIB exposures were minimally affected by co-administration with a single dose of losartan 50 mg (≤ 17% change). By contrast, for losartan and losartan carboxylic acid, C_{max} values were increased by 2.5-fold and 2.2-fold, respectively, in the presence of GLE + PIB and AUC values increased by approximately 57% and 15%, respectively.

Study M14-721 examined the potential for a DDI between GLE + PIB and simvastatin (CYP3A4- and OATP1B1- substrate) or lovastatin (CYP3A4- and OATP1B1-substrate and inhibitor of OATP1B1). When multiple doses of GLE 300 mg QD + PIB 120 mg QD were co-administered with simvastatin 5 mg QD or lovastatin 10 mg QD, exposure to the statins and their active metabolites increased. For instance, simvastatin C_{max} and AUC values increased by 100% and 130%, respectively, and simvastatin hydroxy acid C_{max} and AUC values increased by 9.7-fold and 3.5-fold, respectively, when simvastatin was administered with GLE and PIB compared to simvastatin administered alone. Lovastatin C_{max} and AUC values increased by 17% and 70%, respectively, and lovastatin acid C_{max} and AUC values increased by 4.7-fold and 3.1-fold, respectively, when lovastatin was administered with GLE and PIB compared to lovastatin administered alone. By contrast, simvastatin and lovastatin had only minor effects on GLE exposures (< 34% difference) and did not affect PIB exposures (< 10% difference).

Comment: Study M14-721 compared the PKs of a single dose of GLE + PIB with the PKs of a single dose of GLE + PIB in the presence of simvastatin or lovastatin. Although, Studies M13-356 and M13-355 indicate that when administered alone there was only minor accumulation at steady-state for GLE and slightly greater accumulation for PIB (e.g. PIB exposure increased by 1.39-fold following PIB doses of 180 mg QD) it must be remembered that Studies M15-432 and M13-586 clearly demonstrate that when GLE QD is co-administered with PIB QD, the AUC of PIB increased by approximately 3-fold and the level of accumulation of PIB is unknown when the two drugs are co-administered. Therefore, it would have been more accurate to compare the multi-dose PKs of GLE + PIB in the absence of simvastatin or lovastatin.

Study M14-715 evaluated the effect of multiple doses of 20 mg to 40 mg of the acid-reducing agent, omeprazole, which is a proton pump inhibitor, potent gastric-pH-altering agent and CYP2C19-substrate, on the PKs of a single dose of GLE/PIB (300 mg/120mg) in healthy subjects. In addition, 40 mg omeprazole QD dosing was examined under two conditions in the morning with food and in the evening fasted. Following co-administration of GLE/PIB with omeprazole 20 mg QD, GLE exposures, C_{max} and AUC_{inf}, decreased by 22% and 29%, respectively, whereas, PIB exposure was similar in the presence and absence of omeprazole 20 mg QD. Following co-administration with the higher dose of omeprazole (40 mg QD) in the morning, GLE C_{max} and AUC_{inf} values decreased by 64% and 51%, respectively, whereas, PIB exposure was similar (< 15% difference). Co-administration of GLE/PIB administered 12 h apart from omeprazole 40 mg QD in the evening decreased GLE C_{max} and AUC_{inf} by 46% and 49%, respectively, whereas, PIB exposure was once again similar (< 7% lower).

4.4.3. CYP and P-gp inducers

Two studies, M14-724 and M14-723, examined the PK interaction between CYP inducers and GLE + PIB. The first of these, Study M14-724, examined the interaction between steady state carbamazepine (200 mg QD), which is an inducer of CYP1A2, 2C9 and 3A4 and P-glycoprotein (P-gp) and a substrate of CYP3A4, and a single dose of 300 mg GLE + 120 mg PIB. The results indicate that compared to when GLE + PIB were administered alone, co-administration with steady-state carbamazepine resulted in decreases in GLE C_{max} and AUC_{inf} values of 67% and 66%, respectively, and PIB C_{max} and AUC_{inf} values of 50% and 51%, respectively. By contrast,

carbamazepine and CBZE C_{max}, AUC_{12}, and C12 values were similar (≤ 7% difference) regardless of whether GLE + PIB were present or not.

Study M14-723 examined the interaction between a single 600 mg dose and steady-state rifampin, which is a potent inducer of CYP2B6, 2C8, 2C9, 2C19, 3A4, 3A5 and 3A7; P-gp and an inhibitor organic anion transporting polypeptides (OATP) , with a single dose of GLE 300 mg + PIB 120 mg under non-fasted conditions. The results identified that a single dose of rifampin increased GLE C_{max} and AUC_{inf} values by 6.5-fold and 8.6-fold, respectively, whereas, rifampin had little effect on either PIB C_{max} or AUC_{inf} (≤ 9% change). Similarly, rifampin C_{max} and AUC_{24} were only minimally affected by co-administration with GLE and PIB (≤ 18% increase).

Following multiple doses of rifampin, increases in GLE exposure were relatively small (5 – 40%), whereas, PIB C_{max} and AUC values were decreased by 79% and by 83%, respectively. When GLE and PIB were administered 24 h after the last dose of rifampin, the C_{max} and AUC_{inf} of GLE decreased by 86% and 88%, respectively; and the C_{max} and AUC_{inf} of PIB were decreased by 83% and 87%, respectively.

The sponsor suggests that these findings can be explained as follows:

> *Relative to GLE + PIB administered alone, exposure of GLE was increased when co-administered with the first rifampin dose via OATP inhibition, decreased following the last rifampin dose via enzyme/P-gp induction, and slightly increased when co-administered with steady-state rifampin via competing inhibition and induction forces. Relative to GLE + PIB administered alone, exposure of PIB was not affected when co-administered with the first rifampin dose, but was decreased when co-administered with steady-state rifampin or following the last rifampin dose via enzyme/P-gp induction.*

Comment: The sponsor's explanation regarding the DDI between GLE and rifampin is plausible.

4.4.4. PK Interactions with anti-HIV medications

4.4.4.1. GLE + PIB

A number of studies (M13-603, M13-597 and M15-584) examined the interaction between GLE + PIB and inhibitors of various metabolic pathways. The first of these, Study M13-603, investigated the interaction between GLE + PIB at steady-state and a single dose of atazanavir, which is a CYP3A4 substrate and an inhibitor of OATP1B1/3, CYP3A4 and UGT1A1, and ritonavir, which is an inducer of CYP1A2 and an inhibitor of P-gp and BCRP, CYP3A4 and 2D6, in healthy subjects. The results indicated that a single dose of atazanavir + ritonavir increased the C_{max} and AUC_{24} of steady-state GLE by 4.1- and 6.5-fold, respectively, whereas, PIB C_{max} and AUC_{24} values were 29% and 64% higher, respectively. By contrast, GLE + PIB had little to no effect on exposure to a single dose of atazanavir (≤ 16% increase), whereas, exposure to a single dose of ritonavir was slightly increased (C_{max}, AUC_{24} and C24 were 21%, 30% and 26% higher, respectively).

The next study, M13-597, investigated the interaction between multiple doses of the FDC ATRIPLA, which contains 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir DF) and multiple doses of 300 mg GLE + 120 mg PIB QD in HIV-mono-infected subjects. One of the components of ATRIPLA, efavirenz has been shown to be an inhibitor of CYP3A4, 2C9 and 2C19 and inducer of P-gp/CYP3A. The results indicated that compared to when ATRIPLA was administered alone, co-administration with multiple doses of GLE + PIB had little to no effect on either efavirenz or emtricitabine exposure (≤ 13% difference), whereas, tenofovir exposure increased (C_{max} ↑22%, AUC_{24} ↑29%, and C24 ↑38%). Compared to historical data, GLE and PIB exposures were significantly lower when co-administered with ATRIPLA.

The final study in this group, Study M15-584, examined the potential for a DDI between multiple doses of 300 mg GLE + 120 mg PIB and multiple doses of Genvoya or Triumeq in healthy

subjects. Genvoya is a FDC that contains: elvitegravir, which is an inhibitor of OATP1B1/1B3 and modest inducer of CYP2C9; cobicistat, which is an inhibitor of CYP3A and 2D6; P-gp, BCRP, OATP1B1 and OATP1B3; emtricitabine; and tenofovir alafenamide, whereas Triumeq is a FDC that contains: abacavir; dolutegravir, which is an inhibitor of OCT2 and substrate for UGT1A1; and lamivudine). The results indicated that GLE C_{max} and AUC were increased by 150% to 205% and the corresponding PIB parameters were increased by 24% to 57% when co-administered with Genvoya, whereas, co-administration of GLE + PIB with Genvoya increased C_{max} and AUC of elvitegravir and cobicistat by 29% to 47%, but had little to no effect on emtricitabine or tenofovir exposures (≤ 12% change). In contrast, to the preceding results GLE and PIB C_{max} and AUC were slightly lower (25% to 28%) when administered with Triumeq, whereas, the C_{max} and AUC of abacavir, dolutegravir, and lamivudine were similar in the presence and absence of GLE + PIB (≤ 13% difference).

4.4.4.2. GLE

Sub-study 3 of Study M13-356 assessed the effect of co-administration of 100 mg ritonavir on the PKs of a 200 mg dose of GLE in healthy, fed adults. The results indicated that ritonavir co-administration increased GLE C_{max} and AUC by about 80% to 100% .

4.4.4.3. PIB

Similarly, sub-study 3 of Study M13-355 assessed the effect of co-administration of 100 mg ritonavir on the PKs of a 120 mg dose of PIB in healthy, fed adults. In this study, co-administration with ritonavir increased PIB exposure as PIB C_{max} and AUC values increased by 60% and 89%, respectively, relative to the administration of PIB alone.

4.4.5. P-gp-substrates

Three studies examined the effect of GLE + PIB on P-gp substrates. The first of these, Study M13-582 investigated the potential for a DDI following multiple doses of GLE 400 mg QD + PIB 120 mg QD and a single dose of 0.5 mg digoxin in healthy subjects. Following co-administration with steady-state GLE and PIB, digoxin C_{max} and AUC_{inf} values increased by approximately 72% and 48%, respectively, compared to when digoxin was administered alone. By contrast, a single dose of digoxin had little to no effect on the exposure to steady-state GLE or PIB (≤ 16% difference).

The second study, M14-532 investigated the potential for a DDI following multiple doses of GLE 400 mg QD + PIB 120 mg QD and multiple doses of 400 mg sofosbuvir QD in healthy subjects. When GLE + PIB were co-administered with sofosbuvir, there was little change in steady-state exposure to GLE and PIB (≤ 16%) compared to when the DAA combination alone, whereas, following co-administration, sofosbuvir C_{max} and AUC_{0-24} values increased by 66% and 125%, respectively, compared to when sofosbuvir was administered alone. The C_{max} and AUC_{24} values for the active metabolite of sofosbuvir, GS-331007, were similar in the presence and absence of GLE + PIB; however, the GS-331007 C_{24} was increased by 1.85-fold.

The final study in this group, M13-585 examined the potential for a DDI between a single 150 mg dose of the P-gp-substrate dabigatran and GLE 300 mg QD + PIB 120 mg QD. The results indicated that dabigatran C_{max} and AUC_{inf} values were increased by 2.0- and 2.4-fold, respectively, when co-administered with GLE + PIB. By contrast, multiple-dose exposures of GLE and PIB were similar (≤ 20% change) when administered alone or with a single dose of dabigatran etexilate.

4.4.6. OATP-substrates

Two studies examined the potential for DDI between GLE + PIB and OATP-substrates. The first of these, Study M13-579, examined the effect of GLE and PIB combination on the PKs of pravastatin (OATP1B1- and OATP3-substrate), rosuvastatin (OATP1B1-, OATP1B3- and BCRP-substrate) or atorvastatin (OATP1B1-, OATP1B3- and CYP3A4-substrate). The results indicated that following co-administration with steady-state GLE 400 mg QD + PIB 120 mg QD, the C_{max} and AUC values for pravastatin 10 mg QD were increased by 2.2- and 2.3-fold, respectively, the

C_{max} and AUC values for rosuvastatin 5 mg QD were increased by 5.6- and 2.2-fold, respectively, and the C_{max} and AUC values for atorvastatin 10 mg QD were increased by 22- and 8.3-fold, respectively, compared to the corresponding values when the statins were administered alone. Following steady-state administration with pravastatin 10 mg, rosuvastatin 5 mg or atorvastatin 10 mg, the GLE C_{max} and AUC were similar or increased (up to 59%), whereas, the PIB C_{max} and AUC were minimally affected (≤ 24% increase).

Study M13-599 *also examined the* effect of steady-state GLE 300 mg QD+ PIB 120 mg QD on the PKs of a single dose of valsartan 80 mg (OATP1B1- and OATP1B3-substrate). In this study co-administration of steady-state GLE + PIB increased valsartan C_{max} and AUC_{inf} by 36% and 31%, respectively, compared to when valsartan was administered alone.

4.4.7. Other interactions

Study M13-585 also examined the effect of steady-state GLE 300 mg QD + PIB 120 mg QD on the PKs of a single dose of 50 mg lamotrigine (UGT1A4-substrate). In this study lamotrigine exposure was similar (≤ 4% difference) when administered alone or with GLE and PIB and GLE and PIB exposure were similar (≤ 25% change) in the presence or absence of a single dose of lamotrigine.

Study M13-598 evaluated the effect of a combination therapy of GLE and PIB on the PKs of oral contraceptives, which were *substrates for sulfotransferases,CYP3A4, and UGT. The results indicated that o*ral contraceptive products containing ethinyl estradiol (EE), norgestimate (NGM), levonorgestrel (LNG) or norethindrone (NET) had a minimal impact (≤31%) on steady-state GLE and PIB exposures. Multiple doses of GLE and PIB had minimal impact on NET AUC (decreased 6%) and increased AUC of EE, NG, and NGMN by 28 to 40%, 63 to 68% and 44%, respectively.

Study M13-602 evaluated the effects of steady-state GLE 300 mg QD + PIB 120 mg QD on the PKs of methadone or buprenorphine/naloxone. When the DAAs (GLE + PIB) were co-administered with methadone, (R)-methadone and (S)-methadone exposures were minimally affected (≤ 5% change in central values) compared to administration of methadone alone. When the DAAs were co-administered with buprenorphine/naloxone, buprenorphine C_{max}, AUC_{0-24} and C24 central values were increased by 8%, 17% and 24%, respectively, compared to administration of buprenorphine/naloxone alone. Naloxone C_{max} and AUC_{0-24} central values were changed by ≤ 12% compared to administration of buprenorphine/naloxone alone. Norbuprenorphine C_{max}, AUC_{0-24} and C24 central values were increased by 25%, 30% and 21%, respectively, compared to administration of buprenorphine/naloxone alone.

4.5. Clinical implications of in vitro findings

4.5.1. Substrates of CYP and FMOs

The potential for [^{14}C]-GLE and [^{3}H]PIB to be metabolised by CYPs enzymes and flavin monooxygenases (FMOs) was investigated using recombinant enzymes. For [^{14}C]-GLE, enzymes identified as potential contributors to GLE metabolism included CYP 3A4, 2D6 and 3A5. For [^{3}H]PIB, the only enzyme identified as potential contributor to its metabolism was CYP3A4.

4.5.2. Inhibition of CYP

The potential for GLE and PIB to be direct- or time-dependent inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 was examined in human liver microsomes and recombinant CYP isoforms. GLE inhibited CYP3A4, CYP2C8 and CYP2C9 with IC50 values of 28.3 μM, 31.7 μM and 175 μM, respectively. For all other species of CYP tested IC50 values were greater than 200 μM. For PIB, IC50 values were greater than 30 μM for all isoforms tested. No time dependent CYP inhibition was observed for either GLE or PIB in human liver microsomes.

4.5.3. Induction of CYP

The potential for GLE and PIB to induce CYP3A4, CYP2B6 and CYP1A2 mRNA *in vitro* was evaluated in human hepatocytes. Although in some hepatocyte samples there was activity at CYP3A4, overall the data indicated that both GLE and PIB are not an inducers of CYP1A2, CYP2B6 or CYP3A4.

4.5.4. Inhibition of UGT

The potential for GLE and PIB to inhibit UGTs including UGT1A1, 1A4, 1A6, 1A9 and 2B7 was evaluated in human liver microsomes using probe substrates. The results indicated that GLE did not inhibit UGT1A6, 1A9 and 2B7 at concentrations up to 50 μM, whereas, UGT1A1 and 1A4 were inhibited, with IC 50 values of 17.2 and 14.6 μM, respectively. For PIB, no inhibition was demonstrated for UGT1A6 and 1A9 at concentration up to 50 μM, whereas, it inhibited UGT1A1 and 1A4 with IC50 values of 2.54 and 0.027 μM, respectively.

4.5.5. In vitro drug transporter assessment

GLE inhibited P-gp, BCRP, BSEP, OATP1B1 and OATP1B3 with IC50 values of 0.33 μM, 2.3 μM, 0.95 μM, 0.017 μM and 0.064 μM, respectively, and is a substrate for P-gp, BCRP, OATP1B1 and OATP1B3; however, GLE is not a substrate for OCT1.

PIB inhibited P-gp, BCRP and BSEP with IC50 values of 0.036 μM, 14 μM and 39 μM, respectively. PIB also inhibited OATP1B1 by >50% at 30 μM in the absence and presence of 4% BSA; IC50 value was 1.3 μM in the presence of 4% BSA. PIB is not a substrate for OATP1B1, OATP1B3 or OCT1; however, due to the low passive permeability *in vitro* efflux by P-gp or BCRP could not be determined.

4.6. Evaluator's overall conclusions on pharmacokinetics

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

4.6.1. ADME

- PopPK predicted Ka for GLE and PIB in patients with chronic HCV was 8.63/day and 6.13/day, respectively.
- The absolute bioavailability of GLE and PIB has not been determined. Although not specifically stated, this is most likely due to the poor solubility of both GLE and PIB in water.
- The to-be-marketed FDC formulation of GLE/PIB is identical to the Phase III formulation.
- Under fasting conditions, the AUC values for GLE and PIB were 56% and 36% lower, respectively, following administration of a 300mg/120mg dose of the GLE/PIB FDC tablets compared to the free-combination of Phase IIb tablets.
- Following a 300 mg/120 mg dose of GLE/PIB FDC, food increased exposure to the GLE component by 1.8- to 3.2-fold compared to fasted conditions and exposure to the PIB component by 1.4- to 2.1-fold. Moreover, following administration of the FDC tablet, GLE and PIB exposure under fed conditions was similar to the levels of GLE and PIB exposure attained following administration of the free combination of the Phase IIb tablet formulation under fasted conditions.
- Following administration of increasing doses of GLE + PIB to healthy subjects increases in GLE are greater than dose proportional, whereas, the results for PIB are equivocal. For instance, following single doses of the free combination at dose strengths of 600 mg + 240 mg, GLE C_{max} and AUC_{inf} values were increased by 3.6-fold and 3.9-fold, respectively, and PIB C_{max} and AUC_{inf} were increased by 1.8- and 2.1-fold, respectively, compared to the values

following a dose of GLE 400 mg + PIB 120 mg, whereas, the ratio of the point estimates for GLE C_{max} and AUC_{inf} values following doses of 800 mg + 240 mg of the free combination of GLE + PIB vs. 400 mg + 120 mg of GLE + PIB were 8-fold and 13-fold, respectively, and for PIB were 2.2-fold and 3.0-fold, respectively. * Following administration of multiple escalating doses of GLE 200 mg to 800 mg QD for 10 days, GLE exhibited non-linear PKs with greater than dose proportional increases in exposure following multiple doses. Steady-state GLE was attained following 10 days of dosing and median accumulation ratios for C_{max}, Ctrough and AUC_{0-24} values ranged from 0.8 to 2.4 over the 200 to 800 mg dose range. Following both the 200 mg QD and 400 mg QD doses there was minimal accumulation of GLE.

- Following administration of multiple escalating doses of PIB 30 mg to 600 mg QD for 10 days PIB, C_{max} and AUC_{0-24} values increased in a greater than dose proportional manner between doses ranging from 30 mg to 180 mg and were then approximately linear following the 180 mg and 600 mg doses. In addition, there was minimal accumulation of PIB and steady-state was attained at 10 days.
- The estimated values for the Vc/F and Vp/F for GLE were 130 L and 39.6 L, respectively, and for PIB were 1380 L and 2250 L, respectively.
- There was no concentration dependence in plasma binding for either GLE or PIB when tested at concentrations ranging from 0.1 to 30 μM and no preferential partitioning into red blood cells was observed.
- Following oral administration both [^{14}C]-GLE and [^{14}C]-PIB were primarily cleared via the biliary-faecal route; however, CYP3A metabolism played a secondary role in the metabolism of [^{14}C]-GLE.
- Following a 400 mg dose of [^{14}C]-GLE, nearly the entire radioactive dose (92.1%) was recovered in faeces, whereas, 0.661% was recovered in urine. Following a 120 mg dose of [^{14}C]-PIB, the mean recovery of administered radioactivity was 96.6%, which was entirely contained in the faeces.
- No metabolites for GLE or PIB were identified in human plasma.
- In pooled faeces samples, unchanged GLE accounted for 22.6% of the radioactive dose and seven GLE metabolites were identified. By contrast, following administration of 120 mg [^{14}C]-PIB, unchanged PIB was the only radiochemical component detected in faeces.

4.6.2. PK variability

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

4.6.3. PKs in the target population

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

4.6.4. Special populations

- Following administration of GLE 300 mg + PIB 120 mg, GLE AUC values were 33% and 100% higher in subjects with mild and moderate hepatic impairment, respectively, and

were increased by 11-fold in subjects with severe hepatic impairment compared to subjects with normal hepatic function. Compared to normal subjects, PIB AUC values were similar in subjects with mild hepatic impairment (≤ 20% difference), 26% higher in subjects with moderate hepatic impairment and 114% higher in patients with severe hepatic impairment.

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

4.6.5. PopPK

- PopPK analysis indicated that a two-compartment model with first-order absorption and elimination adequately described the GLE and PIB plasma concentration-time data. For GLE, bodyweight, BMI, BSA, race, genotype, dialysis, prior HCV treatment history and co-administration with RBV did not have significant impact on GLE exposure, whereas, for PIB, dialysis, genotype, prior HCV treatment history and co-administration with RBV had no significant impact on PLE exposure.
- The PopPK analysis also identified the following:
  - Age was a significant covariate for GLE and PIB CL/F such that a 10-year increase in age (65 years versus 55 years) is associated 32% higher GLE exposure and PIB exposure was 13% higher.
  - Gender affected GLE and PIB exposure as GLE exposure was 39% higher in females than in males and PIB was 37% higher in females compared to males.
  - Race was a covariate of PIB CL/F such that PIB exposure was 26% higher in Asian subjects than in Caucasians.
  - GLE and PIB exposures in subjects with compensated cirrhosis were increased by 2.2-fold and were 7% higher, respectively, than in subjects without cirrhosis.
  - Compared to subjects with normal renal function, GLE and PIB exposure was 55% and 13% higher, respectively, in subjects with moderate or severe renal impairment and 86% and 54% higher, respectively, in subjects with end stage renal disease.
  - GLE exposure was 5% lower in subjects who took high dose PPIs and 16% higher in subjects who took opioid medications. PIB exposure was 27% higher in subjects who took BCRP inhibitors.

4.6.6. DDIs

- The C_{max} and AUC values for GLE were similar following 300 mg GLE in the presence or absence of 120 mg PIB.
- The C_{max} and AUC values for PIB were increased by 2.86-fold and 3.14-fold following co-administration of 120 mg PIB with 300 mg GLE compared to when PIB was administered alone.
- Although 300 mg GLE QD and 120 mg PIB QD had little effect on tolbutamide PKs, the AUC_{inf} values for caffeine and midazolam were increased by 35% and 27%, respectively, whereas,

the AUCt values for omeprazole (2C19) and dextromethorphan (2D6) were decreased by 21% and 25%, respectively.

- Although, GLE + PIB QD had little effect on cyclosporine PKs following a 400 mg dose, steady-state GLE and PIB exposure was significantly increased by 5.08- and 1.93-fold, respectively, when cyclosporine was co-administered.
- Co-administration of GLE + PIB with simvastatin or lovastatin results in increased AUC values for the statins and their metabolites ranging from 1.7-fold to 4.5-fold.
- Compared to when GLE + PIB were administered alone, co-administration with steady-state carbamazepine resulted in decreases in GLE C_{max} and AUC_{inf} values of 67% and 66%, respectively, and PIB C_{max} and AUC_{inf} values of 50% and 51%, respectively.
- A single dose of rifampin increased GLE C_{max} and AUC_{inf} values by 6.5-fold and 8.6-fold, respectively, whereas, rifampin had little effect on either PIB C_{max} or AUC_{inf} (≤ 9% change). By contrast, following multiple doses of rifampin, increases in GLE exposure were relatively small (5 – 40%), whereas, PIB C_{max} and AUC values were decreased by 79% and by 83%, respectively.
- A single dose of atazanavir + ritonavir increased the C_{max} and AUC24 of steady-state GLE by 4.1- and 6.5-fold, respectively, whereas, PIB C_{max} and AUC24 values were 29% and 64% higher, respectively.
- Compared to historical data, GLE and PIB exposures were significantly lower when co-administered with ATRIPLA
- GLE C_{max} and AUC were increased by 150% to 205% and the corresponding PIB parameters were increased by 24% to 57% when co-administered with Genvoya.
- Co-administration of GLE + PIB with Genvoya increased C_{max} and AUC of elvitegravir and cobicistat by 29% to 47%.
- GLE + PIB C_{max} and AUC were slightly lower (25% to 28%) when administered with Triumeq.
- Results from the atazanavir+ritonavir study and the ATRIPLA study suggested ritonavir (C_{max} ↑21%, AUC24 ↑30% and C24↑ 26%) and tenofovir (C_{max} ↑22%, AUC24 ↑29%, and C24 ↑38%) exposure was mildly increased in the presence of GLE + PIB.
- Following co-administration of GLE + PIB, digoxin C_{max} and AUC_{inf} values increased by approximately 72% and 48%, respectively, compared to when digoxin was administered alone.
- Following co-administration with GLE + PIB, sofosbuvir C_{max} and AUC_{0-24} values increased by 66% and 125%, respectively, compared to when sofosbuvir was administered alone.
- Dabigatran C_{max} and AUC_{inf} were increased by 2.0- and 2.4-fold when co-administered with GLE + PIB.
- Following co-administration with pravastatin, rosuvastatin or atorvastatin, GLE C_{max} and AUC were similar or increased (up to 59%), whereas, PIB C_{max} and AUC were minimally affected (≤ 24% increase).
- GLE 400 mg QD and PIB 120 mg QD increased: pravastatin C_{max} and AUC values by 2.2- and 2.3-fold, respectively; rosuvastatin C_{max} AUC by 5.6- and 2.2-fold, respectively, and atorvastatin C_{max} and AUC by 22- and 8.3-fold, respectively.
- GLE 300 mg QD + PIB 120 mg QD increased exposure to EE, NGM and LNG by up to 68%.
- Co-administration of GLE + PIB had little effect (< 35%)on the exposure to carbamazepine, CBZE, rifampin, atazanavir, efavirenz or emtricitabine, emtricitabine, abacavir, dolutegravir,

and lamivudine, lamotrigine, NET, (R)-methadone and (S)-methadone, buprenorphine and naloxone.

- Co-administration of digoxin, sofosbuvir, omeprazole 20 mg QD, dabigatran, lamotrigine and NET had no to relatively minor effects on exposure to steady-state GLE or PIB.

4.6.7. Limitations of PK studies

- No studies have directly examined the relative bioavailability of the reference Phase IIb formulation under fasted and fed conditions. Thus it is difficult to accurately compare the PKs of FDC Phase III formulation and the Phase IIb formulations under fed conditions. However, if we compared the GLE and PIB exposure under fasted (results from Study M14-714) and fed (results from Study M14-724) conditions following a single dose of the free combination of 300 mg GLE + PIB to healthy subjects we can see that exposure to the GLE component is increased by ~1.3- to 1.40-fold and for the PIB component is increased by ~1.4- to 1.7-fold under fed conditions compared to when the subjects were fasted. Although this comparison is far from ideal as the study has not been undertaken in the same population, it clearly identifies that food may significantly effect GLE and PIB exposure when given as the free combination, and perhaps calls into question the results of studies, such as M14-868, in which patients have been administered the free combination without instructions regarding whether tablets should be taken with food or not.

5. Pharmacodynamics

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

5.1. Summary of pharmacodynamics

5.1.1. Mechanism of action

The following information regarding the mechanism of action has been taken from the proposed PI version 1:

> *Maviret is a fixed-dose combination of two pangenotypic, direct-acting antiviral agents, GLE (NS3/4A protease inhibitor) and PIB (NS5A inhibitor), which targets multiple steps in the HCV viral lifecycle.*

5.1.2. GLE

GLE is a pangenotypic inhibitor of the HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins), and is essential for viral replication. In a biochemical assay, GLE inhibited the proteolytic activity of recombinant NS3/4A enzymes from clinical isolates of HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a with IC50 value ranging from 3.5 to 11.3 nM.

5.1.3. PIB

PIB is a pangenotypic inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of PIB has been characterised based on cell culture antiviral activity and drug resistance mapping studies.

5.1.4. Pharmacodynamic effects

5.1.4.1. Primary pharmacodynamic effects

Study M13-595 investigated not only the PKs of multiple dose levels of GLE (100 mg to 700 mg) and PIB (15mg to 400 mg) administered as monotherapies for 3 days in treatment-naïve adults with chronic HCV GT1 infection, but also the antiviral activity of the two drugs. A further part of

this study assessed the SVR12 of co-formulated ABT-450, ritonavir, ABT-267 (ABT-450/r/ABT-267), and ABT-333 co-administered with RBV for 12 weeks, which is not relevant to the present submission.

The results indicated that during 3 days of monotherapy, the maximum decrease in mean HCV plasma RNA viral load from baseline was similar in all of the dose groups that GLE, whereas, for PIB the maximum decrease was higher in the 40 mg QD to 400 mg QD dose groups than the 15 mg dose. The decline in HCV viral load was immediate and substantial on Study Day 1 for all dose groups of GLE and for the 40 mg, 120 mg, and 400 mg doses of PIB.

5.1.4.2. Secondary pharmacodynamic effects

Two studies (M15-543 and M14-716) examined the effects of GLE + PIB on QTc. The first of these, Study M15-543, assessed the potential for QTc prolongation following combination administration of GLE and PIB at therapeutic (400 mg + 120 mg) and supra- therapeutic (600 mg + 240 mg) doses in healthy adult subjects. In contrast to 400 mg moxifloxacin (positive control), neither GLE 400 mg + PIB 120 mg nor GLE 600 mg + PIB 240 mg met the threshold for QT prolongation according to the ICH E14 guideline. The mean peak ΔΔQTcF for GLE 600 mg + PIB 240 mg was 3.1 msec with a 95% upper bound of 5.1 msec (< 10 msec), whereas, the mean peak ΔΔQTcF for GLE 400 mg + PIB 120 mg was 2.9 msec with a 95% upper bound of 4.9 msec (< 10 msec). In addition, no statistically significant concentration dependent effects on ΔΔQTcF were observed following concomitant administration of GLE and PIB at GLE 400 mg + PIB 120 mg and GLE 600 mg + PIB 240 mg using a linear mixed-effects model.

Similarly, following doses of GLE 400 mg + PIB 120 and GLE 800 mg + PIB 240 mg dose to healthy adults in Study M14-716, no clinically significant effects on QTc interval prolongation were identified. For instance, for the GLE 400 mg + PIB 120 mg dose, the mean drug effect (ΔΔQTcF) ranged from –2.1 to 1.8 msec, with the maximum 95% upper confidence bound of 5.0 msec, whereas, for the GLE 800 mg + PIB 240 mg dose, the mean drug effect (ΔΔQTcF) ranged from –5.8 to 0.5 msec, with the maximum 95% upper confidence bound of 4.7 msec.

Resistance Results

Study M13-595 also investigated the development of resistance variants following administration of GLE and PIB. The results indicated that none of the 40 genotype 1a- or the 7 genotype 1b-infected subjects who received GLE and had baseline sequence data available had resistance-conferring variants in NS3 pre-existing at baseline. Among the 30 genotype 1a- and 5 genotype 1b-infected subjects with post-baseline sequence data during the GLE monotherapy period, 1 genotype 1a-infected subject had a treatment-emergent A156T variant in NS3.

Among the 33 genotype 1a- and 7 genotype 1b-infected subjects who received PIB and had baseline sequence data available, 5 genotype 1a-infected subjects had M28V, Q30R, H58P, Y93N, and/or Y93C/S and 3 genotype 1b-infected subjects had L31M, P58S, and/or Y93H at baseline. Post-baseline sequence analysis was conducted on 14 genotype 1a- and 5 genotype 1b-infected subjects. Three genotype 1a-infected subjects with pre-existing variants in NS5A at baseline had multiple treatment-emergent variants in NS5A during monotherapy. None of the other 11 genotype 1a- or the 5 genotype 1b-infected subjects who received PIB had treatment-emergent variants at signature amino acid positions in NS5A.

5.1.5. Time course of pharmacodynamic effects

The results of Study M13-595 indicated that the decline in HCV viral load was immediate and substantial on Study Day 1 for all dose groups who received GLE and for subjects who received either 40 mg, 120 mg or 400 mg doses of PIB.

5.1.6. Relationship between drug concentration and pharmacodynamic effects

The results of Study M13-595 indicated that the maximum decrease in plasma RNA viral load from baseline was similar following doses of GLE ranging from 100 mg to 700 mg, whereas, for

PIB the maximum decrease in viral load was higher in groups that received doses ranging from 40 mg QD to 400 mg QD than in the group that received the 15 mg dose.

5.1.7. Genetic, gender and age related differences in pharmacodynamic response

Not examined.

5.1.8. Pharmacodynamic interactions

Not examined.

5.2. Evaluator's overall conclusions on pharmacodynamics

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

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

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

6.2. Phase II dose finding studies

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

6.3. Phase III pivotal studies investigating more than one dose regimen

No dose finding Phase III studies were performed.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

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

7. Clinical efficacy

7.1. Pivotal or main efficacy studies

7.1.1. Study M15-464 (ENDURANCE-2)

7.1.1.1. Study design, objectives, locations and dates

This is a Phase III, multicentre, randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of GLE/PIB FDC in non-cirrhotic adult patients with chronic HCV GT2 infection. It is an on-going study being conducted at 55 sites in Belgium, France, Italy, Korea, Lithuania, Portugal, Taiwan and the US. The study started in November 2015 and the cut-off date for analysis of the primary endpoint was September 2016. The primary analysis was conducted when all patients had completed the Post-Treatment Week 12 visit, or had prematurely discontinued from the study.

The primary objectives were to measure the proportion of patients achieving SVR12 compared with historical SOF +RBV efficacy data and to assess the tolerability and safety of 12 weeks treatment with GLE/PIB compared with placebo. Other objectives were to assess the rate of on-treatment virologic failure and post-treatment relapse and to assess efficacy in patients previously treated with SOF + RBV +/- pegIFN. Up to 321 patients were planned to be randomised 2:1 to one of two treatment groups:

- Arm A: GLE/PIB 300 mg/120 mg given QD for 12 weeks
- Arm B: Matching placebo QD for 12 weeks followed by open-label (OL) GLE/PIB given QD for 12 weeks

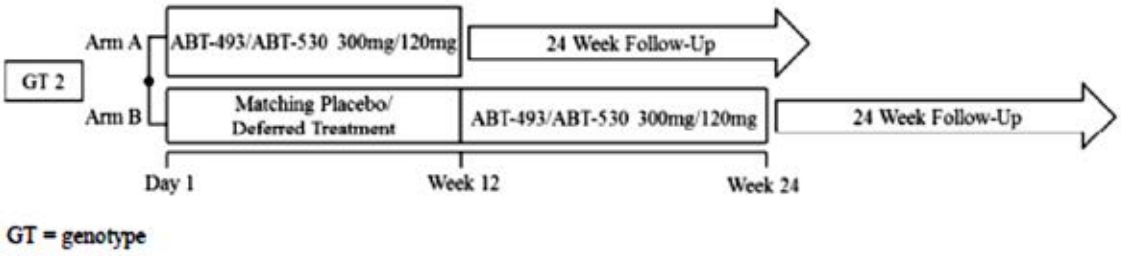
The randomisation was stratified into three groups based on previous treatment experience:

- HCV treatment-naïve
- IFN, or pegIFN +/-RBV
- SOF + RBV +/- pegIFN

The study consisted of three periods as shown below:

- A double-blind treatment period of 12 weeks (GLE/PIB or placebo)
- An OL treatment period of 12 weeks for patients randomised to placebo in the double-blind (DB) treatment period
- A post-treatment period: patients randomised in Arms A and B who completed or prematurely discontinued active study drug were followed for 24 weeks to assess safety, HCV RNA and resistant mutations.

Figure 3: Study M15-464 schematic



The planned duration of the study was up to 36 weeks for patients in Arm A and 48 weeks for patients in Arm B. Patient visits were scheduled for the DB period on Day 1 and Weeks 1, 2, 4, 8 and 12. At each study visit, vital signs were measured and blood samples were drawn for safety assessments, HCV RNA and HCV resistance. Study drug accountability and adherence were assessed at Weeks 4, 8 and 12.

7.1.1.2. Inclusion and exclusion criteria

The key inclusion criteria were: males or females aged ≥18 years; BMI ≥18.0 kg/m^2; HCV RNA ≥10^3 IU/mL at screening with positive anti-HCV antibody; documented chronic HCV GT2 infection; treatment-naïve, or failed previous IFN or pegIFN +/- RBV or SOF + RBV +/- pegIFN therapy; documented non-cirrhosis using protocol defined criteria.

The key exclusion criteria were: co-infection with more than one HCV genotype; HBV or HIV co-infection; any cause of liver disease other than HCV; drug or alcohol abuse within previous 6 months; severe sensitivity to study drug excipients; uncontrolled diabetes; clinically significant abnormalities based on medical history, physical examination, laboratory tests, or ECG; active or suspected malignancy or history of malignancy within the previous 5 years; uncontrolled cardiac, respiratory, gastrointestinal, haematological, neurologic, psychiatric or other disorder unrelated to the existing HCV condition; protocol defined prohibited medications and herbal supplements.

7.1.1.3. Study treatments

- Arm A: Three GLE/PIB 100 mg/40 mg tablets once daily with food at the same time for 12 weeks
- Arm B: Three matching GLE/PIB placebo tablets once daily with food for 12 weeks; followed by three GLE/PIB 100 mg/40 mg tablets once daily with food for 12 weeks

7.1.1.4. Efficacy variables and outcomes

The main efficacy variable was SVR12.

The primary efficacy outcome was the proportion of patients with SVR12.

The secondary variables were:

- On-treatment virologic failure
- Post treatment relapse.

7.1.1.5. Randomisation and blinding methods

Patient randomisation, treatment assignment and drug re-supply were conducted using IRT, with randomisation stratified according to previous treatment experience. During the DB treatment period, the investigators, patients and sponsor were blind to the randomised treatment, virologic results and LFT results. Virologic results were monitored by an unblinded, independent reviewer only for patients in Arm A.

7.1.1.6. Analysis populations

The ITT population included all patients who were randomised and received at least one dose of study medication. The safety population included all randomised patients who received at least one dose of study drug.

7.1.1.7. Sample size

Assuming that 96% of patients in Arm A would achieve SVR12, a sample size of 180 patients in Arm A had >90% power to show non-inferiority to SOF + RBV (a standard of care therapy in patients with GT2 infection), with a 2-sided 95% LCB >89%.

7.1.1.8. Statistical methods

The analyses were performed on the ITT population using SAS® (SAS Institute, Cary, NC). All statistical tests and CIs were 2-sided with an alpha of 0.05. For analysis of SVR12, treatment effects were analysed with missing data imputed by carrying backward the last post-baseline HCV RNA value, as applicable using a pre-specified backward imputation method. Missing data which could not be imputed were treated as treatment failures. Categorical demographic and baseline characteristics were compared with a chi-square test and mean changes of continuous variables were compared using one-way ANOVA.

The primary efficacy endpoint was the proportion of patients with SVR12 for all treatment-naïve patients in Arm A. The percentage of patients with SVR12 when treated with GLE/PIB would be non-inferior to the 95% SVR12 rate of SOF + RBV for 12 weeks if the LCB of the 2-sided 95% CI of the percentage of patients with SVR12 was >89%. The 6% margin was calculated based on historical SVR12 rates in patients with HCV GT2 infection. CIs were calculated using the normal approximation of the binomial distribution unless the primary endpoint was 100% (in which case Wilson's score method was used). Multiplicity was addressed using a fixed sequence testing procedure to control the type 1 error rate. Testing proceeded to the first secondary endpoint only if the primary endpoint was achieved. Other secondary endpoints did not include a fixed sequence testing procedure.

The secondary efficacy endpoint was the superiority of the percentage of treatment-naïve patients in Arm A who were treated with GLE/PIB and achieved SVR12, compared with 95% SVR12 rate of SOF + RBV for 12 weeks. The percentage of patients with SVR12 treated with GLE/PIB would be superior to SOF + RBV if the LCB of the 95% CI of the percentage of patients with SVR12 was >95%. Other secondary efficacy endpoints were tested with 95% CIs using the Wilson's score method. These included the percentage of patients with on-treatment virologic failure, the percentage of patients with post-treatment relapse and the percentage of patients with SVR12 who had previously failed with SOF + RBV +/- pegIFN. Additional analyses were performed on patients who achieved SVR4 and SVR24 and those who relapsed after achieving SVR12. Descriptive statistics were used to assess adverse events and an ANOVA model was used to compare changes in clinical laboratory data.

7.1.1.9. Participant flow

In the DB treatment period, a total of 304 patients were randomised and 302 patients received at least one dose of study treatment (202 patients in Arm A; 100 patients in Arm B). Only one patient discontinued study drug prematurely (an Arm A patient non-compliant with study drug). The median duration of treatment was 84 days (range 47-90) in Arm A and 84 days (range 82-86) in Arm B.

7.1.1.10. Major protocol violations/deviations

No summary table of major protocol deviations is presented in the CSR although individual data listings are provided as an appendix. A total of 11 patients had protocol deviations relating to inclusion/exclusion criteria; seven patients received a prohibited medication or supplement; and two patients were inadvertently dispensed the incorrect randomised treatment. None of the

deviations was considered to have affected the study outcome or conclusions. During the DB treatment period in the ITT population, 195 patients in Arm A and 91 patients in Arm B were 80-120% compliant with study drug (99.42% and 99.29%, respectively).

7.1.1.11. Baseline data

The baseline demographic data were similar in each treatment group. Overall, the majority of patients were female (52.6%) and White (59.9%) or Asian (33.4%). Most patients were aged <65 years (66.9%) and only 5.3% were aged ≥75 years. The mean BMI was <30 kg/m^2 in 83.4% of patients.

The baseline disease characteristics were also similar in each group. Overall, all patients had HCV GT2 infection, 70.2% were treatment-naïve and 29.8% were treatment experienced. The IL28B CC genotype was present in 46.7% of patients. The mean baseline HCV RNA was <6,000,000 IU/mL in 78.5% of patients and ≥6,000,000 IU/mL in 21.5%% of patients. Median baseline HCV RNA levels were 6.25 and 6.39 $\log_{10}$ IU/mL in Arms A and B, respectively. Mean baseline albumin was ≥35 g/L in all patients and mean creatinine clearance was <60 mL/min in 5.6% of patients. Overall, the baseline fibrosis stage was F0-F1 in 79.1% of patients, F2 in 8.9% of patients and F3 in 11.9% of patients.

7.1.1.12. Results for the primary efficacy outcome

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

7.1.1.13. Results for other efficacy outcomes

- *SVR12:* The SVR12 rate in patients (excluding prior SOF + RBV +/- pegIFN failures) in Arm A [99.5% (95% CI: 98.5%, 100.0)] was superior to the historical control rate as the LCB of the 95% CI was >95%. The difference in SVR12 rates between patients in Arm A (excluding prior SOF + RBV +/- pegIFN failures) and the actual historical control rate for SOF + RBV was 4.7% (95% CI: 2.3, 7.2). SVR12 was achieved by 100% (6/6) of patients in Arm A who were previous SOF + RBV +/- pegIFN failures and by both treatment-experienced patients in Arm B during the OL treatment period.
- *Subgroups:* No differences in subgroups were identified as only one patient did not achieve SVR12.
- *Virologic failure:* There were no cases of on-treatment virologic failure or relapse. There was a single case of non-virologic failure due to missing SVR12 data (HCV RNA was not detected 25 days after the last dose of study drug).
- *HCV RNA <LLOQ:* Rapid suppression of HCV RNA occurred in Arm A. HCV RNA <LLOQ at Weeks 4, 8 and 12 was observed in 94.4%, 100% and 100% of patients, respectively. There was 99.5% concordance between SVR4 and SVR12 in the ITT population.
- *Virologic resistance:* In Arm A, 83.2% of patients had baseline polymorphisms at any key NS5A site. No patients had NS3 or NS3 + NS5A polymorphisms. Baseline polymorphisms had no impact on the treatment outcomes as no patients experienced virologic failure.

7.1.1.14. Evaluator commentary

Multiple DAA combinations are approved for use in chronic HCV infection but not all are effective in every HCV genotype, or in subgroups based on prior HCV treatment, underlying cirrhosis, renal impairment and HCV/HIV-1 co-infection. This study is the first of a series of pivotal studies designed to show efficacy for a novel 2-DAA combination in all genotypes and important subgroups.

This randomised study compared GLE/PIB therapy given QD as a FDC for 12 weeks in patients with chronic HCV GT2 infection without cirrhosis. Treatment-naïve patients and patients previously treated with IFN-based therapy or SOF + RBV +/-pegIFN therapy were eligible for the study. The inclusion/exclusion criteria and overall study design were appropriate and the study was powered to demonstrate an efficacy benefit compared with a standard of care historical control therapy (SOF + RBV). Due to the life-threatening nature of the underlying disease, the delayed treatment study design employed in Arm B is widely accepted as an alternative to direct placebo control. Approximately 70% of patients were treatment-naïve and approximately 30% of patients had received previous treatment with IFN-based therapy (27.2%), or SOF-based therapy (2.6%). Recruitment of prior SOF failures was encouraged but more significant numbers could not be found, possibly because SOF-based therapies are generally effective.

Historically, treatment-experienced patients with chronic HCV infection are less likely to respond to subsequent therapies. However, SVR12 was achieved in an outstanding 99.5% of patients given GLE/PIB for 12 weeks, irrespective of prior treatment and without the need for concomitant RBV or pegIFN. The non-inferiority of the SVR12 rate compared with the historical rate for the current standard of care (SOF + RBV for 12 weeks) was confirmed. A total of 83.2% of patients had NS5A polymorphisms at baseline. However, there were no cases of on-treatment virologic failure or post-treatment relapse so no negative predictors of response could be identified. The results of this study strongly support the use of GLE/PIB given for 12 weeks in treatment-naïve or treatment-experienced patients with HCV GT2 infection without cirrhosis.

7.1.2. Study ID M13-594 (ENDURANCE-3)

Study design, objectives, locations and dates

This was a Phase III, partially randomised, open-label, active-controlled, multicentre study comparing the efficacy and safety of GLE/PIB to sofosbuvir with daclatasvir (SOF +DCV) in treatment-naïve adults with chronic HCV GT3 infection without cirrhosis. It is an on-going study being conducted at 77 sites in Australia, Canada, France, Germany, New Zealand, Sweden, Switzerland, the UK and the US.

The study started in December 2015 and the cut-off date for analysis of the primary endpoint was October 2016. This primary analysis was conducted when all patients had completed the Post-treatment Week 12 visit, or had prematurely discontinued from the study.

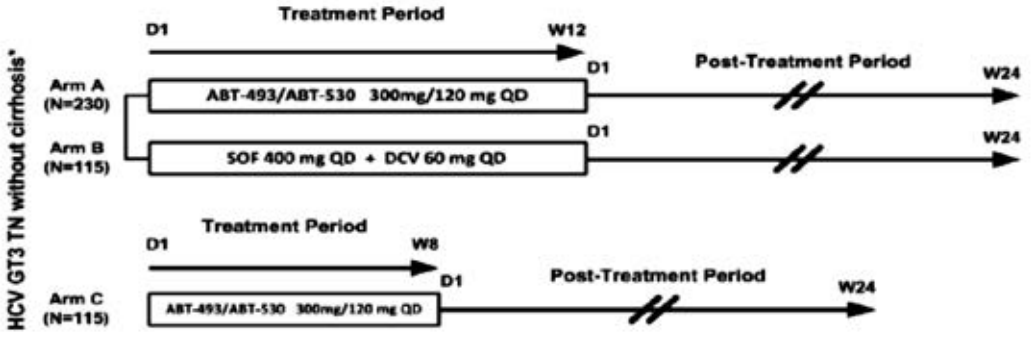
The primary efficacy objectives were to demonstrate non-inferiority in the percentage of patients achieving SVR12 of GLE/PIB given for 12 weeks, compared with SOF + DCV given for 12 weeks; and compared with GLE/PIB given for 8 weeks. The secondary objectives were to demonstrate the superiority of GLE/PIB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

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

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

The study consisted of two periods as shown below.

Figure 4: Study M13-594 schematic.



D = day; DCV = daclatasvir; GT = genotype; HCV = hepatitis C virus; QD = once daily; SOF = sofosbuvir; W = week

The planned duration of the study was up to 36 weeks for patients in Arms A and B and 32 weeks for patients in Arm C. Patient visits were scheduled for the treatment period on Day 1 and Weeks 1, 2, 4, 8 and 12. At each study visit, vital signs were measured and blood samples were drawn for safety assessments, HCV RNA and HCV resistance. Study drug accountability and adherence were assessed at Weeks 4, 8 and 12, if applicable.

7.1.2.1. Inclusion and exclusion criteria

The key inclusion criteria were: males or females aged ≥18 years; positive anti-HCV antibody or HCV RNA; documented chronic HCV GT3 infection; HCV treatment-naïve; documented non-cirrhosis using protocol defined criteria.

The key exclusion criteria were: co-infection with more than one HCV genotype; HBV or HIV co-infection; any cause of liver disease other than HCV; drug or alcohol abuse within previous 6 months; severe sensitivity to study drug excipients; uncontrolled diabetes; clinically significant abnormalities based on medical history, physical examination, laboratory tests, or ECG; active or suspected malignancy or history of malignancy within the previous 5 years; uncontrolled cardiac, respiratory, gastrointestinal, haematological, neurologic, psychiatric or other disorder unrelated to the existing HCV condition; protocol defined prohibited medications and herbal remedies.

7.1.2.2. Study treatments

- Arm A: GLE/PIB three 100 mg/40 mg tablets taken QD with food at the same time of day for 12 weeks.
- Arm B: SOF 400 mg + DCV 60 mg QD for 12 weeks.
- Arm C: GLE/PIB three 100 mg/40 mg tablets QD for 8 weeks with food at the same time of day.

7.1.2.3. Efficacy variables and outcomes

Virologic response was assessed by HCV RNA values measured until 24 weeks after completion of treatment. The primary efficacy variable was SVR12 and the secondary efficacy variables were on-treatment virologic failure and post-treatment relapse.

7.1.2.4. Randomisation and blinding methods

Patients were randomised 2:1 to Arm A or Arm B. Patients were assigned to Arm C when enrolment in Arms A and B was complete. The study was open-label.

7.1.2.5. Analysis populations

The ITT population included all randomised patients who received at least one dose of study drug. The PP population included all randomised patients who received at least one dose of study drug, with the exception of those who had no HCV RNA value in the SVR12 visit window or later (patients with a missing SVR12 value for reasons other than virologic failure or premature discontinuation of study drug) or when the patient had evidence of re-infection.

7.1.2.6. Sample size

A total of 460 patients were planned (230 in Arm A and 115 in each of Arms B and C). With these patient numbers, the study had 90% power to demonstrate non-inferiority to a current standard of care treatment regimen for HCV GT3 infection (SOF + DCV for 12 weeks), with a LCB for the Arm A SVR12 rate of >92%, or with a LCB for the between arm difference (Arm A – Arm B) for SVR12 -6% (assuming an SVR12 rate of 97% in both arms). With a sample size of 115 patients in Arm C, the study had 80% power to demonstrate non-inferiority of the 8 week regimen using the same assumptions. The 92% threshold was selected by applying the 6% non-inferiority margin for SVR12 in the ALLY-3 trial[3].

7.1.2.7. Statistical methods

The analyses were performed on the ITT population using SAS® (SAS Institute, Cary, NC). All statistical tests and CIs were 2-sided with an alpha of 0.05. For analysis of SVR12, treatment effects were analysed with missing data imputed by carrying backward the last post-baseline HCV RNA value, as applicable, using a pre-specified backward imputation method. Missing data which could not be imputed were treated as treatment failures. Categorical demographic and baseline characteristics were compared with a chi-square test and mean changes of continuous variables were compared using one-way ANOVA.

The primary efficacy endpoint was the percentage of patients achieving SVR12. The first primary objective was non-inferiority in the SVR12 rate of the 12 week GLE/PIB treatment regimen compared with the standard of care (SOF + DCV). The percentage of patients with SVR12 when treated with GLE/PIB would be non-inferior to SOF + DCV if the LCB for the treatment difference was above the non-inferiority margin of -6%; or the LCB for the SVR12 rate in Arm A was greater than 92%. The percentage of patients achieving SVR12 in the ITT population was calculated for each arm; and CIs for the SVR12 rates of Arm A and Arm B were calculated using the normal approximation of the binomial distribution. Multiplicity was addressed using the Hochberg procedure and a fixed sequence testing procedure to control the type 1 error rate. Testing proceeded to the first secondary endpoint only if the primary endpoint was achieved. Other secondary endpoints did not include a fixed sequence testing procedure. Similar methodologies were used to test the second primary objective. Non-inferiority in the SVR12 rate of the 8 week GLE/PIB treatment regimen (Arm C) was demonstrated if the LCB of the 97.5% CI for the treatment difference was above the non-inferiority margin of -6%; or the LCB for the SVR12 rate in Arm C was greater than 92%. Multiplicity was also controlled using the Hochberg procedure and a fixed sequence testing procedure.

The first secondary efficacy endpoint was the superiority of Arm A to Arm B based on SVR12 rates. If the LCB of the 95% CI for the difference in SVR12 rates (Arm A minus Arm B) was above 0%, the 12 week GLE/PIB regimen would be considered superior to the SOF + DCV active control treatment. Other secondary efficacy endpoints were tested with 95% CIs using the Wilson's score method. These included the percentage of patients with on-treatment virologic failure and the percentage of patients with post-treatment relapse. Descriptive statistics were

[3] Daklinza (daclatasvir) tablets (package insert): Bristol-Myers-Squibb, 2015

used to assess adverse events and an ANOVA model was used to compare changes in clinical laboratory data.

7.1.2.8. Participant flow

A total of 506 patients were randomised and 505 patients received at least one dose of study drug (233 Arm A; 115 Arm B; and 157 Arm C). Overall, 491 patients completed the study treatment and 14 (2.8%) patients discontinued. The most common reasons for discontinuation were AEs (0.8%), loss to follow-up (0.6%) and non-compliance with study drug (0.4%). There were no withdrawals due to virologic failure. At the time of the primary analysis, a total of 441 patients were on-going.

7.1.2.9. Major protocol violations/deviations

A summary of major protocol deviations is presented in the CSR and individual data listings are provided as an appendix. A total of 11 patients had protocol deviations relating to inclusion/exclusion criteria; one patient received a prohibited medication or supplement; and two patients took their randomised treatment for 1 day or 1 week, respectively. None of the deviations were considered to have affected the study outcome or conclusions. In the ITT population, 99.5% of patients in Arm A and 100% in Arms B and C were 80-120% compliant with study drug.

7.1.2.10. Baseline data

With the exception of country and geographical region, the baseline demographics were comparable in each treatment arm. Overall, the majority of patients were male (52.5%) and White (87.5%). A total of 96.4% patients were aged <65 years and 99.8% were aged <75 years. The majority of patients had a BMI <30 kg/m^2 (84.2%). The baseline disease characteristics were comparable in each treatment arm. All patients had GT3 infection. Baseline median HCV RNA levels were 6.14 $\log_{10}$ IU/mL in Arm A, 6.01 $\log_{10}$ IU/mL in Arm B and 6.06 $\log_{10}$ IU/mL in Arm C. Overall, the IL28B CC genotype was present in 37.6% of patients. The mean baseline HCV RNA was <6,000,000 IU/mL in 77.6% of patients and ≥6,000,000 IU/mL in 22.4%% of patients. Mean baseline albumin was ≥35 g/L in all patients and mean creatinine clearance was <60 mL/min in 1.0% of patients. Overall, the baseline fibrosis stage was F0-F1 in 83.2% of patients, F2 in 5.5% of patients and F3 in 11.3% of patients.

7.1.2.11. Results for the primary efficacy outcome

The first primary efficacy endpoint was achieved. In the ITT population, SVR12 was achieved by 95.3% (95% CI: 92.6, 98.0), 96.5% (95% CI: 93.2, 99.9) and 94.9% (955 CI: 91.5, 98.3) of patients in Arms A, B and C, respectively. The LCB of the 95% CI for the treatment difference between Arm A (GLE/PIB for 12 weeks) and Arm B (SOF + DCV for 12 weeks) was -5.6%, which was above the non-inferiority margin of -6.0%. The LCB of the 95% CI for the SVR12 rate in Arm A was also above the pre-defined threshold of 92%. A sensitivity analysis in the PP population confirmed the result of the primary analysis.

The non-inferiority of GLE/PIB given for 8 weeks compared with GLE/PIB given for 12 weeks (Arm C minus Arm A) was also demonstrated. In the ITT population, SVR12 was achieved by 94.9% (95% CI: 91.5, 98.3) of patients in Arm C, compared with 95.3% (95% CI: 92.6, 98.0) of patients in Arm A. The treatment difference was -0.4% (97.5% CI: -5.4, 4.6) and the LCB of the 97.5% CI for the difference was -5.4% which was above the non-inferiority margin of -6.0%. A sensitivity analysis in the PP population confirmed the result of the primary analysis.

7.1.2.12. Results for other efficacy outcomes

- *SVR12:* The superiority of Arm A to Arm B was not demonstrated because the LCB of the CI for the difference in SVR12 rates was not above 0.0%.
- *Subgroups:* Baseline polymorphisms and fibrosis stage were the only variables associated with SVR12. No differences in demographic subgroups were identified.

- *Virologic failure:* On-treatment virologic failure was experienced by one patient in Arm A and one patient in Arm C. Both patients had GLE/PIB drug levels at least 50% below the median concentrations in the cohort. Virologic relapse was experienced by three patients in Arm A (95% CI: 0.5, 3.9), one patient in Arm B (95% CI: 0.2, 4.8) and five patients in Arm C (95% CI: 1.4, 7.6). Exposure levels to GLE/PIB were comparable in patients with virologic relapse and in those achieving SVR12. The differences in virologic relapse between treatments were not statistically significant. The patients who did not achieve SVR12 for reasons other than virologic failure are shown; most patients had undetectable HCV RNA at their last visits.
- *HCV RNA <LLOQ:* Rapid suppression of HCV RNA occurred in each treatment arm. In Arms A, B and C, HCV RNA <LLOQ was observed at Week 4 in 92.1%, 94.6% and 90.8% of patients, respectively. HCV RNA <LLOQ was observed at Week 8 in 99.6%, 100% and 99.3% of patients, respectively. HCV RNA <LLOQ was observed at Week 12 in 99.5% and 100% of patients in Arms A and B. In Arms A, B and C, there was 99.6%, 97.4%, 99.4% concordance between SVR4 and SVR12 in the ITT population.
- *Virologic resistance:* The number and percentage of patients with GT3 infection with baseline polymorphisms at any key NS3 and/or NS5A site are shown. Baseline polymorphisms at NS3 or NS5A sites had little or no impact on SVR12 rates. However, SVR12 rates were significantly reduced in the small number of patients with baseline polymorphisms at both sites (SVR12 Arm A 66.7%; SVR12 Arm C 50.0%).

7.1.2.13. Evaluator commentary

This partially randomised study compared GLE/PIB given for 8 or 12 weeks with SOF + DCV given for 12 weeks in treatment-naïve, non-cirrhotic patients with HCV GT3 infection. Treatment with GLE/PIB 300 mg/120 mg for 8 weeks was non-inferior to treatment for 12 weeks with SVR12 rates of 94.9% and 95.3% respectively. GLE/PIB 300 mg/120 mg given for 12 weeks was also non-inferior to SOF + DCV given for 12 weeks. The small numbers of study drug discontinuations were mostly for reasons other than AEs.

On-treatment virologic failure occurred in one patient in each of the 8 and 12 week treatment arms, but both cases were associated with low exposure. Virologic relapse occurred in three patients in the 12 week group and five patients in the 8 week group. Failure to achieve SVR12 occurred mainly in patients with both NS3 and NS5A polymorphisms at baseline.

The results of this study strongly support the use of GLE/PIB given QD as a FDC for 12 weeks in treatment-naïve patients with HCV GT3 infection without cirrhosis. The results also strongly support the use of the 2-DAA treatment for 8 weeks without the need for RBV. There were only two cases of on-treatment virologic failure and both were associated with poor compliance. Post-treatment viral relapse was more common in the 8 week arm, but there were no statistically significant differences between the 8 and 12 week treatment groups.

7.1.3. Study ID M13-583 (ENDURANCE-4)

7.1.3.1. Study design, objectives, locations and dates

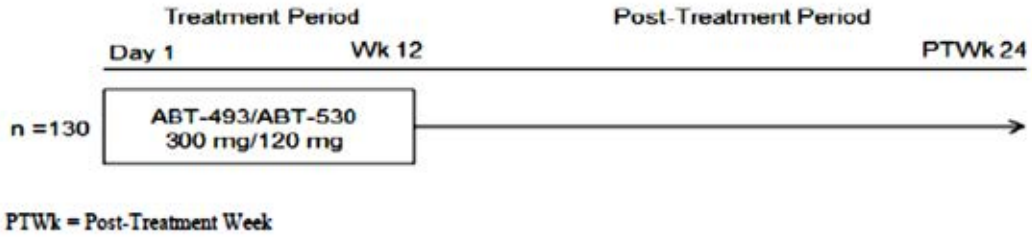
This was a Phase III, single-arm, open-label, multicentre study of the efficacy and safety of GLE/PIB in treatment-naïve or treatment-experienced adults with chronic HCV GT4, 5 or 6 infection without cirrhosis. It is an on-going study being conducted at 31 sites in Belgium, Canada, France, Italy, Portugal, Spain, the UK and South Africa.

The study started in November 2015 and the cut-off date for analysis of the primary endpoint was October 2016. The primary analysis was conducted when all patients had completed the Post-treatment Week 12 visit, or had prematurely discontinued from the study.

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

Approximately 130 patients were planned (70 GT4; 30 GT5; and 30 GT6). As shown below, patients were treated with GLE/PIB 300 mg/120 mg QD for 12 weeks, with a further 24 weeks post-treatment period.

Figure 5: Study M13-583 schematic



The planned duration of the study was up to 36 weeks. Patient visits were scheduled for the treatment period on Day 1 and Weeks 1, 2, 4, 8 and 12. At each study visit, vital signs were measured and blood samples were drawn for safety assessments, HCV RNA and HCV resistance. Study drug accountability and adherence were assessed at Weeks 4, 8 and 12.

7.1.3.2. Inclusion and exclusion criteria

The key inclusion criteria were: males or females aged ≥18 years; positive anti-HCV antibody or HCV RNA; documented chronic HCV GT4, 5 or 6 infections; HCV treatment-naïve, or failed prior IFN or pegIFN with or without RBV, or SOF + RBV with or without pegIFN therapy: documented non-cirrhosis using protocol defined criteria.

The key exclusion criteria were: co-infection with more than one HCV genotype; HBV or HIV co-infection; any cause of liver disease other than HCV; drug or alcohol abuse within previous 6 months; severe sensitivity to study drug excipients; uncontrolled diabetes; clinically significant abnormalities based on medical history, physical examination, laboratory tests, or ECG; active or suspected malignancy or history of malignancy within the previous 5 years; uncontrolled cardiac, respiratory, gastrointestinal, haematological, neurologic, psychiatric or other disorder unrelated to the existing HCV condition; protocol defined prohibited medications and herbal remedies.

7.1.3.3. Study treatments

Open-label GLE/PIB 300 mg/120 mg QD given with food at the same time of day for 12 weeks.

7.1.3.4. Efficacy variables and outcomes

Virologic response was assessed by HCV RNA values measured until 24 weeks after completion of treatment. The primary efficacy variable was SVR12 and the secondary efficacy variables were on-treatment virologic failure and post-treatment relapse.

7.1.3.5. Randomisation and blinding methods

The study was open-label and no randomisation was applied.

7.1.3.6. Analysis populations

The ITT population included all randomised patients who received at least one dose of study drug.

7.1.3.7. Sample size

No formal determination of sample size was made as GT4, 5 and 6 infections are uncommon. If the observed SVR12 rate was 97% in the planned population of 130 patients, the 95% CI would be 94.0 - 99.9%.

7.1.3.8. Statistical methods

All analyses were conducted using SAS®. The primary efficacy endpoint was the percentage of patients in the ITT population who achieved SVR12. For analysis of SVR12, treatment effects were analysed with missing data imputed by carrying backward the last post-baseline HCV RNA value, as applicable, using a pre-specified backward imputation method. Missing data which could not be imputed were treated as treatment failures. The number and percentages were summarised using a 2-sided 95% CI, calculated using the normal approximation to the binomial distribution. The Wilson's score method was used to calculate the CI if the SVR12 rate was 100%. Similar methods were used for analysis of the secondary efficacy endpoints. Missing data were imputed and no correction for multiplicity was required.

7.1.3.9. Participant flow

A total of 121 patients were enrolled and received at least one dose of study drug. A total of 118 patients completed study drug and three (2.5%) patients discontinued. Two patients discontinued study drug because of AEs and one patient was non-compliant. A total of 92 patients are ongoing in the post-treatment period.

7.1.3.10. Major protocol violations/deviations

One patient had a major protocol deviation related to inclusion/exclusion criteria; and three patients received prohibited concomitant medications. All patients were at least 80-120% compliant with drug therapy.

7.1.3.11. Baseline data

The majority of patients were male (63.6%) and White (71.2%), or Asian (20.3%). A total of 89.3% of patients were aged <65 years and 97.5% were aged <75 years. The majority of patients (82.6%) had a BMI <30 kg/m^2. Most patients were treatment-naïve (67.8%) and the remainder (32.2%) were treatment-experienced (all IFN- based). All patients had GT4 infection (62.8%), GT5 infection (21.5%), or GT6 infection (15.7%). Overall, the IL28B CC genotype was present in 24.8% of patients. The mean baseline HCV RNA was <6,000,000 IU/mL in 81.8% of patients and ≥6,000,000 IU/mL in 18.2%% of patients. Mean baseline albumin was ≥35 g/L in all patients and mean creatinine clearance was <60 mL/min in 5.0% of patients. Overall, the baseline fibrosis stage was F0-F1 in 86.0% of patients.

7.1.3.12. Results for the primary efficacy outcome

A total of 99.2% (95% CI: 97.6, 100.0) of patients achieved SVR12.

7.1.3.13. Results for other efficacy outcomes

- *SVR12:* Only one patient (0.8%) failed to achieve SVR12 (due to premature study drug discontinuation in a patient with GT4 infection). There were no cases of on-treatment virologic failure or relapse.
- *Subgroups:* No differences in subgroups were identified as only one patient did not achieve SVR12.
- *Virologic failure:* There were no cases of on-treatment virologic failure or relapse. There was a single case of non-virologic failure due to study drug discontinuation after Day 16.
- *HCV RNA <LLOQ:* At Weeks 4, 8 and 12, HCV RNA <LLOQ was observed in 93.3%, 100% and 100% of patients, respectively. There was 100% concordance between SVR4 and SVR12 in the ITT population.

- *Virologic resistance:* Baseline polymorphisms at any key NS5A site were detected in 61.1%, 15.4% and 63.6% of patients with GT4, GT5 and GT6 infections, respectively. Baseline polymorphisms at any key NS3 site were detected in 0%, 46.2% and 9.1% of patients with GT4, GT5 and GT6 infections, respectively. Overall, only three patients had NS3 + NS5A polymorphisms. Baseline polymorphisms had no impact on the treatment outcomes as no patients experienced virologic failure.

7.1.3.14. Evaluator commentary

In this single-arm, open-label study of patients with HCV GT4-6 without cirrhosis, 99.2% of patients achieved SVR12 with GLE/PIB given for 12 weeks, irrespective of whether they were treatment-naïve or treatment-experienced. Only one patient did not achieve SVR12 but there were no cases of virologic failure. The study design was appropriate for patients with uncommon HCV genotypes. An active control group would have been optimal and larger patients would have been desirable. However, these proved unnecessary given that almost 100% efficacy was achieved in each of the genotypes tested. This was achieved irrespective of viral or host factors, including baseline demographics, HCV genotype, baseline viral load and previous treatment. The study results strongly support the use of GLE/PIB given QD for 12 weeks in patients with GT4, GT5, or GT6 infection in treatment-naïve or treatment-experienced (IFN-based) non-cirrhotic patients.

7.1.4. Study ID M14-868

7.1.4.1. Study design, objectives, locations and dates

This was an expanded Phase II, multicentre, partially randomised, open-label study to investigate the efficacy and safety of GLE + PIB co-administered with or without RBV adult patients with chronic HCV GT2, 3, 4, 5, or 6 infection with or without cirrhosis. It is an on-going study being conducted at 81 sites in Australia, Canada, France, Korea, New Zealand, Taiwan, the UK and the US. The study started in September 2014 and the cut-off date for analysis of the primary endpoint was November 2016. The primary analysis was conducted when all patients had completed the Week 12 visit, or had prematurely discontinued from the study. The study consisted of fours parts and the primary objective was to measure the proportion of patients achieving SVR12 in each part. In Part 4, there was a specific assessment of SVR12 with GLE +PIB compared with historical SOF +RBV efficacy data in GT2, DAA-naïve patients without cirrhosis. Other objectives common to each study part were to measure SVR4 and to assess the rate of on-treatment virologic failure, post-treatment relapse and emergence and persistence of viral variants. Parts 1 and 2 were considered exploratory; and Parts 3 and 4 were considered confirmatory pivotal registration studies. Approximately 685 patients were planned (175 Part 1; 150 Part 2; 200 Part 3; and 160 Part 4).

Part 1 (Exploratory): Treatment-naïve and treatment-experienced GT2-infected patients without cirrhosis were randomised 1:1:1 into one of three treatment arms (25 patients per arm).

- Arm A: GLE 300 mg QD +PIB 120 mg QD for 12 weeks.
- Arm B: GLE 200 mg QD + PIB 120 mg QD for 12 weeks.
- Arm C: GLE 200 mg QD + PIB 120 mg QD + RBV (1,000 mg or 1,200 mg divided BID) for 12 weeks.

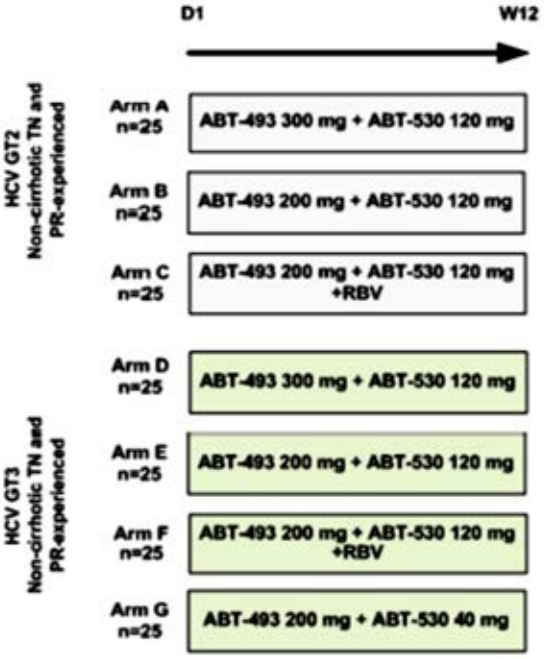
Treatment-naïve and treatment-experienced GT3- infected patients without cirrhosis were randomised 1:1:1:1 into one of four treatment arms (25 patients per arm).

- Arm D: GLE 300 mg QD + PIB 120 mg QD for 12 weeks.
- Arm E: GLE 200 mg QD + PIB 120 mg QD for 12 weeks.

- Arm F: GLE 200 mg QD + PIB 120 mg QD + RBV (1,000 mg or 1,200 mg divided BID) for 12 weeks.
- Arm G: GLE 200 mg QD + PIB 40 mg QD for 12 weeks.

The randomisation in Part 1 was stratified based on previous treatment experience. The study schematic is shown below.

Figure 6: Study M14-868 schematic (Part 1).



GT = genotype; HCV = hepatitis C virus; PR = pegylated interferon/RBV; RBV = ribavirin; TN = treatment-naive

Part 2 (Exploratory): Based on the results of Part 1, a further nine treatment cohorts were planned in Part 2 (Arms H - P). However, following a review of Part 1 data once all patients reached Post-treatment Week 4, only Arms J, L, O and P were progressed.

Treatment-naïve and treatment-experienced GT2-infected patients without cirrhosis (50 patients planned):

- Arm J: GLE 300 mg QD +PIB 120 mg QD for 8 weeks.

GT3-infected patients without cirrhosis:

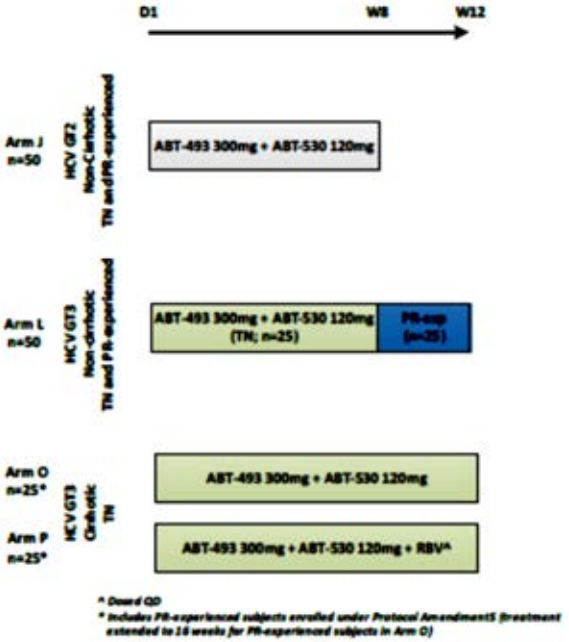
- Arm L_{TN}: treatment-naïve patients treated with GLE 300 mg QD + PIB 120 mg QD for 8 weeks (25 patients planned).
- Arm L_{TE}: treatment-experienced patients treated with GLE 300 mg + PIB 120 mg for 12 weeks (25 patients planned).

GT3-infected treatment-naïve patients with cirrhosis were randomised 1:1 into one of two treatment arms (25 patients per arm planned):

- Arm O: GLE 300 mg QD + PIB 120 mg QD for 12 weeks.
- Arm P: GLE 300 mg QD + PIB 120 mg QD + RBV 800 mg QD for 12 weeks.

The Part 2 study schematic is shown below.

Figure 7: Study M14-868 schematic (Part 2).



GT = genotype; HCV = hepatitis C virus; PR = pegylated interferon/RBV; RBV = ribavirin; TN = treatment-naive; QD = once daily

Part 3 (Confirmatory): Enrolment in Part 3 was determined by pre-defined efficacy criteria from Part 2 once all applicable patients in Arms L and O had reached Post-treatment Week 4.

Non-cirrhotic and/or cirrhotic patients with GT3 infection were randomised 1:1 into Arms Q and R with stratification by presence or absence of cirrhosis and by prior HCV treatment for cirrhotic patients. Approximately 200 patients were planned with approximately 100 patients in each arm (40 without cirrhosis and 60 with cirrhosis).

GT3-infected treatment-naïve patients with cirrhosis were enrolled only into:

- Arm Q: GLE /PIB 300 mg/120 mg QD for 12 weeks.

GT3-infected treatment-experienced patients without cirrhosis were randomised 1:1 into one of two treatment arms:

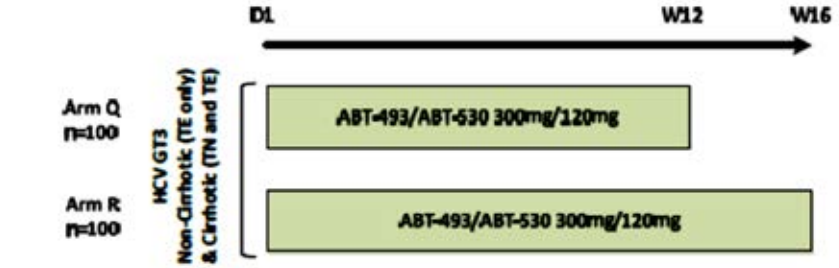
- Arm Q: GLE /PIB 300 mg/120 mg QD for 12 weeks.
- Arm R: GLE/PIB 300 mg/120 mg QD for 16 weeks.

GT3-infected treatment-experienced patients with cirrhosis were enrolled only into:

- Arm R: GLE/PIB 300 mg/120 mg QD for 16 weeks.

The Part 3 study schematic is shown below.

Figure 8: Study M14-868 schematic (Part 3).



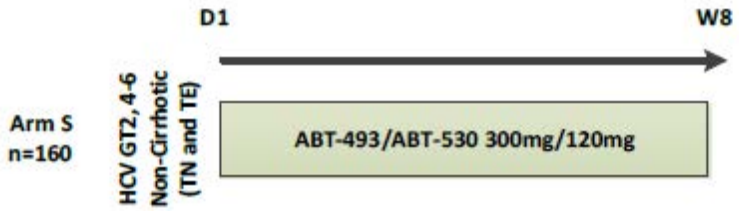
GT = genotype; HCV = hepatitis C virus; TE = treatment-experienced; TN = treatment-naïve

Part 4 (Confirmatory): Approximately 100 GT2-infected treatment-naïve and treatment-experienced patients and approximately 60 treatment-naïve and treatment-experienced patients with GT4 -6 infections without cirrhosis were enrolled into Arm S.

- Arm S: GLE /PIB 300 mg/120 mg QD for 8 weeks.

The Part 4 study schematic is shown below.

Figure 9: Study M14-868 schematic (Part 4).



GT = genotype; HCV = hepatitis C virus; TE = treatment-experienced; TN = treatment-naïve

7.1.4.2. Inclusion and exclusion criteria

The key inclusion criteria were: males or females aged >18 years; HCV GT2 -6 with the appropriate genotype for each study arm; chronic HCV infection based on pre-defined criteria; treatment-naïve or treatment-experienced (IFN or pegIFN +/- RBV; or SOF + RBV +/- pegIFN) and documented non-cirrhotic or cirrhotic based on protocol-defined criteria.

The key exclusion criteria were: patients with low HCV RNA load using pre-defined criteria; co-infection with more than one HCV genotype; HBV or HIV co-infection; any cause of liver disease other than HCV; cirrhosis with Child-Pugh B or C classification or history of hepatic decompensation (Parts 2 and 3); drug or alcohol abuse within previous 6 months that could preclude adherence to the protocol; severe sensitivity to study drug excipients; uncontrolled diabetes; clinically significant abnormalities based on medical history, physical examination, laboratory tests, or ECG; active or suspected malignancy or history of malignancy within the previous 5 years; uncontrolled cardiac, respiratory, gastrointestinal, haematological, neurologic, psychiatric or other disorder unrelated to the existing HCV condition; protocol defined prohibited medications and herbal remedies.

7.1.4.3. Study treatments

Each dose of study drug (GLE 100 mg, PIB 40 mg, GLE/PIB 100 mg/40 mg, or RBV 200 mg) was dispensed as tablets via the IRT system.

7.1.4.4. Efficacy variables and outcomes

Virologic response was assessed by HCV RNA values measured until 24 weeks after completion of treatment. The primary efficacy variable was SVR12 and the secondary efficacy variables were on-treatment virologic failure and post-treatment relapse. The outcomes were assessed in relation to the dose of study drug and the treatment duration.

7.1.4.5. Randomisation and blinding methods

Randomisation procedures were conducted using IRT. The study was open-label.

7.1.4.6. Analysis populations

All analyses were performed on the ITT population with the PP population used as a sensitivity analysis.

7.1.4.7. Sample size

The primary efficacy endpoint was SVR12. If the SVR12 rate was 96%, 25 patients in each arm would have a 95% CI of 80% to 99% using the Wilson score method. If the SVR12 rate was 96%, 50 patients in each arm would have a 95% CI of 87% to 99%. If the SVR12 rate was 96%, 100 patients in each arm would have a 95% CI of 90% to 98%. In Part 4, assuming an SVR12 rate of 97%, 90 DAA-naïve patients with GT2 infection would have at least 80% power to show non-inferiority to the standard of care treatment at the time of study design (SOF + RBV for 12 weeks), if the 95% CI LCB was greater than 89%.

7.1.4.8. Statistical methods

All analyses were conducted using SAS®. All tests and CIs were 2-sided with an alpha level of 0.05. For analysis of SVR12, treatment effects were analysed with missing data imputed by carrying backward the last post-baseline HCV RNA value, as applicable, using a pre-specified backward imputation method. Missing data which could not be imputed were treated as treatment failures. Summary statistics were used to assess the percentage of patients who achieved SVR12 in each treatment group. 95% CIs were calculated using Wilson score methods. In Part 4, the percentage of DAA -naïve patients with GT2 infection without cirrhosis would be non-inferior to the current standard of care treatment at the time of study design (SOF + RBV for 12 weeks), if the 95% CI LCB was greater than 89%. The secondary endpoints were assessed in the same manner. Subgroup analyses were performed based on genotype, IL28B genotype, prior treatment history and baseline HCV RNA levels.

7.1.4.9. Participant flow

- ***Part 1****:* In Arms A, B and C, a total of 74 patients were enrolled and 73 completed the study drug. In Arms D, E, F and G, a total of 122 patients were enrolled and 116 completed study drug. One patient in Arm A withdrew consent. There were five discontinuations in Arms D – G, most commonly due to AEs (1.7%), virologic failure (0.8%) and loss to follow-up (1.7%).
- ***Part 2****:* In Arms J, L, O and P, a total of 163 patients were enrolled and 160 completed the study drug. There were two discontinuations, one due to virologic failure in Arm L. In addition, one patient never received study drug.
- ***Part 3****:* In Arms Q and R, a total of 132 patients were enrolled and 129 completed the study drug. There were two discontinuations (one patient in Arm R experienced virologic failure and one patient in Arm Q was discontinued for non-compliance). In addition, one patient never received study drug.
- ***Part 4****:* In Arm S, a total of 203 patients were enrolled and 201 completed the study drug. There were two discontinuations but neither was due to virologic failure.

7.1.4.10. Major protocol violations/deviations

In Parts 1, 2, 3 and 4, there were 8, 10, 15 and 6 significant protocol deviations, respectively; however, none were considered to have affected the study outcome. In Parts 1, 2, and 4, respectively, all but 4, 2, 2 patients were 80% to 100% treatment compliant. All patients with available compliance data in Part 3 were ≥80% compliant.

7.1.4.11. Baseline data

- ***Part 1****:* The majority of patients were male (46.7% to 72.0%) and White (88% to 96.7%), with mean ages of 47.6 to 55.7 years and a mean BMI <30 kg/m^2 in most patients (60% to 83.9%). Baseline disease characteristics were comparable in each arm. All patients were either GT2 or GT3-infected with IL28B CC genotype in 33.3% to 54.2% of patients. Mean HCV RNA levels ranged from 6.32 to 6.82 $\log_{10}$ IU/mL and HCV RNA levels were ≥1,000,000 IU/mL in 66.7% to 88.0% of patients.
- ***Part 2****:* The majority of patients were male (53.6% to 66.7%) and White (88.9% to 94.4%), with mean ages of 49.4 to 55.7 years and a mean BMI <30 kg/m^2 in most patients (74.1% to 81.1%). Baseline disease characteristics were comparable in each arm. All patients had either GT2 or GT3 infection, with IL28B CC genotype in 32.1% to 42.9% of patients. Mean HCV RNA levels ranged from 6.24 to 6.58 $\log_{10}$ IU/mL and HCV RNA levels were ≥1,000,000 IU/mL in 66.7% to 82.1% of patients.
- ***Part 3:*** The majority of patients were male (60.0% to 76.6%) and White (77.3% to 92.5%), with mean ages of 54.6 to 58.7 years and a mean BMI <30 kg/m^2 in most patients (62.5% to 72.7%). Baseline disease characteristics were comparable in each arm. All patients had GT3 infection with IL28B CC genotype in 13.6% to 50.0% of patients. Mean HCV RNA levels ranged from 6.07 to 6.35 $\log_{10}$ IU/mL and HCV RNA levels were ≥1,000,000 IU/mL in 54.5% to 70.2% of patients.
- ***Part 4:*** Approximately half of the patients were male (42.1% to 63.8%) and most were White (60.3% to 82.8%), with mean ages of 48.4 to 53.5 years and a mean BMI <30 kg/m^2 in most patients (69% to 86.2%). Baseline disease characteristics were comparable in each group. All patients had GT2 (71.4%), GT4 (22.7%), GT5 (1.0%), or GT6 (4.9%) infection with IL28B CC genotype in 32.8% to 47.6% of patients. Mean HCV RNA levels ranged from 5.71 to 6.30 $\log_{10}$ IU/mL and HCV RNA levels were ≥1,000,000 IU/mL in 32.8% to 71.0% of patients.

7.1.4.12. Results for the primary efficacy outcome

Patients with GT2 infection

The SVR12 rates for treatment-naïve and treatment-experienced patients with GT2 infection without cirrhosis in Parts 1 and 2 are shown. In Arm A (GLE 300 mg + PIB 120 mg QD for 12 weeks), SVR12 was achieved by 96% of patients (95% CI: 80.5, 99.3). In Arm B (GLE 200 mg + PIB 120 mg QD for 12 weeks), SVR12 was achieved by 100% of patients (95% CI: 86.2, 100). In Arm C (GLE 200 mg + PIB 120 mg QD + RBV for 12 weeks), SVR12 was achieved by 100% of patients (95% CI: 86.7, 100). In Arm J (GLE 300 mg + PIB 120 mg QD for 8 weeks), SVR12 was achieved by 98.1% of patients (95% CI: 90.2, 99.7).

Patients with GT3 infection

The SVR12 rates for treatment-naïve and treatment-experienced patients with GT3 infection without cirrhosis in Part 1 are shown. In Arm D (GLE 300 mg + PIB 120 mg QD for 12 weeks), SVR12 was achieved by 93.3% of patients (95% CI: 78.7, 98.2). In Arm E (GLE 200 mg + PIB 120 mg QD for 12 weeks), SVR12 was achieved by 93.3% of patients (95% CI: 78.7, 98.2). In Arm F (GLE 200 mg + PIB 120 mg QD + RBV for 12 weeks), SVR12 was achieved by 93.5% of patients (95% CI: 79.3, 98.2). In Arm G (GLE 200 mg + PIB 40 mg QD for 12 weeks), SVR12 was achieved by 83.3% of patients (95% CI: 66.4, 92.7).

The SVR12 rates for treatment-naïve and treatment-experienced patients with GT3 infection with or without cirrhosis in Part 2 are shown. In Arm L (treatment-naïve patients without cirrhosis treated with GLE 300 mg + PIB 120 mg QD for 8 weeks), SVR12 was achieved by 96.6% of patients (95% CI: 82.8, 99.4). In Arm L (treatment-experienced patients without cirrhosis given GLE 300 mg + PIB 120 mg QD for 12 weeks), SVR12 was achieved by 91.7% of patients (95% CI: 74.2, 97.7). In Arm O (treatment-naïve patients with cirrhosis treated with GLE 300 mg + PIB 120 mg QD for 12 weeks), SVR12 was achieved by 100% of patients (95% CI: 86.2, 100). In Arm O (treatment-experienced patients with cirrhosis treated with GLE 300 mg + PIB 120 mg QD for 16 weeks), SVR12 was achieved by 75.0% of patients (95% CI: 30.1, 95.4). In Arm P (treatment-naïve and treatment-experienced patients with cirrhosis treated with GLE 300 mg + PIB 120 mg QD + RBV 800 mg QD for 12 weeks), SVR12 was achieved by 100% of patients (95% CI: 87.5, 100).

The SVR12 rates for treatment-naïve and treatment-experienced patients with GT3 infection with or without cirrhosis in Part 3 are shown. In Arm Q (treatment-experienced patients without cirrhosis treated with GLE/PIB 300 mg/120 mg QD for 12 weeks), SVR12 was achieved by 90.9% of patients (95% CI: 72.2, 97.5). In Arm R (treatment-experienced patients without cirrhosis given GLE/PIB 300 mg/120 mg QD for 16 weeks), SVR12 was achieved by 95.5% of patients (95% CI: 78.2, 99.2). In Arm Q (treatment-naïve patients with cirrhosis treated with GLE/PIB 300 mg/120 mg QD for 12 weeks), SVR12 was achieved by 97.5% of patients (95% CI: 87.1, 99.6). In Arm R (treatment-experienced patients with cirrhosis treated with GLE/PIB 300 mg/120 mg QD for 16 weeks), SVR12 was achieved by 95.7% of patients (95% CI: 85.8, 98.8).

Patients with GT2 or GT4-6 infection

The SVR12 rates for treatment-naïve and treatment-experienced patients with GT2 and GT4-6 infection without cirrhosis in Part 4 are shown. In Arm S (treatment-naïve and treatment-experienced patients with GT2 infection without cirrhosis treated with GLE/PIB 300 mg/120 mg QD for 8 weeks), SVR12 was achieved by 97.9% of patients (95% CI: 94.1, 99.3). In treatment-naïve and treatment-experienced patients with GT4-6 infection without cirrhosis given GLE/PIB 300 mg/120 mg QD for 8 weeks, SVR12 was achieved by 93.1% of patients (95% CI: 83.6, 97.3).

7.1.4.13. Results for other efficacy outcomes

Patients with GT2 infection

*In Parts 1 and 2, t*here were rapid reductions in HCV RNA and no cases of virologic failure. HCV RNA was <LLOQ at Weeks 4, 8 and 12 in all arms. In Parts 1 and 2, NS5A polymorphisms were present in 72.0% of patients, NS3 polymorphisms were present in one patient (0.8%) and there were no cases of NS3 + NS5A polymorphism.

Patients with GT3 infection

In Parts 1 and 2, a total of ten patients experienced virologic failure. Three patients experienced on-treatment virologic failure and seven patients experienced relapse. Six of the ten patients with virologic failure received a dose of GLE and/or PIB less than 300 mg/120 mg. The three patients who relapsed following GLE 300 mg + PIB 120 mg were treatment-experienced and two of the three had baseline A30K or Y93H NS5A polymorphisms. Overall, there were rapid reductions in HCV RNA and HCV RNA was <LLOQ at Weeks 4 in all but two patients. In Parts 1 and 2, NS5A only polymorphisms were present in 21.0% of patients, NS3 only polymorphisms were present in 1.7% of patients and NS3 + NS5A polymorphism was present in 1.3% of patients. In Part 3, NS5A only polymorphisms were present in 18.6% of patients, NS3 only polymorphisms were present in 1.6% of patients and no patients had NS3 + NS5A polymorphisms.

Patients with GT2 or GT4-6 infection

In Arm S (treatment-naïve and treatment-experienced patients with GT4-6 infection without cirrhosis treated with GLE/PIB 300 mg/120 mg QD for 8 weeks), there were no cases of virologic failure and four cases of non-virologic failure (6.9%). In treatment-naïve and treatment-experienced patients with GT2 infection without cirrhosis given GLE/PIB 300 mg/120 mg QD for 8 weeks, there were two cases of virologic relapse (1.4%). There were rapid reductions in HCV RNA and no cases of virologic failure. HCV RNA was <LLOQ at Weeks 4, 6 and 8 in all arms. Overall any NS5A polymorphisms were present in 67.4% of patients, any NS3 polymorphisms were present in two patients (1.2%) and NS3 + NS5A polymorphisms were present in two patients (1.2%).

7.1.4.14. Evaluator commentary

This was a complex exploratory/confirmatory study with multiple treatment arms assessing efficacy in patients with GT2-6 infection treated for 8, 12 or 16 weeks. Treatment-naïve and treatment-experienced patients with and without cirrhosis were given various doses of GLE + PIB or GLE/PIB with or without RBV. Although it was a Phase II study, it may be considered pivotal as it supports the dosage and treatment duration recommendations in the proposed PI.

In Parts 1 and 2 of the study, the optimal dose for GLE + PIB was shown to be 300 mg + 120 mg in patients with GT2 and GT3 infection without cirrhosis and the addition of RBV did not enhance efficacy. In patients with GT2 infection SVR12 rates were typically >95%, although SVR12 rates in patients with GT3 infection were generally lower. Treatment with GLE 300 mg + PIB 120 mg given for 8 weeks was effective in both treatment-naïve and -experienced GT2 and treatment-naïve GT3 populations. Relapse was associated with previous treatment and with baseline NS5A polymorphism. Overall, the results demonstrate that GLE 300 mg + PIB 120 mg is highly effective in non-cirrhotic patients with GT2 or GT3 (treatment-naïve patients only) infection when given for 8 weeks. However, lower SVR12 rates are observed in treatment-experienced patients with GT3 infection compared to treatment-naïve patients when treated for 12 weeks. High SVR12 rates were observed irrespective of demographic variables or disease characteristics.

In Part 3, treatment-naïve patients with GT3 infection with cirrhosis, and treatment-experienced patients with GT3 infection with or without cirrhosis were treated with GLE 300 mg + PIB 120 mg for 12 or 16 weeks. High SVR12 rates were achieved in all treatment arms. In treatment-naïve GT3 patients with cirrhosis treated for 12 weeks, the SVR12 rate was 98%. In treatment-experienced patients with or without cirrhosis, the 16 week regimen achieved SVR12 rates >95%, compared with only 91% in patients without cirrhosis treated for 12 weeks. In each group, similar SVR12 rates were achieved irrespective of baseline host or viral factors. In Part 4, high efficacy rates were observed in patients with GT2 and GT4-6 infections without cirrhosis treated for 8 weeks. There were limited numbers of patients with GT5 (n=2) and GT6 (n=10) infection, but SVR12 rates were comparable to the overall rates (100% for GT5; 90.0% for GT6 with no virologic failures).

Overall, the results support the dosage (GLE 300mg/PIB 120 mg given QD) and treatment duration recommendations in the proposed PI [8, 12 or 16 weeks depending on genotype (GT2-6), prior HCV treatment history (naïve or experienced) and presence or absence of cirrhosis].

7.1.5. Study ID M13-590 (ENDURANCE-1)

7.1.5.1. Study design, objectives, locations and dates

This is a Phase III, multicentre, randomised, open-label study to investigate the efficacy and safety of GLE/PIB in treatment-naïve and treatment-experienced, non-cirrhotic adult patients with chronic HCV GT1 infection. It is an on-going study being conducted at 115 sites in Australia, Austria, Belgium, Canada, Chile, France, Germany, Hungary, Israel, Italy, Korea, Lithuania, Mexico, New Zealand, Poland, Portugal, Romania, Spain, Sweden, Switzerland,

Taiwan, the UK and the US. The study started in October 2015 and the cut-off date for analysis of the primary endpoint was September 2016. The primary analysis was conducted when all patients had completed the Week 12 visit, or had prematurely discontinued from the study.

The primary efficacy objectives were:

- to show the non-inferiority of SVR12 rates in DAA-naïve, HCV GT1 mono-infected patients following treatment with GLE/PIB for 12 weeks, compared with historical efficacy data in the same patient population treated with the standard of care regimen of OBV/PTV/r + DSV +/- RBV or SOF/LDV for 12 weeks.
- to show the non-inferiority in SVR12 rates in the same patient population treated for 8 weeks versus 12 weeks.

The secondary objectives were:

- SVR12 rates in mono-infected HCV GT1-infected patients.
- SVR12 rates in all HCV GT1 patients.
- SVR12 rates in patients co-infected with HCV GT1 and HIV-1.
- SVR12 rates in SOF treatment-experienced HCV GT1 patients.
- the percentage of patients with on-treatment virologic failure.
- the percentage of patients with post-treatment relapse.

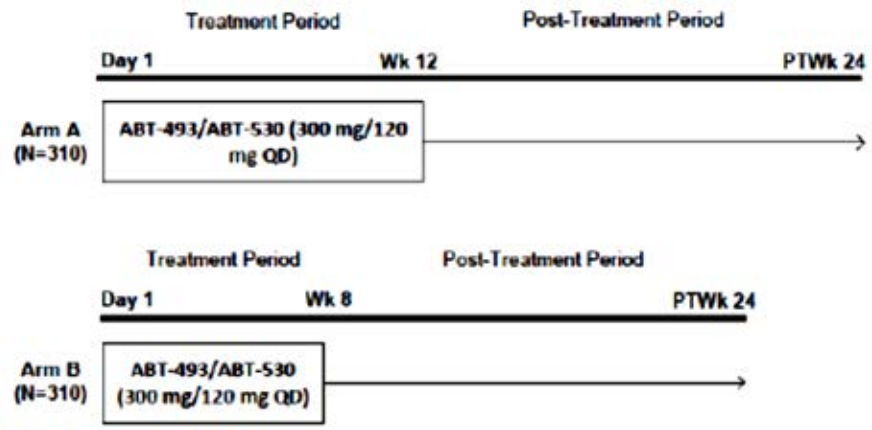
It was planned to enrol approximately 620 HCV GT1-infected, treatment-naïve or treatment-experienced patients without cirrhosis, randomised 1:1 into one of two treatment arms:

- Arm A: GLE/PIB 300 mg/120 mg given QD for 12 weeks.
- Arm B: GLE/PIB 300 mg/120 mg given QD for 8 weeks.

The randomisation was stratified by viral load at screening (< or ≥ 6 million IU/mL) and by HCV GT1 subtype (1b or non-1b).

The study consisted of two periods as shown below. An open-label treatment period of 12 weeks or 8 weeks was followed by a post-treatment period of 24 weeks. Patients randomised in Arms A and B who completed or prematurely discontinued active study drug were followed for 24 weeks to assess safety, HCV RNA and resistant mutations.

Figure 10: Study M13-590 schematic.



PTWk = Post-Treatment Week; QD = once daily; Wk = week

The planned duration of the study was up to 36 or 32 weeks for all patients. Patient visits were scheduled for the treatment period on Day 1 and Weeks 1, 2, 4, 8 and 12 (for Arm A only). At

each study visit, vital signs were measured and blood samples were drawn for safety assessments, HCV RNA and HCV resistance. Study drug accountability and adherence were assessed at Weeks 4, 8 and 12.

7.1.5.2. Inclusion and exclusion criteria

The key inclusion criteria were: males or females aged ≥18 years; BMI ≥18.0 kg/m^2; HCV RNA ≥1000 IU/mL at screening with positive anti-HCV antibody; documented chronic HCV GT1 infection; DAA treatment-naïve, or failed previous therapies IFN or pegIFN +/- RBV; documented non-cirrhosis using protocol defined criteria.

The key exclusion criteria were: co-infection with more than one HCV genotype; HBV or HIV co-infection; any cause of liver disease other than HCV; drug or alcohol abuse within previous 6 months that could preclude adherence to the protocol; severe sensitivity to study drug excipients; uncontrolled diabetes; clinically significant abnormalities based on medical history, physical examination, laboratory tests, or ECG; active or suspected malignancy or history of malignancy within the previous 5 years; uncontrolled cardiac, respiratory, gastrointestinal, haematological, neurologic, psychiatric or other disorder unrelated to the existing HCV condition; history of solid organ transplantation; protocol defined prohibited medications and herbal supplements.

Note: the eligibility criteria were later changed by protocol amendment to include patients with HCV/HIV-1 co-infection; and/or patients who had previously received SOF. Secondary endpoints were later updated by protocol amendment to evaluate the percentage of patients with HCV/HIV-1 co-infection with SVR12, and the percentage of patients who had previously received SOF with SVR12.

7.1.5.3. Study treatments

- Arm A: GLE/PIB 300 mg/120 mg tablets QD for 12 weeks.
- Arm B: GLE/PIB 300 mg/120 mg tablets once daily for 8 weeks.

7.1.5.4. Efficacy variables and outcomes

The primary efficacy variable was SVR12. The secondary variables were on-treatment virologic failure and post-treatment relapse.

7.1.5.5. Randomisation and blinding methods

The randomisation was stratified by viral load at screening (< or ≥ 6 million IU/mL) and by HCV GT1 subtype (1b or non-1b) using IRT. The study was open-label.

7.1.5.6. Analysis populations

The main analysis populations were:

- The ITT population (n=703) included all randomised patients who received at least one dose of study drug.
- The ITT-PS population (n=667) included all randomised HCV mono-infected DAA-naïve patients (that is, without HIV-1 co-infection).
- The PP population (ITT-PS-PP, n=663) included all randomised patients in the ITT-PS, with the exception of patients who discontinued before Week 8, patients who experienced virologic failure prior to Week 8, patients with missing SVR12 values and non-responders due to re-infection.
- The ITT mono-infected subpopulation (ITT-MS, n=670) included all patients in the ITT population who were HCV mono-infected, including those who were DAA-experienced.

7.1.5.7. Sample size

Approximately 620 patients were planned to be enrolled, with at least 270 patients in each treatment arm to be mono-infected HCV GT1, DAA-naïve for the primary analysis. With 270 patients in each arm and assuming that 97% of patients in Arm A achieved SVR12, the study had 90% power to demonstrate non-inferiority of the 12 week treatment arm compared to the historical control SVR12 rate, with a 95% CI LCB above 91%. The non-inferiority of the 8 week treatment arm compared with the 12 week treatment arm was based on a -5% non-inferiority margin with a 2-sided significance level of 0.05. Assuming 270 patients in each arm and an SVR12 rate of 97% in each arm, the study had 90% power to demonstrate non-inferiority of the 8 week treatment arm compared with the 12 week treatment arm.

7.1.5.8. Statistical methods

SAS was used for all analyses. All tests and CIs were 2-sided with an alpha level of 0.05. For analysis of SVR12, treatment effects were analysed with missing data imputed by carrying backward the last post-baseline HCV RNA value, as applicable, using a pre-specified backward imputation method. Missing data which could not be imputed were treated as treatment failures. For analysis of SVR12, the percentage of patients in each arm and the difference between rates were summarised with a 2-sided 95% Wilson score CI. For demographics and baseline disease characteristics, summary statistics were used for continuous variable and numbers and percentages were used for categorical variables.

The primary efficacy endpoints were:

- the percentage of patients in the ITT-PS population achieving SVR12 in Arm A (12 weeks treatment) with the LCB of the 95% CI greater than 91% in the ITT subpopulation of mono-infected HCV GT1-infected DAA-naïve patients.
- Non-inferiority of Arm B (8 week treatment) to Arm A (12 week treatment) using a non-inferiority margin of 5% in the ITT-PS-PP population.
- Non-inferiority of Arm B (8 week treatment) to Arm A (12 week treatment) using a non-inferiority margin of 5% in the ITT-PS population.

A fixed testing procedure was used for the ranked primary endpoints to control the type 1 error. Only if the first primary endpoint was achieved did the testing proceed to the second primary endpoint. Only if the second primary endpoint was achieved did the testing proceed to the third primary endpoint.

The secondary endpoints were assessed without fixed-sequence testing:

- The percentage of patients achieving SVR12 in the ITT-MS population.
- The percentage of patients achieving SVR12 in the ITT population.
- The overall percentage of patients with SVR12.

7.1.5.9. Participant flow

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

7.1.5.10. Major protocol violations/deviations

Ten patients had significant protocol deviations related to inclusion/exclusion criteria and 17 patients had deviations related to prohibited concomitant medications. Compliance data were available in 659 patients and all but four patients were >80% compliant with treatment.

7.1.5.11. Baseline data

The baseline demographics and disease characteristics were comparable in each treatment group. Overall, most patients were female (51.2%) and White (84.1%). Most patients were aged <65 years (89.0%) and 98.9% were aged <75 years. Most patients had BMI <30 kg/m^2 (85.2%). The majority of patients had either GT1a (42.7%) or GT1b (56.9%) infection. Overall, 62.0% of patients were treatment-naïve and 38% were treatment-experienced (nearly all IFN-based). Overall, 95.3% of patients were HCV mono-infected and 26.7% had the IL28B CC genotype. Baseline HCV RNA levels were <6,000,000 IU/mL in 86.9% of patients and <10,000,000 IU/mL in 95.4% of patients. A total of 33 patients (4.7%) were HCV/HIV-1 co-infected. All were receiving ART and nearly all (n=28) had baseline CD4+ counts ≥500 cells/mm^3.

7.1.5.12. Results for the primary efficacy outcome

In the ITT-PS population, SVR12 was achieved by 99.7% (95% CI: 99.1, 100.0) of patients in Arm A (12 weeks treatment) and 99.1% (95% CI: 98.1, 100.0) in Arm B (8 weeks treatment). In the ITT-PS-PP[4] population, SVR12 was achieved by 100% (95% CI: 98.9, 100.0) of patients in Arm A and by 100% (95% CI: 98.9, 100.0) of patients in Arm B.

- The first primary endpoint was achieved. Non-inferiority of 12 weeks treatment to the historical control was demonstrated as the 95% LCB for SVR12 in the ITT-PS was >91%.
- The second primary endpoint was achieved. In the ITT-PS-PP population, non-inferiority of 8 weeks treatment to 12 weeks treatment was demonstrated as the 95% LCB for the difference in SVR12 was >-5%.
- The third primary endpoint was achieved. Non-inferiority of 8 weeks treatment to 12 weeks treatment was demonstrated in the ITT-PS population as the 95% LCB for the difference in SVR12 was >-5%.

7.1.5.13. Results for other efficacy outcomes

In the ITT-MS population, SVR12 was achieved by 99.7% of patients in Arm A and 99.1% in Arm B. In the ITT population with HCV/HIV-1 co-infection, SVR12 was achieved by 18 patients (100.0%) in Arm A and 15 patients (100%) in Arm B.

Only one patient had on-treatment virologic failure, there were no cases of relapse and only three patients had non-virologic failure.

- *SVR12:* Only one patient (0.3%) failed to achieve SVR12 due to virologic failure.
- *Subgroups:* No differences in subgroups were identified as only one patient did not achieve SVR12 due to virologic failure.
- *Virologic failure:* There was one case of on-treatment virologic failure and no cases of relapse.
- *HCV RNA <LLOQ:* In Arm A at Weeks 4, 8 and 12, HCV RNA <LLOQ was observed in 93.8%, 99.7% and 100% of patients, respectively. In Arm B at Weeks 4 and 8, HCV RNA <LLOQ was observed in 95.1% and 99.7% of patients, respectively. There was 100% concordance between SVR4 and SVR12 in the ITT population.
- *Virologic resistance:* In Arm A, baseline polymorphisms at any key NS5A site were detected in 27.0% of patients, one patient had any NS3 polymorphism and no patients had NS3 + NS5A polymorphism. In Arm B, baseline polymorphisms at any key NS5A site were detected in 27.7% of patients, six patients (1.8%) had any NS3 polymorphism and two patients

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

(0.6%) had NS3 + NS5A polymorphism. Baseline polymorphisms had no impact on the treatment outcomes as only one patient experienced virologic failure.

7.1.5.14. Evaluator commentary

This study assessed the efficacy of the GLE/PIB FDC proposed for marketing in treatment-naïve or treatment-experienced patients with GT1 infection without cirrhosis. Treatment durations of 8 and 12 weeks were compared. It also included a small cohort (n=33) of patients with HCV/HIV-1 co-infection, all of whom achieved SVR12. In DAA-naïve mono-infected patients, treatment with GLE/PIB for 12 weeks was non-inferior to standard of care DAA combinations at the time of study design (OBV/PTV/r + dasabuvir +/- RBV or SOF/LDV for 12 weeks). SVR12 rates were 99.7% in the 12 week group and 99.1% in the 8 week group. There was a single case of virologic failure in the 8 week group but there were no cases of post-treatment relapse. The overall results strongly support the dosage and treatment duration recommendations in the proposed PI.

7.1.6. Study ID M14-172(EXPEDITION-1)

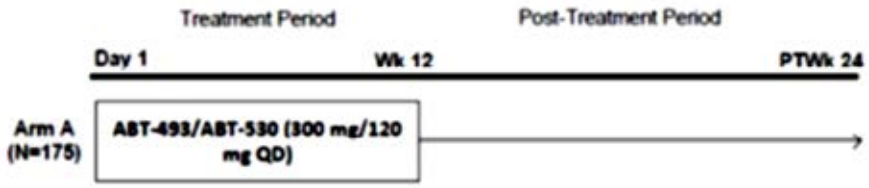
7.1.6.1. Study design, objectives, locations and dates

This is a Phase III, single arm, open-label study of GLE/PIB in treatment-naïve or treatment-experienced adults with chronic HCV GT1, 2, 4, 5 or 6 infections and compensated cirrhosis. It is an on-going study being conducted at 40 sites in Belgium, Canada, Germany, South Africa, Spain and the US. The study started in December 2015 and the cut-off date for analysis of the primary endpoint was November 2016. The primary analysis was conducted when all patients had completed the Post-treatment Week 12 visit, or had prematurely discontinued from the study.

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

Approximately 175 patients were planned. As shown below, patients were treated with GLE/PIB 300 mg/120 mg QD for 12 weeks, with a further 24 weeks post-treatment period.

Figure 11: Study M14-172 schematic.



The planned duration of the study was up to 36 weeks. Patient visits were scheduled for the treatment period on Day 1 and Weeks 1, 2, 4, 8 and 12. At each study visit, vital signs were measured and blood samples were drawn for safety assessments, HCV RNA and HCV resistance. Study drug accountability and adherence were assessed at Weeks 4, 8 and 12.

7.1.6.2. Inclusion and exclusion criteria

The key inclusion criteria were: males or females aged ≥18 years; BMI ≥18.0 kg/m^2; HCV RNA ≥1000 IU/mL at screening with positive anti-HCV antibody; documented chronic HCV GT1, 2, 4, 5, or 6 infection; HCV treatment-naïve, or failed previous therapies IFN or pegIFN +/- RBV or SOF + RBV; compensated cirrhosis with Child-Pugh score <6; cirrhosis documented using protocol defined criteria.

The key exclusion criteria were: co-infection with more than one HCV genotype; HBV or HIV co-infection; any cause of liver disease other than HCV; drug or alcohol abuse within previous 6 months; severe sensitivity to study drug excipients; uncontrolled diabetes; clinically significant abnormalities based on medical history, physical examination, laboratory tests, or ECG; active or suspected malignancy or history of malignancy within the previous 5 years; uncontrolled cardiac, respiratory, gastrointestinal, haematological, neurologic, psychiatric or other disorder unrelated to the existing HCV condition; history of solid organ transplantation; protocol defined prohibited medications and herbal supplements.

7.1.6.3. Study treatments

GLE/PIB was provided as three 100 mg/40 mg tablets QD with food. Study drug was dispensed via IRT.

7.1.6.4. Efficacy variables and outcomes

The primary efficacy variable was SVR12. The secondary efficacy variables were on-treatment virologic failure and post-treatment relapse.

7.1.6.5. Randomisation and blinding methods

The study was open-label with no randomisation schedule.

7.1.6.6. Analysis populations

The ITT population included all patients who received at least one dose of study drug (n=146). The mITT population included the ITT population excluding patients who did not have infection with GT1, 2, 4, 5 or 6.

7.1.6.7. Sample size

No formal hypotheses were tested. If the SVR12 rate was 96% in 175 patients, the 2-sided 95% CI would be 93.1%, 98.9%.

7.1.6.8. Statistical methods

The primary endpoint was SVR12. For analysis of SVR12, treatment effects were analysed with missing data imputed by carrying backward the last post-baseline HCV RNA value, as applicable, using a pre-specified backward imputation method. Missing data which could not be imputed were treated as treatment failures. The number and percentage of patients achieving SVR12 was assessed with a 2-sided 95% CI using the normal approximation to the binomial distribution. If the SVR12 rate was 100%, the Wilson's score method was used to calculate the CI. The percentages of patients with on-treatment virologic failure and post-treatment relapse were summarised with 2-sided 95% Wilson score methods.

7.1.6.9. Participant flow

A total of 146 patients were enrolled and treated and 144 completed study drug. Two patients discontinued but there were no cases of virologic failure or relapse. All 134 patients with compliance data were >80% compliant with study drug.

7.1.6.10. Major protocol violations/deviations

Two major protocol deviations were reported due to prohibited concomitant medications. Neither was considered to have affected the study outcomes.

7.1.6.11. Baseline data

The majority of patients were male (61.6%) and White (82.2%). Most patients were aged <65 years (71.9%) and 89.7% were aged <75 years. Most patients had BMI <30 kg/m^2 (56.8%). HCV genotypes 1, 2, 4, 5 and 6 were present in 59.6%, 23.3%, 11.0%, 1.4% and 4.8% of patients, respectively. GT1a and 1b infection subtypes were present in 32.9% and 26.7% of patients, respectively. The IL28B genotype was CC in 26.7% of patients. At baseline, most patients were

Child-Pugh score 5 (87.0%) and 11.6% were Child-Pugh score 6. Most patients were treatment-naïve (75.3%) and 24.7% were treatment-experienced.

7.1.6.12. Results for the primary efficacy outcome

In treatment-naïve and treatment-experienced patients with GT1, 2, 4, 5 and 6 infection and compensated cirrhosis, SVR12 was achieved by 99.3% (95% CI: 98.0, 100.0) of the ITT population.

7.1.6.13. Results for other efficacy outcomes

There were no cases of on-treatment virologic failure and one case of relapse. No baseline negative predictors were identified as only one patient relapsed. Although it was not a pre-defined secondary endpoint, the SVR12 rate was superior to historical control rates in the same patient population.

- *SVR12:* SVR12 was achieved in 93% of patients following OBV/PTV/r + DSV + RBV with a treatment difference of 5.8% (95% CI: 2.3, 9.4). SVR12 was achieved by 82% of patients following SOF + RBV with a difference of 18.0% (95% CI: 7.4, 28.6).
- *Subgroups:* No differences in subgroups were identified as only one patient did not achieve SVR12.
- *Virologic failure:* There were no cases of on-treatment virologic failure but one patient experienced relapse.
- *HCV RNA <LLOQ:* A Weeks 4, 8 and 12, HCV RNA <LLOQ was observed in 92.5%, 100% and 100% of patients, respectively. There was 99.3% concordance between SVR4 and SVR12 in the ITT population.
- *Virologic resistance:* Baseline polymorphisms at any key NS3 site were detected in 1.1%, 3.8%, 6.7% and 50% of patients with GT1, GT2, GT4 and GT5 infection, respectively. No NS3 polymorphisms were detected in patients with GT6 infection. Baseline polymorphisms at any key NS5A site were detected in 27.0%, 81.5%, 53.3% and 42.9% of patients with GT1, GT2, GT4 and GT6 infection, respectively. No NS5A polymorphisms were detected in patients with GT5 infection. Baseline NS3 + NS5A polymorphisms were detected in 4.0% and 6.7% of patients with GT2 and GT4 infection, respectively. No NS3 + NS5A polymorphisms were detected in patients with GT1, GT5, or GT6 infection. Baseline polymorphisms had no impact on the treatment outcomes as only one patient experienced virologic failure.

7.1.6.14. Evaluator commentary

This study assessed the efficacy of the GLE/PIB given for 12 weeks in treatment-naïve or treatment-experienced patients with any genotype except GT3. The patients had compensated cirrhosis, a subgroup in which SVR12 has been difficult to achieve with other treatment regimens. An outstanding SVR12 rate of 99.3% was achieved with only one case of virologic relapse.

7.1.7. Study ID M15-462 (EXPEDITION-4)

7.1.7.1. Study design, objectives, locations and dates

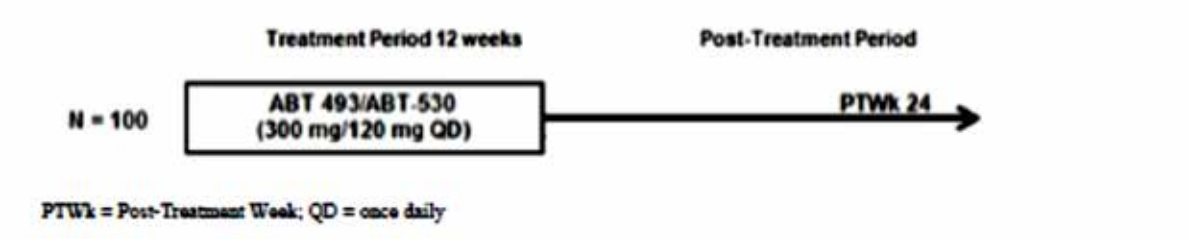
This was a Phase III, single-arm, open-label study of the antiviral activity and safety of GLE/PIB in treatment-naïve or treatment-experienced adults with chronic HCV GT1-6 infection, with or without cirrhosis and severe renal impairment including patients on dialysis. It was conducted at 30 sites Australia, Belgium, Canada, France, Greece, Italy, New Zealand and the UK. It was conducted between December 2015 and October 2016 for the primary analysis.

The primary efficacy objective was to assess SVR12 in patients with HCV GT1-6 infection and chronic renal impairment following 12 weeks treatment with GLE/PIB. The secondary

objectives were to assess the percentage of patients with on-treatment virologic failure and post-treatment relapse.

The study consisted of two periods as shown below. There was an open-label treatment period of 12 weeks, followed by a post-treatment period of 24 weeks.

Figure 12: Study M15-462 schematic.



Approximately 100 patients with CKD Stage 4 (eGFR <30-15 mL/min/1.73m^2) or Stage 5 (eGFR <15 mL/min/1.73m^2 or requiring dialysis) were planned.

The planned duration of the study was up to 36 weeks for all patients. Patient visits were scheduled for the Day 1 and Weeks 1, 2, 4, 8 and 12. At each study visit, vital signs were measured and blood samples were drawn for safety assessments, HCV RNA and HCV resistance. Study drug accountability and adherence were assessed at Weeks 4, 8 and 12.

7.1.7.2. Inclusion and exclusion criteria

The key inclusion criteria were: males or females aged ≥18 years; eGFR <30 mL/min/1.73m^2 (MDRD formula); BMI ≥18.0 kg/m^2; HCV RNA ≥1000 IU/mL at screening with positive anti-HCV antibody; documented chronic HCV GT1-6 infection; and DAA treatment-naïve, or failed previous therapies IFN or pegIFN +/- RBV, pegIFN + SOF, or SOF + RBV; documented cirrhotic or non-cirrhotic based on protocol-defined criteria; among HCV GT3, only TN without cirrhosis or with compensated cirrhosis were eligible.

The key exclusion criteria were: co-infection with more than one HCV genotype; HBV or HIV co-infection; any cause of liver disease other than HCV; history of acute renal failure in the previous 3 months; planned renal transplantation during the course of the study; prior HCV treatment failures with regimens containing PIs and/or NS5A inhibitors; drug or alcohol abuse within previous 6 months; severe sensitivity to study drug excipients; uncontrolled diabetes; clinically significant abnormalities based on medical history, physical examination, laboratory tests, or ECG; active or suspected malignancy or history of malignancy within the previous 5 years; uncontrolled cardiac, respiratory, gastrointestinal, haematological, neurologic, psychiatric or other disorder unrelated to the existing HCV condition; history of solid organ transplantation; protocol defined prohibited medications and herbal supplements.

7.1.7.3. Study treatments

GLE/PIB was given as three 100 mg/40 mg FDC tablets QD for 12 weeks. The drug was dispensed at each study visit via IRT.

7.1.7.4. Efficacy variables and outcomes

The primary efficacy variable was SVR12. The secondary variables were on-treatment virologic failure and post-treatment relapse.

7.1.7.5. Randomisation and blinding methods

The study was open-label and there was no randomisation schedule.

7.1.7.6. Analysis populations

The main analysis populations were:

- The ITT population (n=104) included all randomised patients who received at least one dose of study drug.
- The mITT-GT population excluded patients without an eligible genotype.
- The mITT-GT-VF population excluded patients who did not achieve SVR12 for reasons other than virologic failure.

7.1.7.7. Sample size

No formal hypotheses were tested. If the SVR12 rate was 95% in 100 patients, the 2-sided 95% normal approximation ratio would be 90.7% to 99.3%.

7.1.7.8. Statistical methods

SAS® was used for all analyses. The primary efficacy endpoint was the percentage of patients in the ITT population achieving SVR12. For analysis of SVR12, treatment effects were analysed with missing data imputed by carrying backward the last post-baseline HCV RNA value, as applicable, using a pre-specified backward imputation method. Missing data which could not be imputed were treated as treatment failures. The secondary endpoints were on-treatment virologic failure and post-treatment relapse. The number and percentage of patients achieving SVR12 was assessed with a 2-sided 95% CI using the normal approximation to the binomial distribution. If the SVR12 rate was 100%, the Wilson score method was used to calculate the CI. The percentages of patients with on-treatment virologic failure and post-treatment relapse were summarised with 2-sided 95% Wilson score methods.

7.1.7.9. Participant flow

A total of 104 patients were randomised and received at least one dose of study drug. A total of 100 patients completed study drug and four patients (3.8%) discontinued study drug. All withdrawals were due to AEs.

7.1.7.10. Major protocol violations/deviations

Six patients had significant protocol deviations related to inclusion/exclusion criteria and five patients had a deviation related to prohibited concomitant medications. None of the deviations were considered to have affected the study outcomes. Compliance data were available in 86 patients and all but one patient were ≥80% compliant with treatment.

7.1.7.11. Baseline data

Overall, most patients were male (76.0%) and either White (61.5%) or Black (24.0%). Most patients were aged <65 years (73.1%) and 93.3% were aged <75 years. Most patients had BMI <30 kg/m^2 (76.0%). Genotypes 1, 2, 3, 4, 5 and 6 were present in 51.9%, 16.3%, 10.6%, 19.2%, 1.0% and 1.0% of patients, respectively. Overall, 57.7% of patients were treatment-naïve and 42.3% were treatment-experienced (nearly all IFN-based). The IL28B CC genotype was present in 23.1% of patients. Baseline HCV RNA levels were <6,000,000 IU/mL in 92.3% of patients and <10,000,000 IU/mL in 96.2% of patients. Cirrhosis was present in 19.2% of patients and 80.8% were non-cirrhotic. Baseline eGFR was <15 mL/min/1.73m^2 in 82.7% of patients and ≥15 mL/min/1.73m^2 in 17.3% of patients. Most patients required dialysis (81.7%). Of patients not requiring dialysis, 12.5% were Stage 4 and 5.8% were Stage 5. All patients requiring dialysis were receiving haemodialysis.

7.1.7.12. Results for the primary efficacy outcome

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

7.1.7.13. Results for other efficacy outcomes

- *Subgroups:* No differences in subgroups were identified as only two patients did not achieve SVR12 (due to premature discontinuation of study drug and missing SVR12 data, respectively).

- *Virologic failure:* There were no cases of on-treatment virologic failure or relapse.
- *HCV RNA <LLOQ:* A Weeks 4, 8 and 12, HCV RNA <LLOQ was observed in 95.1%, 100% and 100% of patients, respectively. There was 99.0% concordance between SVR4 and SVR12 in the ITT population.
- *Virologic resistance:* Baseline polymorphisms at any key NS3 site were detected in 2.2% of the overall population. Baseline polymorphisms at any key NS5A site were detected in 28.3% of patients. No baseline NS3 + NS5A polymorphisms were detected. No NS3 + NS5A polymorphisms were detected in patients with GT5 infection. Baseline polymorphisms had no impact on the treatment outcomes as no patients experienced virologic failure.

7.1.7.14. Evaluator commentary

This open-label study assessed the efficacy of the GLE/PIB FDC given for 12 weeks in treatment-naïve or treatment-experienced patients with any HCV genotype (GT3 only TN without cirrhosis or with compensated cirrhosis) and with chronic renal impairment. Patient numbers were necessarily limited, particularly patients with GT5 or GT6 infection. Nonetheless, SVR12 was achieved by 98.1% of patients with no cases of virologic failure or relapse. In patients with renal impairment without HCV infection (study M13-600), exposure to GLE or PIB increased by up to 56% in patients with end-stage renal disease who were not receiving dialysis. In patients receiving haemodialysis, GLE and PIB exposures before and after dialysis differed by ≤18%. The efficacy and PK studies support the recommendation for no dosage adjustment in patients with any degree of renal impairment, including those on renal dialysis.

7.1.8. Study ID M14-867 (SURVEYOR-1)

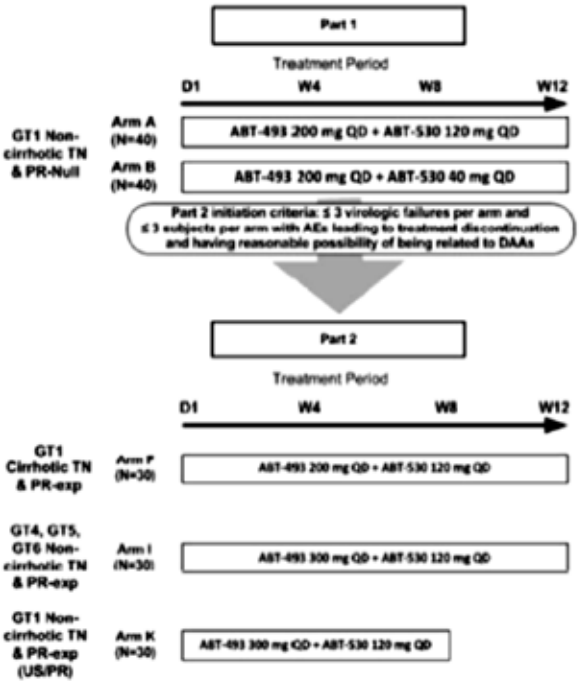
7.1.8.1. Study design, objectives, locations and dates

This was a Phase II, open-label, two part, multicentre study of co-administered GLE + PIB with or without RBV in treatment-naïve or treatment-experienced adult patients with HCV infection with compensated cirrhosis or without cirrhosis. It was conducted at 28 sites in Australia, Canada, New Zealand and the US between August 2014 and February 2016. The primary efficacy objective was to assess SVR12 in patients with HCV GT1, GT4-6 infection with compensated cirrhosis (GT1 only) or without cirrhosis (GT1, or GT4-6) following 12 weeks treatment with GLE + PIB given at various doses with or without RBV. The secondary objectives were to assess the percentage of patients with on-treatment virologic failure and post-treatment relapse.

Note: RBV was initially planned but not administered in any study arms.

The study consisted of two independent parts enrolled sequentially (below). In Part 1, patients received GLE + PIB for 12 weeks; in Part 2, patients received GLE + PIB for 8 or 12 weeks.

Figure 13: Study M14-867 schematic.



In Part 1, approximately 80 GT1-infected treatment-naïve and PR null responders without cirrhosis were enrolled into one of two treatment arms:

- Arm A: GLE 200 mg QD + PIB 120 mg QD for 12 weeks.
- Arm B: GLE 200 mg QD + PIB 40 mg for 12 weeks.

Part 2 was initiated after review of the data from Part 1. In Part 2, there were eight arms but only three arms were enrolled by sponsor decision:

GT1-infected treatment-naïve or PR-experienced patients without cirrhosis were to be enrolled into one of three treatment arms, with 30 patients planned in each arm.

- Arm C: GLE 200 mg QD + PIB 120 mg QD for 8 weeks (never opened).
- Arm D: GLE 200 mg QD + PIB 40 mg QD for 8 weeks (never opened).
- Arm K: GLE 300 mg QD + PIB 120 mg QD for 8 weeks (enrolled).

GT1-infected treatment-naïve or PR-experienced patients with compensated cirrhosis were to be enrolled into one of four treatment arms, with 30 patients planned in each arm.

- Arm E: GLE 200 mg QD + PIB 120 mg QD + RBV 800 mg QD for 12 weeks (never opened).
- Arm F: GLE 200 mg QD + PIB 120 mg QD for 12 weeks (enrolled).
- Arm G: GLE 200 mg QD + PIB 40 mg QD + RBV 800 mg QD for 12 weeks (never opened).
- Arm H: GLE 200 mg QD + PIB 40 mg QD for 12 weeks (never opened)

Treatment-naïve or PR-experienced patients with GT4, GT5, or GT6 infection without cirrhosis were to be enrolled into one of two treatment arms:

- Arm I: GLE 300 mg QD + PIB 120 mg QD for 12 weeks (enrolled).
- Arm J: GLE 200 mg QD + PIB 40 mg QD for 12 weeks (never opened).

7.1.8.2. Inclusion and exclusion criteria

The key inclusion criteria were: males or females aged ≥18 years; BMI ≥18.0 to <38 kg/m^2; HCV RNA ≥1000 IU/mL at screening with positive anti-HCV antibody; documented chronic HCV GT1, or GT4-6 infection; and treatment-naïve or PR-null responder (Part 1)/PR experienced (Part 2) based on protocol-defined criteria; documented cirrhotic or non-cirrhotic based on protocol-defined criteria.

The key exclusion criteria were: co-infection with more than one HCV genotype; HBV or HIV co-infection; any cause of liver disease other than HCV; prior use of an HCV DAA; drug or alcohol abuse within previous 6 months; severe sensitivity to study drug excipients; uncontrolled diabetes; clinically significant abnormalities based on medical history, physical examination, laboratory tests, or ECG; active or suspected malignancy or history of malignancy within the previous 5 years; uncontrolled cardiac, respiratory, gastrointestinal, haematological, neurologic, psychiatric or other disorder unrelated to the existing HCV condition; history of solid organ transplantation; protocol defined prohibited medications and herbal supplements.

7.1.8.3. Study treatments

GLE was given as 100 mg tablets and PIB was given as 40 mg tablets taken QD with or without food. The drug was dispensed at each study visit via IRT.

7.1.8.4. Efficacy variables and outcomes

The primary efficacy variable was SVR12. The secondary variables were on-treatment virologic failure and post-treatment relapse.

7.1.8.5. Randomisation and blinding methods

The study was open-label. Randomisation was not used to assign patients to treatment arms.

7.1.8.6. Analysis populations

The ITT population (n=174) included all randomised patients who received at least one dose of study drug.

7.1.8.7. Sample size

No formal hypotheses were tested. If the SVR12 rate was 95%, 40 patients in each arm of Part1 would result in a 2-sided 95% CI of 84% to 99% using the Wilson score method. If the SVR12 rates were approximately 93% or 97%, 30 patients in each arm of Part1 would result in a 2-sided 95% CI of 79% to 98% or 83% to 99%, respectively, using the Wilson score method.

7.1.8.8. Statistical methods

SAS® was used for all analyses. All tests and CIs were 2-sided with alpha=0.05. The primary efficacy endpoint was the percentage of patients in the ITT population achieving SVR12. For analysis of SVR12, treatment effects were analysed with missing data imputed by carrying backward the last post-baseline HCV RNA value, as applicable, using a pre-specified backward imputation method. Missing data which could not be imputed were treated as treatment failures. The secondary endpoints were on-treatment virologic failure and post-treatment relapse. The number and percentage of patients achieving SVR12 was assessed with a 2-sided 95% CI using the Wilson score interval. The percentages of patients with on-treatment virologic failure and post-treatment relapse were summarised with 2-sided 95% CIs using the Wilson score method.

7.1.8.9. Participant flow

A total of 174 patients were randomised and received at least one dose of study drug in Parts 1 and 2. A total of 172 patients completed study drug and four patients discontinued study drug.

7.1.8.10. Major protocol violations/deviations

Eight patients had significant protocol deviations related to inclusion/exclusion criteria. One patient had an incomplete cirrhosis work-up and four patients had deviations related to prohibited concomitant medications. None of the deviations were considered to have affected the study outcomes. Compliance data were available in 154 patients and all but three patients were ≥91% compliant with treatment. One patient was withdrawn for non-compliance but achieved SVR12. The remaining two patients completed 12 weeks treatment and achieved SVR12.

7.1.8.11. Baseline data

In Arms A and B (Part 1), respectively, 59.5% and 46.2% of patients were male and 85.7% and 89.7% were White. The mean ages in each arm were 52.4 and 52.5 years and most patients were aged <65 years (95.2% and 87.2%). Most patients had BMI <30 kg/m^2 (69.0% and 69.2%). In Arms K, F and I (Part 2), 55.9%, 74.1% and 50.0% of patients were male and 97.1%, 88.9% and 56.3% were White. The mean ages in each arm were 53.5, 58.9 and 55.0 years and most patients were aged <65 years (82.4%, 85.2% and 81.3%). Most patients had BMI <30 kg/m^2 (70.6%, 66.7% and 84.4%).

In Arms A and B (Part 1), respectively, nearly all patients had GT1a (81.0% and 76.9%) or GT1b (14.3% and 23.1%) infection and the IL28B CC subtype was present in 21.4% and 17.9% of patients, respectively. HCV RNA levels were <6,000,000 IU/mL in 54.8% and 48.7% of patients. Most patients in the non-cirrhotic groups had fibrosis stage F0 - F1 (54.8% and 69.2%). Most patients were treatment-naïve (64.3% and 64.1%).

In Arms K and F (Part 2), respectively, all patients were GT1a (70.6% and 74.1%) or GT1b (29.4% and 25.9%). In Arm I, most patients had GT4 (62.5%) or GT6 infection (34.4%) and only one patient (3.1%) had GT5 infection. In Arms K, F and I (Part 2), the IL28B CC subtype was present in 32.4%, 14.8% and 40.6% of patients, respectively. Most patients were treatment-naïve (85.3%, 77.8% and 84.4%) and most patients had HCV RNA levels <6,000,000 IU/mL (61.8%, 55.6%, 62.5%). In Arms K and I (non-cirrhotic groups), most patients had fibrosis stage F0 - F1 (70.6% and 75.0%). In Arm F (compensated cirrhotic patients) all patients had stage F4 cirrhosis.

7.1.8.12. Results for the primary efficacy outcome

In the ITT population of Part 1 (GT1, no cirrhosis), SVR12 was achieved by 100% (95% CI: 91.2, 100) of patients in Arm A (GLE 200 mg + PIB 120 mg for 12 weeks) and 97.4% (95% CI: 86.8, 99.5) of patients in Arm B (GLE 200 mg + PIB 40 mg).

In the ITT population of Part 2, SVR12 was achieved by 97.1% (95% CI: 85.1, 99.5) of patients in Arm K (GT1, no cirrhosis) given GLE 300 mg + PIB 120 mg; 96.3% (81.7, 99.3) of patients in Arm F (GT1, compensated cirrhosis) given GLE 200 mg + PIB 120 mg; and 100% (95% CI: 89.8, 100) of patients in Arms I (GT4-6, no cirrhosis) given GLE 300 mg + PIB 120 mg.

7.1.8.13. Results for other efficacy outcomes

In Part 1, there were no cases of on-treatment virologic failure, but there was one case of relapse in Arm B (in a patient receiving GLE 200 mg + PIB 40 mg). In Part 2, there were no cases of on-treatment virologic failure, but there was one case of relapse in Arm F (in a patient receiving GLE 200 mg + PIB 120 mg).

- *Subgroups:* No differences in subgroups were identified as only one patient did not achieve SVR12.
- *Virologic failure:* In Part1, there were no cases of on-treatment virologic failure but there was one case of relapse in Arm B (in a patient receiving GLE 200 mg + PIB 40 mg QD). In Part 2, there were no cases of on-treatment virologic failure but there was one case of relapse in Arm F (in a patient receiving GLE 200 mg + PIB 120 mg).

- *HCV RNA <LLOQ:* HCV RNA <LLOQ at Week 4 was observed in 97.5% to 100% of the treatment arms and in 100% of patients at Weeks 8 and 12.
- *Virologic resistance:* Baseline polymorphisms had no impact on the treatment outcomes as only two patients experienced virologic failure (both on lower doses of GLE or PIB).

7.1.8.14. Evaluator commentary

This Phase II study assessed the efficacy of various doses of GLE (200 mg or 300 mg QD) + PIB (40 mg or 120 mg) in a mixed population of treatment-naïve or treatment-experienced patients with GT1 or GT4-6 infection with or with cirrhosis. Outstanding SVR12 rates >96% were achieved in cirrhotic or non-cirrhotic patients with any HCV genotype infection. There were no cases of on-treatment virologic failure. There were two cases of relapse but both occurred in patients receiving lower than recommended doses of GLE or PIB.

7.1.9. Study ID M15-410

7.1.9.1. Study design, objectives, locations and dates

This was a Phase II, randomised, open-label, multicentre study of co-administered GLE + PIB with or without RBV, or GLE/PIB in adult patients with HCV infection who had failed prior DAA-containing therapy. It was conducted at 31 sites in Australia, France, Spain, the UK and the US between April 2015 and October 2016 for the primary analysis. Part 1 was an exploratory study in which the efficacy of GLE + PBE with or without RBV was assessed in approximately 50 patients randomised 1:1:1 to one of three treatment arms:

- Arm A: GLE 200 mg QD + PIB 80 mg QD for 12 weeks.
- Arm B: GLE 300 mg QD + PIB 120 mg QD + RBV 800 mg QD for 12 weeks.
- Arm C: GLE 300 mg + PIB 120 mg QD for 12 weeks.

Note: Enrolment in Arm A was stopped when the sponsor ceased development of the lower GLE + PIB doses.

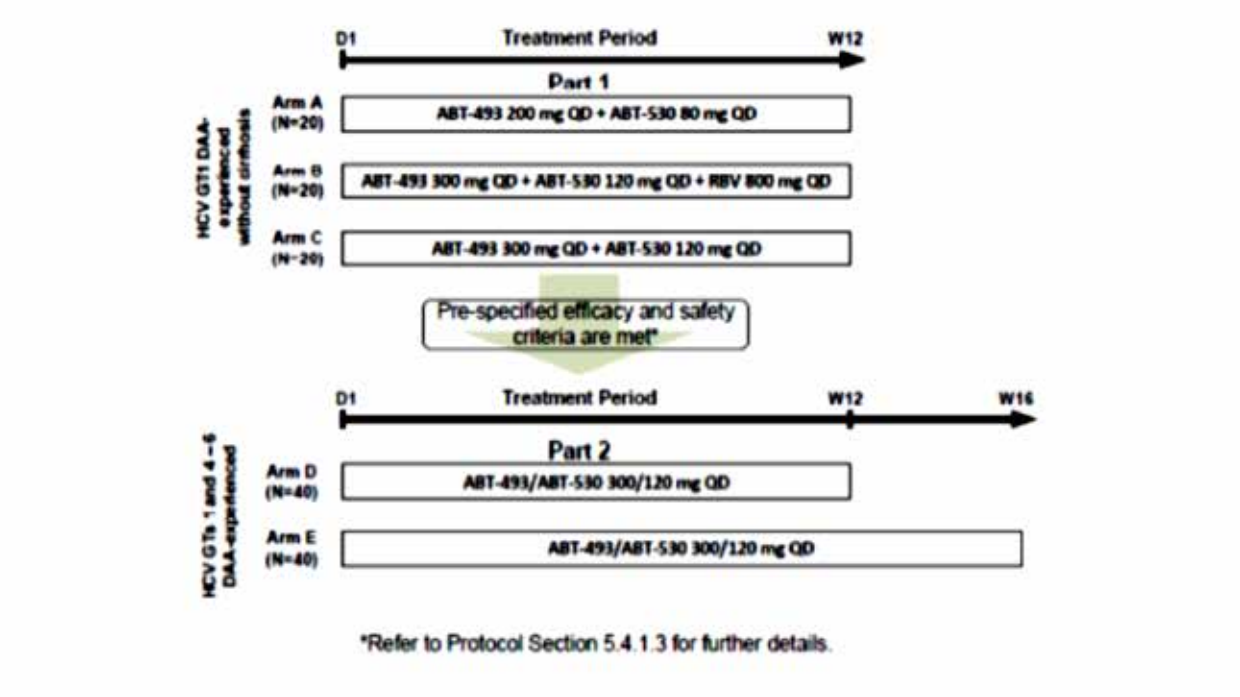
Part 2 of the study was conducted after review of the Part 1 data. Approximately 80 DAA treatment-experienced patients with GT1 or GT4-6 infection with compensated liver disease with or without cirrhosis were randomised 1:1 to one of two treatment arms:

- Arm D: GLE/PIB 300 mg/120 mg QD for 12 weeks.
- Arm E: GLE/PIB 300 mg/120 mg QD for 16 weeks.

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

The primary efficacy endpoint was the percentage of patients who achieved SVR12. The numbers and percentage of patients achieving SVR12 in each arm were summarised with 95% CIs using Wilson score intervals. The main secondary endpoints were SVR4, on-treatment virologic failure and post-treatment relapse. The study schematic is shown below.

Figure 14: Study M15-410 schematic.



7.1.9.2. Inclusion and exclusion criteria

The key inclusion criteria were: males or females aged between 18 and 70 years; BMI ≥18.0 to <38 kg/m^2; HCV RNA ≥1000 IU/mL at screening with positive anti-HCV antibody; documented chronic HCV GT1 infection (in Part 1), or GT4-6 infection (in Part 2); a history of previous DAA-containing treatment, or on-treatment failure of the previous DAA-containing treatment, or post-treatment relapse; documented non-cirrhotic (Parts 1 and 2) or cirrhotic based on protocol-defined criteria; cirrhotic patients in Part 2 required to have Child-Pugh score ≤6 at screening with no evidence of hepatic decompensation; no evidence of HCC.

The key exclusion criteria were: co-infection with more than one HCV genotype; HBV or HIV co-infection; any cause of liver disease other than HCV; prior use of an HCV DAA; drug or alcohol abuse within previous 6 months; severe sensitivity to study drug excipients; uncontrolled diabetes; clinically significant abnormalities based on medical history, physical examination, laboratory tests, or ECG; active or suspected malignancy or history of malignancy within the previous 5 years; uncontrolled cardiac, respiratory, gastrointestinal, haematological, neurologic, psychiatric or other disorder unrelated to the existing HCV condition; history of solid organ transplantation; protocol defined prohibited medications and herbal supplements.

7.1.9.3. Study treatments

The study treatments were GLE + PIB +/- RBV tablets in Part 1 and GLE/PIB in Part 2. GLE was given as three 100 mg tablets QD with or without food, PIB was given as three 40 mg tablets taken QD with or without food and RBV was given as four 200 mg tablets given QD with food. GLE/PIB was given as three tablets daily with or without food. The drug was dispensed at each study visit via IRT.

7.1.9.4. Efficacy variables and outcomes

The primary efficacy variable was SVR12. The secondary variables were on-treatment virologic failure and post-treatment relapse.

7.1.9.5. Randomisation and blinding methods

The study was open-label. Randomisation was conducted via IRT. In Part 1, patients were randomised 1:1:1 to Arms A, B, or C. When Arm A was stopped, the remaining patients were randomised 1:1 to Arms B or C. In Part 1, randomisation was stratified by GT1 (1b or non-1b) and previous DAA regimen class (NS5A-experienced, PI-experienced/NS5A-naive, Other). In Part 2, patients were randomised 1:1 to Arm D or Arm E. Randomisation was stratified by HCV genotype (GT1 or GT4-6) and previous DAA regimen class (NS5A-experienced, PI-experienced/NS5A-naïve, Other).

7.1.9.6. Analysis populations

The ITT population (n=50 in Part 1 and n=91 in Part 2) included all randomised patients who received at least one dose of study drug. The mITT-GT-VF population (n=48 in Part 1 and n=91 in Part 2) excluded patients with an ineligible HCV genotype and patients who did not achieve SVR12 for reasons other than virologic failure. In Part 2, an additional PP set (n=87) was analysed to compare Arms D and E.

7.1.9.7. Sample size

No formal hypotheses were tested. If the SVR12 rate was 95%, 20 patients in each arm of Part1 would result in a 2-sided 95% CI of 76% to 99% using the Wilson score method. If the SVR12 rates were approximately 95% in Part 2, 40 patients in each arm would result in a 2-sided 95% CI of 83% to 99% using the Wilson score method.

7.1.9.8. Statistical methods

SAS was used for all analyses. All tests and CIs were 2-sided with alpha=0.05. The primary analysis was performed after all patients completed the post-treatment Week 12 visit or prematurely discontinued the study. The primary efficacy endpoint was the percentage of patients in the ITT population achieving SVR12. The difference in SVR12 rates between treatment arms was analysed using the stratum-adjusted Mantel-Haenszel proportion with a continuity correction for variance. For analysis of SVR12, treatment effects were analysed with missing data imputed by carrying backward the last post-baseline HCV RNA value, as applicable, using a pre-specified backward imputation method. Missing data which could not be imputed were treated as treatment failures. The secondary endpoints were on-treatment virologic failure and post-treatment relapse. The number and percentage of patients achieving SVR12 was assessed with a 2-sided 95% CI using the Wilson score interval. The percentages of patients with on-treatment virologic failure and post-treatment relapse were summarised with 2-sided 95% CIs using the Wilson score method.

7.1.9.9. Participant flow

In Part 1, 50 patients were randomised and treated and 48 completed study drug. Study drug discontinuations occurred in one patient in Arm C due to virologic failure and in one patient in Arm B due to loss to follow-up (the patient completed the SVR24 visit). One patient discontinued in Arm C due to virologic failure and one patient was lost to follow-up. In Part 2, 91 patients were randomised and treated and 87 completed study drug. Four patients, all in Arm E, experienced virologic failure.[5]

7.1.9.10. Major protocol violations/deviations

In Part 1, two patients had significant protocol deviations related to exclusion criteria and one patient had a deviation related to prohibited concomitant medications. None of the deviations were considered to have affected the study outcomes. In Part 2, four patients had protocol deviations related to inclusion/exclusion criteria and one patient had a deviation related to

[5] Arm D also had 5 virologic failures.

prohibited concomitant medications. None of the deviations were considered to have affected the study outcomes.

In Part 1, compliance data were available in 45 patients and all but one patient was >80% compliant with GLE and PIB treatment. A total of 90.5% of patients were compliant with RBV treatment. In Part 2, compliance data were available for 84 patients and all were 100% compliant with GLE/PIB treatment.

7.1.9.11. Baseline data

Overall, most Part 1 patients were male (82.0%) and White (66.0%) or Black (34.0%), with a mean age of 56.5 years. Most patients had a BMI <30 kg/m^2 (64.0%). Overall, most Part 2 patients were male (70.3%) and White (75.8%), with a mean age of 55.6 years. Most patients had a BMI <30 kg/m^2 (61.5%).

Most Part 1 patients had GT1a infection (Arm A 66.7%, Arm B 90.9%, Arm C 81.8%) and the remainder had GT1b infection. Overall, the IL28B CC subtype was present in 13.6% to 33.3% of patients, respectively. HCV RNA levels were <6,000,000 IU/mL in 50.0% to 100% of patients. Most patients in the non-cirrhotic groups had fibrosis stage F0 - F1 (50.0% to 77.3%). In each of Arms B and C, 50% of patients were NS5A experienced, 50% were NS5A naïve /PI experienced and 18.2% of patients were NS5A experienced/PI naïve.

Overall, most Part 2 patients had GT1a infection (73.6%) or GT1b infection (20.9%). The IL28B CC subtype was present in 12.2% of patients and HCV RNA levels were <6,000,000 IU/mL in 85.7% of patients. The overall fibrosis stages were F0 - F1 53.8%, F2 4.4%, F3 13.2% and F4 28.6%. Overall, 29.7% of patients were PI experienced/NS5A naïve, 70.3% of patients were NS5A experienced, 33.0% were NS5A experienced/PI experienced and 37.4% of patients were NS5A experienced/PI naïve.

7.1.9.12. Results for the primary efficacy outcome

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

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

7.1.9.13. Results for other efficacy outcomes

- *Subgroups:* No meaningful differences in subgroups were identified as few patients did not achieve SVR12.
- *Virologic failure:* In Part 1, there was one case (4.5%) of virologic failure in each of Arms B and C. In Part 2, in Arm D (12 weeks treatment) and Arm E (16 weeks treatment) on-treatment virologic failure occurred in one (2.3%) and four (8.5%) patients, respectively. The relapse rate was lower in Arm E (0.0%) compared with the Arm D (9.3%). In both arms, NS5A/PI experienced patients had a higher rate of virologic failure (20.0%) compared with NS5A-experienced/PI-naïve patients (8.8%) and PI-experienced/NS5A-naïve patients (0%).
- *HCV RNA <LLOQ:* In Part 1, rapid suppression of HCV RNA occurred in Arm A. HCV RNA <LLOQ at Weeks 4, 8 and 12 was observed in 83.3%, 100% and 100% of patients, respectively. In Arm B, HCV RNA <LLOQ at Weeks 4, 8 and 12 was observed in 100%, 100% and 100% of patients, respectively. In Arm C, HCV RNA <LLOQ at Weeks 4, 8 and 12 was observed in 95.5%, 95.5% and 100% of patients, respectively. In Part 1, concordance between SVR4 and SVR12 was demonstrated by 100.0%, 100% and 90.9% of patients in Arms A, B and C, respectively.

In Part 2, in Arm D, HCV RNA <LLOQ at Weeks 4, 8 and 12 was observed in 90.9%, 100% and 97.7% of patients, respectively. In Arm E, HCV RNA <LLOQ at Weeks 4, 8 and 12 was observed

in 87.0%, 95.7% and 95.6% of patients, respectively. In Part 2, concordance between SVR4 and SVR12 was 97.7% in Arm D and 100% in Arm E.

- *Virologic resistance:* In Part 1, in Arm A, 83.2% of patients had baseline polymorphisms (at 15% detection threshold) at any key NS5A site. No patients had NS3 or NS3 + NS5A polymorphisms. In Arm B, there was one patient with NS3 only polymorphisms at baseline, and SVR12 was achieved. In patients with NS5A only polymorphisms, 88.9% of patients achieved SVR12. In patients with NS3 + NS5A polymorphisms at baseline, SVR12 was achieved by 100% of patients. In Arm C, there were two patients with NS3 only polymorphisms at baseline and SVR12 was achieved. In patients with NS5A only polymorphisms, 100% of patients achieved SVR12. In the one patient with NS3 + NS5A polymorphisms at baseline, SVR12 was not achieved.. In Part 1, baseline polymorphisms had no meaningful impact on the treatment outcomes as the number of treatment failures was limited.

In Part 2, in patients in both arms who were NS5A-experienced, 80.6% of patients had NS5A baseline polymorphisms. In PI-experienced/NS5A-naïve patients, 23.1% of patients had NS3 baseline polymorphisms and 42.3% of patients had any key polymorphism at baseline. In NS5A and PI-experienced patients, 80% had any type of polymorphism. In general, virologic failure rates in both treatment arms were higher in patients with multiple baseline polymorphisms. However, there did not appear to be pattern which predicted virologic failure.

7.1.9.14. Evaluator commentary

This study was exploratory in Part 1 and confirmatory in Part 2. It may be considered pivotal because it directly assessed SVR12 rates in patients with GT1 or GT4-6 infection who had previously failed therapy with approved DAA treatment regimens. The management of treatment failures with DAA regimens will become increasingly relevant as the use of pegIFN and RBV declines. An arm of patients treated with GLE 200 mg + PIB 80 mg was stopped when the sponsor ceased development of the lower dose regimen. In Part 1 of the study, there was one case of relapse in patients receiving GLE 300 mg + PIB 120 mg + RBV and one case of on-treatment failure in patients receiving the same combination without RBV. In light of this and other results, the sponsor decided to pursue the 2-DAA combination without RBV. In Part 2, treatment for 16 weeks was compared with treatment for 12 weeks. SVR12 rates were comparable in the two groups (91.5% and 88.6%, respectively). There were more cases of on-treatment virologic failure in patients given treatment for 16 weeks (8.5% vs 2.3%), but relapse was experienced more frequently in patients in patients treated for 12 weeks (0% vs 9.3%). As might be predicted, NS5A/PI treatment-experienced patients had a significantly higher rate of virologic failure than those who had received NS5A-based or PI-based monotherapy. In general, multiple polymorphisms at baseline are associated with virologic failure but no predictive patterns were identified.

7.2. Other efficacy studies

7.2.1. Study ID M14-213

7.2.1.1. Methodology

This was a Phase IIa, open-label, pilot study of the antiviral activity and safety of paritaprevir (ABT 450, a NS3/NS4A protease inhibitor) with ritonavir (ABT-450/r) dosed in combination with ABT-530 (PIB), with and without RBV in treatment-naïve patients with chronic HCV GT3 infection. It was conducted at three sites in the US, starting in April 2014 and completing in March 2015. The primary efficacy objective was to measure the percentage of patients achieving SVR12 following treatment with ABT-450/r dosed in combination with PIB, given for 12 weeks, with or without RBV. The secondary efficacy objective was to assess the development and persistence of viral resistance. Approximately 20 patients (10 patients in each arm) were

planned. Standard inclusion/exclusion criteria were applied as documented in previous studies. Patients in Arm 1 received ABT-450/r 150 mg/100 mg QD + PIB 120 mg QD + RBV at a weight-based dosage for 12 weeks. HCV RNA levels were assessed at the study visits and during the 24 week post-treatment follow-up period. Patients in Arm 2 were to receive the same DAA treatment regime without the addition of RBV. However, the sponsor elected not to conduct Arm 2 after the results of Arm 1 were reviewed.

7.2.1.2. Results

In Arm 1, 10 patients were enrolled and 9 patients completed the study. The majority of patients were male (80%) and all were White with a mean age of 52.5 years. Mean BMI was 27.2 kg/m^2. All patients had GT3 infection with mean HCV RNA 5.84 log_{10} IU/mL at baseline. SVR12 was achieved in 90% (95% CI: 55.5, 99.7) of patients, with one patient experiencing virologic breakthrough at Week 6.

7.2.1.3. Evaluator commentary: other efficacy studies

M14-213 is the only efficacy study without significant regulatory impact. It was a small pilot study of a novel NS5A inhibitor tested in combination with PI. The results were suboptimal despite the addition of RBV to the 2-DAA combination. The sponsor ceased development in favour of alternative 2-DAA combinations without the need for RBV. The study is not considered further.

7.3. Analyses performed across trials: pooled and meta-analyses

A pooled analysis of all randomised patients in the Phase II and III studies was performed. A total of 2369 randomised patients received at least one dose of study medication and 2332 patients completed study drug treatment. A total of 560 patients completed the studies for the primary analysis, 37 discontinued and 1779 are ongoing. Study drug discontinuation occurred in 1.6% of patients, due mainly to AEs (0.5%), virologic failure (0.3%) and non-compliance with study drug.

Most patients were male (55.6%) with a mean age of 52.5 years. Most patients were White (80.2%), Asian (11.5%) or Black (6.3%). The mean BMI was 26.7 kg/m^2. The patients were treatment-naïve (69.2%), or treatment-experienced (30.8%). Most treatment-experienced patients had previously received PR based therapy (23.0%), 3.0% had received SOF + RBV and 4.8% of patients had received PI and/or NS5A inhibitors. Most patients in the treated population had HCV GT1 (n=998), GT2 (n=466), or GT3 (n=643) infection. GT4, GT5, or GT6 infections were present in 182, 32 and 48 patients, respectively. The IL28B CC genotype was present in 32.4% of patients. Most patients were non-cirrhotic (87.0%) without significant renal impairment (95.6%). Baseline HCV RNA levels <6 million IU/mL were reported in 78.2% of patients and <10 million IU/mL in 88.9% of patients. The majority of patients had no polymorphisms at baseline (79.0%). The presence of NS3 only, NS5A only, or both NS3 and NS5A polymorphisms were reported in 1.6%, 18.6% and 0.8% of patients respectively.

In the ITT population of the Phase II and III analysis set, SVR12 was achieved in 86.4% to 100% of patients in all treatment arms given GLE 300 mg + PIB 120 mg in combination, or as the FDC for 8, 12, or 16 weeks. In studies M13-590, M15-464 and M14-868, the non-inferiority of GLE/PIB given for 12 weeks compared to historical controls (SOF regimens excepted) was demonstrated. In study M13-594, the non-inferiority of GLE/PIB for 12 weeks compared with SOF + DCV for 12 weeks was demonstrated. GLE/PIB for 8 weeks was shown to be non-inferior to 12 weeks treatment in three treatment arms in studies M13-590, M13-594 and M14-464.

In the pooled population, SVR12 rates were >95% in all genotypic infections regardless of treatment experience and treatment duration. SVR12 rates were >95% in all genotypes and >96% in patients of any genotype with Stage 4 or 5 chronic renal disease. In the pooled population, SVR12 rates were >97% in treatment-naïve or treatment experienced (PRS)

patients with GT1, 2, 4, 5, or 6 infections. SVR12 rates were marginally lower in patients with GT3 infection compared with other genotypes infections. SVR12 was achieved by 97.4% of the pooled population, 96.6% of patients with cirrhosis and 100% of patients with renal impairment. SVR12 rates were ≥89.0% in GT1 and GT4 patients previously treated with a PI and/or an NS5A inhibitor. In the Phase II and III Analysis Set at the primary analysis cut-off point, SVR24 data were available in 586 patients. In this limited population, SVR12 predicted SVR24 in 99.8% of the overall population.

In the ITT pooled population, on-treatment virologic failure was experienced in 0.5% of patients across all genotypes and previous treatment experience. Relapse was experienced by 0.9% of patients, study drug was discontinued prematurely in 0.5% of patients and missing SVR12 data were reported in 0.7% of patients. Post-treatment relapse was experienced by 0.5%, 0.4% and 2.4% of patients with GT1, GT2 and GT3 infections. No patients with GT4-6 infection relapsed. Non-cirrhotic patients with GT3 infection and previous PRS experience treated for 12 weeks had the highest relapse rate (5.8%) and a 16 week treatment course is recommended in this patient group.

The pooled analysis demonstrated high SVR12 rates with GLE/PIB regardless of baseline demographics or disease characteristics. These included race, ethnicity, HCV genotype, HCV treatment history, IL28B genotype, baseline fibrosis, BMI, laboratory variables, baseline renal function, cirrhosis and HIV-1 co-infection. Small but statistically significant differences in SVR12 rates were noted in some subgroups. These included gender (females 98.7%, males 96.4%), baseline HCV RNA level (<1 million IU/mL 98.5%, ≥1 million IU/mL 96.6%) and history of cardiovascular disease (with disease 98.6%, without disease 96.8%). There were significant differences in SVR12 rates between patients with baseline polymorphisms in NS3 only (100.0%), NS5A only (96.0%), both NS3 and NS5A (61.1%) and none (98.0%). SVR12 rates were significantly higher in compliant patients (97.8%) than in non-compliant patients (94.0%). None of the statistically significant differences in sub-groups are considered clinically significant, or warrant changes to GLE/PIB dose or treatment duration.

7.4. Evaluator's conclusions on clinical efficacy

In the registration studies, the efficacy of GLE/PIB was assessed in treatment-naïve and treatment-experienced patients with any genotype infection, at the same fixed dose but for different durations of treatment (8, 12 or 16 weeks). Dose selection was based on Phase II studies which supported the GLE/PIB dose of 300 mg/120 mg used without RBV. The study designs were in line with the relevant EMA and FDA guidelines for the use of DAAs in patients with chronic HCV and scientific advice was provided by both bodies. The primary efficacy endpoint for all studies was SVR12 with on-treatment virologic failure and post-treatment relapse as the key secondary endpoints. Two randomised, controlled studies compared the efficacy of GLE/PIB against placebo and against SOF + DCV, the most effective active control for HCV GT3 infection at the time the studies were planned. In addition, a series of single-arm studies assessed efficacy in subpopulations including patients with compensated cirrhosis, severe renal impairment, patients with genotype 1-6 infection, patients with HCV/HIV-1 co-infection and patients who failed prior therapy with DAA-containing regimens. Inclusion and exclusion criteria were broadly similar across studies, with protocol-defined criteria for the presence or absence of cirrhosis. All statistical analyses were based on the ITT populations, including all patients who received at least one dose of study drug. Meta-analyses and pooled data analyses were conducted with sensitivity analyses as indicated. The baseline demographics were representative of the HCV population in Australia with treatment-naïve and treatment-experienced male and female patients. Most patients were White (80.2%) or Asian (11.5%), with small numbers of other racial groups. Only a limited number of patients (2.0%) were aged ≥75 years.

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

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

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

- In patients with GT1 infection (M13-590), treatment given for 12 weeks was non-inferior to historical control regimens given for 12 weeks with an SVR12 rate of 99.7%. Treatment given for 8 weeks was also non-inferior to 12 weeks therapy with an SVR12 rate of 99.1%.
- In patients with GT2 infection (M15-464), treatment given for 12 weeks was non-inferior to SOF + RBV for 12 weeks with an SVR12 rate of 99.5%.
- In patients with GT3 infection (M13-594), treatment given for 12 weeks was non-inferior to SOF + DCV given for 12 weeks with an SVR12 rate of 95.3%. Non-inferiority of GLE/PIB 12 weeks as compared to SOF+DCV 12 weeks was achieved in the ITT and PP population. Treatment given for 8 weeks was also non-inferior to 12 weeks therapy with an SVR12 rate of 94.9%.
- In patients with GT4-GT6 infection (M13-583), the SVR12 rate was 99.2% with 12 weeks treatment.
- In patients with GT1, GT2, GT4-GT6 infection and compensated cirrhosis (M14-172), the overall SVR12 rate was 99.3% with 12 weeks treatment.
- In patients with GT1-GT6 infection (M15-462), the overall SVR12 rate was 98.1% with 12 weeks treatment.
- In patients with GT1, GT4-GT6 infection (M14-867), the SVR12 rates were 97.1% in GT1-infected patients treated for 8 weeks and 100% in GT4-GT6 patients treated for 12 weeks.
- In patients with GT2-GT3 infection (M14-868, Parts 1 and 2), non-cirrhotic patients with GT2 infection achieved an SVR12 rate of 96.0% and non-cirrhotic patients with GT3 infection achieved an SVR12 rate of 93.3% with 12 weeks treatment. In non-cirrhotic patients with GT2 infection, SVR12 was achieved in 98.1% of patients treated for 8 weeks. In non-cirrhotic patients with GT3 infection, SVR12 was achieved in 96.6% of treatment naïve patients treated for 8 weeks. In cirrhotic patients with GT3 infection, SVR12 was achieved in 100% of treatment naïve patients treated for 12 weeks and in 75.0% of treatment-experienced patients (n=4) treated for 16 weeks.
- In patients with GT3 infection (M14-868, Part 3), SVR12 was achieved in 97.5% of treatment-naïve patients with cirrhosis treated for 12 weeks and by 90.9% of treatment-experienced patients without cirrhosis treated for 12 weeks. SVR12 was achieved in 95.7% of treatment-experienced patients with cirrhosis treated for 16 weeks and in 95.5% of patients without cirrhosis treated for 16 weeks.
- In patients with GT2, GT4-GT6 infection (M14-868, Part 4), SVR12 was achieved in 97.9% of treatment-naïve and treatment-experienced patients with GT2 infection without cirrhosis treated for 8 weeks and by 93.1% of treatment naïve and treatment-experienced patients with GT4-GT6 infection also treated for 8 weeks.
- In patients with GT1 infection (M15-410, Part 1), SVR12 was achieved in 86.4% of DAA treatment-experienced patients without cirrhosis for 12 weeks.
- In patients with GT1 and GT4 infection (M15-410, Part 2), SVR12 was achieved in 88.6% of DAA treatment-experienced patients with or without cirrhosis treated for 12 weeks and by 91.5% of patients treated for 16 weeks.

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

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

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

Table 2: Recommended GLE/PIB duration in treatment-naïve patients

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

GLE = glecaprevir; PIB = pibrentasvir

Table 3: Recommended GLE/PIB duration in treatment-experienced patients.

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

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

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

Table 4: Summary of SVR12 rates for recommended treatment duration in the Phase II and III Analysis Set

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

8. Clinical safety

8.1. Studies providing evaluable safety data

The Safety Analysis Sets are summarised:

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

8.2. Studies with evaluable safety data: dose finding and pharmacology

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

8.3. Patient exposure

Overall exposure in the placebo-controlled analysis set is shown in Table 5. Mean exposure in 202 patients in the GLE/PIB 12 week group was 84.4 days with a range of 47-90 days. The total exposure was 46.7 patient-years. Overall exposure in the active-controlled analysis set is shown in Table 6. Mean exposure in 233 patients in the GLE/PIB 12 week group was 83.3 days with a range of 5-89 days. The total exposure was 53.2 patient-years. Overall exposure in the Phase II and III analysis set is shown in Table 7. Totals of 850 (37.5%), 1,295 (57.2%) and 120 (5.3%) patients were assigned to treatment for 8, 12 and 16 weeks, respectively. Mean exposure to study drug in 2,265 patients was 75.4 days with a range of 2-116 days. The total exposure was 467.9 patient-years.

Table 5: Study drug exposure in the placebo-controlled analysis set.

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

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

Table 6: Study drug exposure in the active-controlled analysis set.

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

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

Table 7: Study drug exposure in the Phase II and III analysis set.

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

SD = standard deviation

a. Excluding Study M15-462.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Integrated safety analyses

Comment: The safety of GLE/PIB has been assessed in 21 different treatment arms of the Phase II/3 study program. To provide a relevant overview, the sponsor has provided data summarised in the placebo-controlled analysis set (study M15-464); the active-controlled analysis set (study M13-594); and the Phase II and III analysis set. Data presented by SOC are analysed for all safety populations and included in the Integrated Summary of Safety (ISS) Safety in specific patient subgroups. This approach is acceptable as no meaningful differences between the active and control groups described by SOC were identified.

AEs were reported commonly in all groups but overall the incidence of severe AEs, SAEs and discontinuations due to AEs was low. No on-treatment deaths were reported.

- **Placebo-Controlled Analysis Set:** AEs were reported more commonly in patients treated with GLE/PIB 300 mg/120 mg for 12 weeks (64.9%), compared with patients treated with placebo for 12 weeks (58.0%), a risk difference of 6.9%. Severe AEs (Grade 3 or higher) were also reported more commonly in the active treatment group (2.5% vs 1.0%). No severe AE by PT was reported in more than one patient. In the GLE/PIB and placebo groups, the most common AEs were headache (11.9% vs 12.0%), fatigue (11.4% vs 10.0%), diarrhoea (9.9% vs 3.0%), asthaenia (9.4% vs 8.0%), nausea (7.4% vs 3.0%) and pruritus (5.9% vs 6.0%). Diarrhoea and nausea were notably more common in the active treatment group but the differences were not statistically significant for nausea. With the possible exceptions of diarrhoea and nausea, no clinically meaningful differences between groups in any SOC category were identified, in particular GI disorders, skin disorders and cardiac disorders.
- **Active-Controlled Analysis Set:** AEs were reported more commonly in patients treated with GLE/PIB 300 mg/120 mg for 12 weeks (76.0%), compared with patients treated with SOF + DCV for 12 weeks (69.6%), a risk difference of 6.4%. Severe AEs (Grade 3 or higher) were also reported more commonly in the GLE/PIB (4.7% vs 1.7%). In the GLE/PIB and SOF + DCV groups, the most common AEs were headache (25.8% vs 20.0%), fatigue (18.9% vs 13.9%), nausea (13.7% vs 13.0%), diarrhoea (6.4% vs 3.5%), upper respiratory tract infection (6.4% vs 3.5%) and nasopharyngitis (5.2% vs 6.1%), insomnia (3.9% vs 5.2%) and asthaenia (1.7% vs 6.1%). The only statistically significant difference was for the AE of asthaenia. No clinically meaningful differences between groups in any SOC category were identified, in particular GI disorders, skin disorders and cardiac disorders.
- **Phase II and III Analysis Set:** AEs were reported in 67.5% of patients but only 2.9% of AEs were Grade 3 or higher. Only four severe events were considered drug related, one case each of asthaenia, abdominal pain, migraine and raised ALT. The most common AEs were headache (18.1%), fatigue (14.6%), nausea (9.2%) and diarrhoea (6.4%). There were more events in the GLE/PIB groups compared with the control groups; however, the great majority of events were mild in severity.

8.4.2. Treatment related adverse events (adverse drug reactions)

8.4.2.1. Integrated safety analyses

- **Placebo-Controlled Analysis Set:** ADRs were reported in 31.7% of the GLE/PIB group compared with 33.0% in the placebo group. There were no clinically meaningful or statistically significant differences in the incidences of any ADR between the treatment groups. The most common ADRs in the GLE/PIB and placebo groups were headache (8.9% vs 6.0%), fatigue (8.4% vs 8.0%), asthaenia (6.9% vs 7.0%) and nausea (6.4% vs 2.0%).

- **Active-Controlled Analysis Set:** ADRs were reported in 48.1% of the GLE/PIB group compared with 43.5% in the SOF + DCV group. There were no clinically meaningful or statistically significant differences in the incidences of any ADR between the treatment groups. The most common ADRs in the GLE/PIB and SOF + DCV groups were headache (16.7% vs 14.8%), fatigue (14.2% vs 12.2%) and nausea (11.6% vs 12.2%).
- **Phase II and III Analysis Set:** ADRs were reported in 41% of the full analysis set. The most commonly reported ADRs were headache (13.2%), fatigue (11.4%), nausea (7.6%) and diarrhoea (3.8%).

8.4.3. Deaths and other serious adverse events

8.4.3.1. Integrated safety analyses

No on-treatment deaths were reported in the Phase II and III set. Overall, seven deaths were reported but most occurred months after completing study drug treatment and all were considered unrelated to study treatment. AEs leading to death were cerebral haemorrhage (in two patients), metastatic hepatic cancer, pneumonia, accidental drug overdose, adenocarcinoma and unknown cause. Other SAEs were reported in 1.5% to 2.1% across all analysis sets. No pattern was observed and only two SAEs were considered drug related by the investigator (two transient ischaemic attacks in one patient).

8.4.4. Discontinuations due to adverse events

8.4.4.1. Integrated safety analyses

There were few premature study drug discontinuations. In the Phase II and III set, 0.4% of patients discontinued due to any AE and 0.1% discontinued due to an ADR. Three patients discontinued study drug prematurely because of ADRs, each Grade 2 in severity. One patient had a transient ischaemic attack, one patient experienced dyspepsia and one patient had multiple symptoms of nausea, diarrhoea, dizziness, fatigue, malaise, abdominal pain and headache on Day 4 of treatment.

8.5. Evaluation of issues with possible regulatory impact

8.5.1. Liver function and liver toxicity

8.5.1.1. Integrated safety analyses

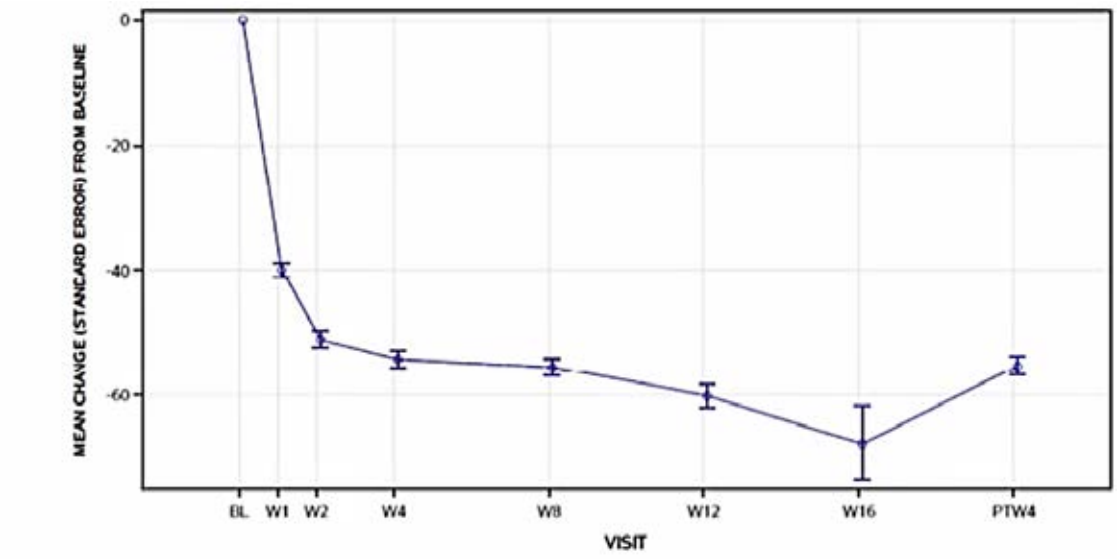
Hepatic events of special interest included potential hepatotoxicity, hepatic decompensation or failure and HCC. No issues with possible regulatory impact were identified.

Only four patients had clinically relevant ALT elevations in the Phase II and III set, but none of the patients discontinued prematurely because of LFT abnormalities. In three patients, the ALT elevations were considered temporary fluctuations of no clinical significance. Only one patient met the criteria for potential hepatotoxicity.[6] A transient Grade 3 ALT elevation with a Grade 2 bilirubin elevation were considered probably related to the passage of gallstones noted on liver ultrasound. The pattern of LFT abnormalities was considered obstructive rather than drug-induced liver injury. Modest bilirubin increases of mean 0.05 mg/dL occurred in all patients in the Phase II and III Analysis Set. These typically occurred at Week 1 but returned towards baseline thereafter, consistent with known GLE-mediated inhibition of bilirubin metabolism. Bilirubin elevations of potential clinical interest were uncommon. Total bilirubin elevations ≥2 x ULN and > baseline were reported in 1.2% of patients and total bilirubin ≥2 x ULN and >baseline and direct/total bilirubin ratio >0.4 were reported in 0.2% of patients. Mean changes

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

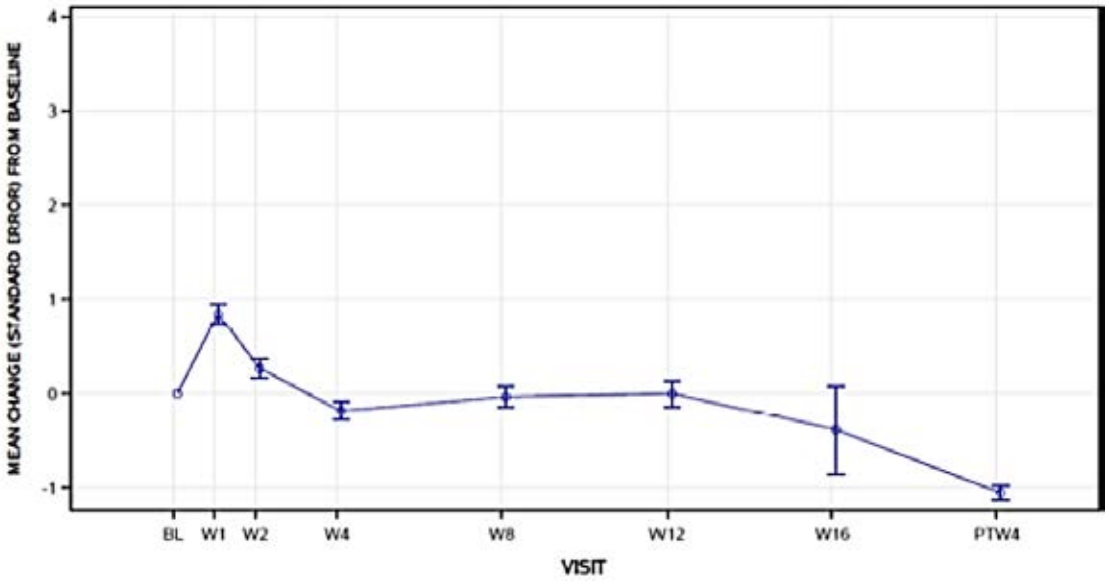
in ALT and bilirubin over time are shown. Mean ALT rapidly decreased in response to reduced liver inflammation.

Figure 15: Mean change in ALT (U/L) over time in the Phase II and III set.



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

Figure 16: Mean change in total bilirubin (µmol/L) over time in the Phase II and III set.



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

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

8.5.2. Renal function and renal toxicity

8.5.2.1. Integrated safety analyses

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

8.5.3. Other clinical chemistry

8.5.3.1. Integrated safety analyses

- Controlled studies: The numbers of patients with any Grade 3/4 laboratory abnormalities are shown in Table 8.

Table 8: Patients with Grade 3/4 laboratory abnormalities in controlled studies

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

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

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

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

8.5.4. Haematology and haematological toxicity

8.5.4.1. Integrated safety analyses

- Placebo-Controlled Analysis Set: There were no Grade 3/4 abnormalities related to haemoglobin, platelets, or leucocytes. There were three reports (1.5%) of neutropaenia in the GLE/PIB group compared with none in the placebo group.
- Active-Controlled Analysis Set: There were no Grade 3/4 abnormalities related to haemoglobin, or platelets. There were single reports of leucopaenia (0.4%) and neutropaenia (0.4%) in the GLE/PIB group compared with none in the SOF + DCV group.

- Phase II and III Analysis Set: There were few clinically significant haematological laboratory abnormalities in the full safety set. Grade 3/4 abnormalities were reported for low haemoglobin (<0.1%), reduced platelet count (0.2%), neutropaenia (0.5%) and leucopaenia (<0.1%).

8.5.5. Other laboratory tests

8.5.5.1. Integrated safety analyses

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

8.5.6. Electrocardiograph findings and cardiovascular safety

8.5.6.1. Integrated safety analyses

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

8.5.7. Vital signs and clinical examination findings

8.5.7.1. Integrated safety analyses

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

8.5.8. Immunogenicity and immunological events

Not applicable.

8.5.9. Serious skin reactions

8.5.9.1. Integrated safety analyses

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

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

8.5.10. Other safety parameters

Not applicable.

8.6. Other safety issues

8.6.1. Safety in special populations

The patterns of AEs in special populations were comparable to the overall safety population. No dosage adjustments are required in any of the subgroups specified below.

Severe renal disease: In study M15-462, SAEs and ≥Grade 3 AEs were reported in 24% of patients with severe renal disease. However, AEs and ADRs leading to study drug discontinuation were reported in only 3.8% and 1.9% of patients, respectively. The most commonly reported AE was pruritus (20.2%), a symptom commonly associated with severe renal disease. However, the pattern of AEs was otherwise comparable to the overall safety population.

Comment: The sponsor suggests that the high frequency of AEs in patients with severe renal disease was related to the underlying disease, in particular pruritus. The low incidence of AEs and ADRs leading to study drug discontinuation support this view.

HCV/HIV-1 co-infection: Patients with HCV/HIV-1 co-infection had a comparable safety profile to patients with HCV mono-infection (M13-590).

Elderly: AEs, severe AEs, and SAEs were reported more commonly in 328 patients aged ≥65 years, compared with aged <65 years (n=2,041). However, ADRs were comparable in both populations.

Comment: The sponsor suggests that the higher incidence of AEs in the elderly may be attributed to higher rates of comorbidities in the older population. This is a reasonable argument as the incidence of ADRs was comparable in the two populations.

Gender: There were no meaningful gender differences. AEs and ADRs were marginally more common in females, but severe AEs and SAEs were marginally less common.

Ethnicity: No differences related to race or ethnicity were observed in Black/Hispanic or Latino populations.

Comment: Differences in Asian populations have not been provided (see Clinical Questions).

Patients with cirrhosis: The safety profile of GLE/PIB was comparable in cirrhotic and non-cirrhotic patients.

BMI: In the Phase II and III analysis set, there were no clinically meaningful differences between patients with BMI <30 kg/m^2 compared with patients with BMI ≥30 kg/m^2.

8.7. Safety related to drug-drug interactions and other interactions

No AEs related to specific drug-drug interactions have been documented in the pivotal clinical trials. GLE and PIB are not metabolised by CYP450 or UGT pathways. GLE and/or PIB exposure may be increased by P-gp, BCRP, or OATP1/OAT1B3, or decreased by drugs that induce P-gp. Safety issues related to potential DDIs are appropriately highlighted in the proposed PI.

8.8. Post marketing experience

Not applicable.

8.9. Evaluator's overall conclusions on clinical safety

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

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

In the Phase II and III analysis set, AEs, AEs ≥ Grade 3, SAEs and discontinuations due to AEs were reported in 67.5%, 2.9%, 2.1% and 0.4% of patients, respectively. There were six deaths but none were considered drug related. By PT, the most common AEs were headache (18.1%),

fatigue (14.6%) and nausea (9.2%), but most AEs were only mild in severity. In M15-464, the pattern of AEs was comparable in the GLE/PIB and placebo groups, most commonly headache (11.9% vs 12.0%) and fatigue (11.4% vs 10.0%). Diarrhoea was reported in 9.9% of patients receiving active treatment with a risk difference of 6.9% compared with placebo. However, diarrhoea was reported in only 6% of the Phase II and III analysis set. In M13-594, the pattern of AEs was comparable in the GLE/PIB and SOF +DCV groups, most commonly headache (25.8% vs 20.0%), fatigue (18.9% vs 13.9%) and nausea (13.7% vs 13.0%). The pattern of AEs analysed by SOC was similar in patients given GLE/PIB compared with those in the placebo and active control groups. No clinically meaningful changes in haematological and chemistry variables were reported. ALT levels were significantly improved and no cases of drug induced liver injury were detected. Only two patients (<0.1%) experienced Grade 3 ALT elevations and only eight patients (0.4%) experienced Grade 3 elevations in bilirubin. No safety signals related to ECGs were detected.

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

9. First round benefit-risk assessment

9.1. First round assessment of benefits

See table below.

Table 9: First round assessment of benefits

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

Benefits	Strengths and Uncertainties
	RBV.
Effective in patients with or without compensated cirrhosis, including cirrhotic patients with GT3 infection.	Adequate patient numbers with and without cirrhosis have been studied.
Effective in treatment-naïve and treatment-experienced patients (including those who previously received DAA-based therapies).	Strong Phase II and III study data confirming efficacy in patients with any treatment history. Relatively few patients have been studied with previous DAA treatment.
Effective when given for 8 weeks in patients without cirrhosis.	Statistically significant non-inferiority of 8 weeks versus 12 weeks treatment in non-cirrhotic patients.
Renal elimination is minimal. Well tolerated without dosage adjustment in patients with chronic renal impairment.	Strong evidence of effectiveness in a stand-alone study of patients with chronic kidney disease.
Effective in patients with HCV/HIV-1 co-infection.	Limited patient numbers but 100% SVR12 rate in patients with HCV/HIV-1 co-infection.
Virologic failure uncommon so reduced risk of drug resistant strains in community.	Safety data available in 2369 patients but only limited data from controlled clinical studies.
Well tolerated with low incidence of ADRs and SAEs. No evidence of drug related liver injury.	Controlled data limited but convincing
Safety profile comparable to placebo and SOF + DCV. No specific ADRs have been identified.	

1.1 First round assessment of risks

See table below.

Table 10: First round assessment of risks

Risks	Strengths and Uncertainties
Well tolerated but there is a risk of unidentified, uncommon ADRs.	Well tolerated in 2,369 patients.
Potential for DDIs.	Metabolic pathways have been characterised and the potential for DDIs has been identified in the proposed PI.

Risks	Strengths and Uncertainties
Potential for HBV re-activation.	Patients with HCV/HBV co-infection have not been studied.
No data available for use in liver and renal transplant patients, paediatric patients and patients with decompensated cirrhosis.	Studies are planned or on-going.

9.2. First round assessment of benefit-risk balance

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

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

10. First round recommendation regarding authorisation

Authorisation is recommended for Maviret for the following indication:

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

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

11. Clinical questions

11.1. Pharmacokinetics

1. Why has the bioequivalence of the Phase III formulation and the Phase II formulation under fed conditions not been directly examined?
2. Can the sponsor please justify why the bioequivalence of the FIH PIB formulation and the 40 mg Phase IIa and 2b PIB formulations have not been examined?
3. Can the sponsor please comment on a possible mechanism for the adverse DDI identified between cyclosporine and GLE + PIB identified in Study M13-605?

11.2. Pharmacodynamics

No questions at this time.

11.3. Efficacy

4. Treatment-experienced patients with NS3 + NS5A polymorphisms at baseline are least likely to achieve SVR12 even with 16 weeks treatment, even though the likelihood is an impressive >80%. Is the sponsor considering options for extending treatment duration or co-medication with RBV in this group?

11.4. Safety

5. The RMP states that no additional risk minimisation activities are proposed for patients with HCV/HBV co-infection, a significant subgroup of Asians. Please provide a rationale for not conducting a clinical trial to assess efficacy and safety in this population.
6. Safety in Black/Hispanic and Latino populations is summarised in the Summary of Clinical Safety but there is no information relating to Asians. Please provide these data or provide a link to the relevant section.

12. Second round evaluation

12.1. Clinical questions

The initial questions raised by the TGA have been stated followed by the evaluator's comments on the sponsor's response.

12.1.1. Pharmacokinetics

1. Why has the bioequivalence of the Phase III formulation and the Phase II formulation under fed conditions not been directly examined?

12.1.1.1. Sponsor's response

In Study M14-714, AbbVie established that under fasting conditions the bioavailability as determined by AUC_{inf} values of glecaprevir and pibrentasvir in the Phase III formulation were 56% and 36% lower, respectively, than for the Phase II formulation under fasting conditions. Food increased the bioavailability of glecaprevir and pibrentasvir in the Phase III formulation so that exposures of the Phase III formulation under fed conditions were similar to the Phase II formulation under fasting conditions. In contrast to the Phase II formulation which was administered with or without food to patients in Phase II clinical studies, the Phase III formulation was administered with food to patients in all registrational Phase III and Phase II extension studies to account for this difference.

Food slightly increased the bioavailability of the Phase II formulations. In the cross-study pharmacokinetic report (R&D/16/0237), the geomean AUC_{inf} for glecaprevir 300 mg + pibrentasvir 120 mg administered as a single dose in healthy subjects was higher when administered with food than under fasting conditions (↑ 43% glecaprevir, ↑ 26% pibrentasvir). Based on these analyses it suggested the Phase III formulation may have lower bioavailability than the Phase II formulation when administered with food. Quantification of the magnitude of this difference would provide limited value to the program.

12.1.1.2. Evaluator's response

The evaluator is satisfied with the Sponsor's response.

2. Can the sponsor please justify why the bioequivalence of the FIH PIB formulation and the 40 mg Phase IIa and 2b PIB formulations have not been examined?

12.1.1.3. Sponsor's response

Unlike the Phase IIa and 2b PIB formulations which were extensively used in various Phase I and Phase II studies, the FIH PIB formulation was only used in the FIH study and some early bioavailability study for formulation screening. Variability of PIB exposure was also smaller than GLE. Characterization of the bioequivalence between FIH PIB formulation and the 40 mg Phase IIa and 2b is not necessary as the information (exposure, safety and tolerability) generated by FIH formulation can be bridged based on PIB exposure across studies. In the cross-study pharmacokinetic report (R&D/16/0237), exposures of pibrentasvir 120 mg single doses were compared for the FIH and Phase IIa formulations. C_{max} and AUC values were similar or higher for the Phase IIa formulation as compared to the FIH formulation. The same report also established similarity in exposures of Phase IIa and Phase IIb PIB formulations, consistent with the minor change in composition of these tablets. Please see below for reference.

Table 11: Single Dose Pharmacokinetics of PIB 120 mg as FIH or Phase IIa Tablets

Dose	Formulation	Subjects (N)	C_{max}[a] (ng/mL)	T_{max}[b] (h)	AUC[c] (ng•h/mL)	$t_{1/2}$[d] (h)
120 mg	FIH	30	64.8 (57.0 to 85.2)	3.0 (3.0 to 5.0)	419 (363 to 552)	16.4 (14.4 to 17.6)
120 mg	Phase 2a	8[e]	87.4	3.5	463	--

a. Overall geometric mean and range of geometric means. C_{max} included for first dose of multiple dose studies.
b. Weighted median and range of study medians.
c. Overall geometric mean and range of geometric means. AUC_{inf} for single dose or AUC_{24} for first of multiple doses.
d. Weighted median and range of study harmonic means; N = 21 for GLE FIH, N = 15 for GLE Ph2a.
e. Study M13-586 Arm 1 Cohort 2, first of multiple doses.

Cross reference: PK Report R&D/16/0237 Table 5

12.1.1.4. Evaluator's response

The evaluator is satisfied with the Sponsor's response.

3. Can the sponsor please comment on a possible mechanism for the adverse DDI identified between cyclosporine and GLE + PIB identified in Study M13-605?

12.1.1.5. Sponsor's response

Cyclosporine is an inhibitor of multiple drug transporters including P-gp, BCRP, and OATP1B17. Glecaprevir is a substrate of P-gp, BCRP, and OATP1B1. Pibrentasvir is a substrate of P-gp and/or BCRP. Increases in glecaprevir and pibrentasvir exposures when co-administered with cyclosporine in Study M13-605 were due to inhibition of these transporters. The larger magnitude of interaction for glecaprevir with cyclosporine than for pibrentasvir is due to the additional involvement of the OATP1B1 component.

Ritonavir-boosted protease inhibitor regimens can also inhibit P-gp, BCRP, and OATP1B1. Similar increases in glecaprevir and pibrentasvir exposures were observed when co-administered with atazanavir + ritonavir in Study M13-603 and lopinavir/ritonavir in Study M13-587.

12.1.1.6. Evaluator's response

The evaluator is satisfied with the sponsor's response.

[7] Monograph for cyclosporine. Metabolism and Transport Drug Interaction Database. University of Washington Drug School of Pharmacy Drug Interaction Database Program. Available from: www.druginteractioninfo.org. Accessed on: 08 August 2017.

12.1.2. Pharmacodynamics

No questions.

12.1.3. Efficacy

4. Treatment-experienced patients with NS3 + NS5A polymorphisms at baseline are least likely to achieve SVR12 even with 16 weeks treatment, even though the likelihood is an impressive >80%. Is the sponsor considering options for extending treatment duration or co-medication with RBV in this group?

12.1.3.1. Sponsor's response

AbbVie would like to clarify that in Part 2 of the MAGELLAN-1 (Study M15-410) study, the SVR12 rates in the presence of baseline polymorphisms (regardless of type of prior DAA experience) at the key subset of amino acid positions in both NS3 and NS5A were 80% (4/5) for 12 weeks (Arm D) and 25% (1/4) for 16 weeks (Arm E) of treatment (Study M15-410 CSR Table 36). In subjects who were both NS5A inhibitor- and PI-experienced (without regard to the presence/absence of baseline polymorphisms) in Part 2 of the study, SVR12 rates were 78.6% (11/14) for 12 weeks and 81.3% (13/16) for 16 weeks of treatment (Study M15-410 CSR Table 29). For 12 weeks of treatment, there were no on-treatment virologic failures, but 3/14 (21.4%) subjects experienced relapse; for 16 weeks of treatment there were 3/16 (18.8%) on-treatment virologic failures, but no relapses.

Because the virologic failures with 16 weeks of treatment were not relapses, but rather on-treatment breakthroughs, prolongation of treatment beyond 16 weeks or the addition of RBV would not be expected to improve efficacy. The impact of adding ribavirin (RBV) on efficacy was explored in Part 1 of the study and was found not to be beneficial; the RBV-containing arm (Arm B) had 1 relapse, while the arm without RBV (Arm C) had 1 on-treatment virologic failure (Study M15-410 CSR Table 18). These 2 subjects were both NS5A inhibitor- and PI-experienced. Thus, there is no evidence to support the extension of treatment duration beyond 16 weeks and/or adding RBV for patients who previously failed both NS5A and protease inhibitors.

12.1.3.2. Evaluator's response

The sponsor's response is satisfactory. The sponsor notes that virologic failures with 16 weeks of treatment were not relapses, but rather treatment breakthroughs. As such, extending treatment beyond 16 weeks would not improve efficacy. The impact of adding RBV did not improve efficacy in Part 1 of the study.

12.1.4. Safety

5. The RMP states that no additional risk minimisation activities are proposed for patients with HCV/HBV co-infection, a significant subgroup of Asians. Please provide a rationale for not conducting a clinical trial to assess efficacy and safety in this population.

12.1.4.1. Sponsor's response

Screening for HBV infection is part of the standard of care and is required before starting any HCV therapy including GLE/PIB. As recommended by the most current guidelines worldwide (including Australian guidelines[8]), HBV testing should include Hepatitis B surface antigen (HBsAg), antibody against Hepatitis B surface (anti-HBs) and antibody against Hepatitis B core (anti-HBc). These serology markers are effective for detecting patients with HBV co-infection, irrespective of their HBV disease state (active forms, inactive carrier state or occult infection)

[8] Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (January 2017). Melbourne: Gastroenterological Society of Australia, 2017

and will prevent patients who are unaware of their HBV infection to initiate treatment until a comprehensive assessment and referral to specialist are performed.

Therefore, the risk of using GLE/PIB inadvertently in patients co-infected with HBV and a subsequent HBV reactivation is negligible as HBV testing is required prior HCV treatment initiation. In this context, a clinical trial would not provide any additional information to minimize the risk of HBV reactivation.

From a risk minimisation and surveillance perspective, AbbVie considers that the risk of HBV reactivation in this group is sufficiently addressed in the Australian Product Information (Risk of Hepatitis B Virus Reactivation in the Precautions Section) and the Risk Management Plan (Hepatitis B Virus Reactivation as an Important Identified Risk), respectively.

As an Important Identified Risk in the RMP, the class risk of HBV reactivation, and in turn the use of GLE/PIB in HCV/HBV co-infected patients, will be closely monitored by routine pharmacovigilance activities, which includes the use of a Hepatic Questionnaire (for general hepatic events) and a targeted follow-up questionnaire for HBV reactivation.

These routine pharmacovigilance activities will enable AbbVie to further characterize this class risk in co-infected patients treated with GLE/PIB. Additional information will be presented in the periodic safety update reports (PSURs).

12.1.4.2. Evaluator's response

The sponsor's response is satisfactory. The sponsor notes that screening for HBV is part of the standard of care recommended in the Australian guidelines. Inadvertent prescribing of GLE/PIB in patients with HCV/HBV co-infection should not occur.

6. Safety in Black/Hispanic and Latino populations is summarised in the Summary of Clinical Safety but there is no information relating to Asians. Please provide these data or provide a link to the relevant section.

12.1.4.3. Sponsor's response

HCV-infected patients of Asian ethnicity (N = 272) were enrolled in the Phase II and III clinical trials. Overall, there were no relevant differences in AE profiles by ethnicity.

The safety profile of GLE/PIB in Asians is comparable to the safety profile of GLE/PIB in Caucasians or the entire Phase II and III safety population.

Safety information categorized by ethnicities of Asian, Caucasian, and Other subjects was summarised in the following safety tables in the Integrated Summary of Safety:

- Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Events Grouped By Race (Phase II and III Analysis Set)
- Number and Percentage of Subjects with Treatment-Emergent Adverse Events By Preferred Term Grouped By Race (Phase II and III Analysis Set)
- Number and Percentage of Subjects with a Maximum Toxicity Grade 1, 2, 3, or 4 in Laboratory Tests During Treatment Period – Grade Must Be More Extreme Than Baseline – By Race (Phase II and III Analysis Set)

12.1.4.4. Evaluator's response

The sponsor's response is satisfactory. Links have been provided to the relevant sections of the eCTD. A total of 272 patients of Asian ethnicity were enrolled in the Phase II and III studies. The safety profile of GLE/PIB in Asians is comparable to the profile in White populations.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

No changes to the first round assessment.

13.2. Second round assessment of risks

No changes to the first round assessment.

13.3. Second round assessment of benefit-risk balance

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

14. Second round recommendation regarding authorisation

No changes to the first round assessment.

Authorisation is recommended for Maviret for the following indication:

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

Approval is subject to the proposed PI changes.

15. References

None.

Therapeutic Goods Administration

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