22 June 2017
EMA/449689/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Maviret

International non-proprietary name: glecaprevir / pibrentasvir

Procedure No. EMEA/H/C/004430/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AASLD	American Association for the Study of Liver Disease
AE	adverse event
ALT	alanine aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	breast cancer resistance protein
BMI	body mass index
BOC	boceprevir
BP	baseline polymorphism
BSEP	bile salt export pump
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD	chronic kidney disease
Cmax	maximum plasma concentration
Cmin	minimum plasma concentration
C-P	Child-Pugh
CV	coefficient of variation
CYP	cytochrome P450
DAA	direct-acting antiviral agent
DCV	daclatasvir
DDI	drug-drug interaction
DSV	dasabuvir
eGFR	estimated glomerular filtration rate
EASL	European Association for Study of Liver
ELB	elbasvir
ESRD	end-stage renal disease
f_e	fraction of dose eliminated in the urine
FDC	fixed dose combination
GLE	glecaprevir
GT	genotype
GZV	grazoprevir
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus-1
HV	healthy volunteers
ICH	International Council for Harmonisation
IFN	interferon
IRR	Integrated Resistance Report
ITT	intention-to-treat
IVIVC	in vitro and in vivo correlation
LDV	ledipasvir
Max	maximum
Min	minimum
mITT-VF	modified intention-to-treat population excluding subjects who did not achieve SVR12 due to nonvirologic reasons
N/A	not applicable
NPRS	TN subjects + P/R- or SOF/R-experienced subjects
NS3	nonstructural viral protein 3
NS3/4A	nonstructural viral protein 3/4A
NS5A	nonstructural viral protein 5A
OATP	organic anion transporting polypeptide
OBV	ombitasvir
OTVF	on-treatment virologic failure
P	pegylated interferon or interferon
P/R	regimens containing interferon, pegylated interferon, and ribavirin
pegIFN	pegylated interferon
P-gp	P-glycoprotein

PI	protease inhibitor
PIB	pibrentasvir
PPK	population pharmacokinetic
PRS	regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir
PTV	paritaprevir
QD	once daily
r	ritonavir
RBV	ribavirin
Relapse$_{12}$	relapse before or during the SVR12 window
RNA	ribonucleic acid
RVR	rapid virologic response
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Product Characteristics
SMV	simeprevir
SOF	sofosbuvir
SOF/R	regimens containing sofosbuvir and ribavirin
SVR	sustained virologic response
SVR$_{12}$	sustained virologic response 12 weeks post dosing
TDF	tenofovir disoproxil fumarate
TE	treatment-experienced
TE-PRS	treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir
TVR	telaprevir
TN	treatment-naïve
UGT	uridine glucuronosyltransferase
ULN	upper limit of normal
US	United States
VEL	velpatasvir

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AbbVie Ltd. submitted on 21 December 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Maviret, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 1 April 2016.

The applicant applied for the following indication: treatment of chronic hepatitis C virus (HCV) infection in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that glecaprevir and pibrentasvir were considered to be new active substances.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0152/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0152/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substances glecaprevir and pibrentasvir contained in the above medicinal product to be considered as new active substances, as the applicant claims that they are not constituents of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 26 June 2014, 24 September 2015, 22 October

2015, 17 December 2015 and 1 April 2016. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Joseph Emmerich Co-Rapporteur: Filip Josephson

- The application was received by the EMA on 21 December 2016.
- Accelerated Assessment procedure was agreed-upon by CHMP on 15 December 2016.
- The procedure started on 20 January 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 27 March 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 22 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 March 2017. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 6 April 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 19 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 May 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 9 June 2017.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 June 2017.
- During the meeting on 19-22 June 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Maviret on 22 June 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Maviret (glecaprevir/pibrentasvir (GLE/PIB)) is a fixed-dose combination developed for the treatment of chronic hepatitis C virus (HCV) infection in adults.

2.1.2. Epidemiology

Hepatitis C viral (HCV) infection is a global health problem, with over 170 million individuals chronically infected worldwide. It is also a major European public health challenge, with a prevalence of 0.4-3.5% in different EU member states. Approximately 15 million persons are chronically infected with HCV throughout Europe. The prevalence of HCV in the general adult population ranges from ≤0.5% (Northern European countries) to ≥3% (Greece, Italy, and Eastern European countries).

It is the most common single cause of liver transplantation in the European Union.

Depending on various risk factors, between 10-40% of patients with chronic HCV infection will develop cirrhosis over time. Death related to the complications of cirrhosis (mainly liver decompensation and hepatocellular carcinoma, HCC) may occur at an incidence of approximately 4% per year. In 2010, more than 0.5 million deaths worldwide were attributed to infection with HCV. Curing hepatitis C was shown to significantly reduce the risk of disease progression and related mortality, as well as the development of HCC.

2.1.3. Aetiology and pathogenesis

There are 6 major hepatitis C virus (HCV) genotypes and numerous subtypes with prevalence varying by geographic region.

Genotype 1 is the most prevalent in Europe accounting for 70% of chronically infected Europeans with GT1b subtype predominating over GT1a in most European countries including those with the highest prevalence. Genotype 3 is the next most common genotype in Europe, ranging from 24.8% to 30.4% of HCV cases followed by GT2 which ranges from 0.1% to 10.4%. Genotype 5 has only been reported in Western Europe, comprising not more than 2% of all HCV genotypes; GT6 comprises less than 1% of HCV genotypes in any of the EU nations. HCV GT4 has become increasingly prevalent in Southern European countries where prevalence rates among HCV-infected patients of 10–24% have been reported.

Chronic hepatitis C is a serious disease and is the leading cause of liver transplantation in the developed world and the most common chronic blood borne infection in both the United States and Europe with approximately 80% of infected individuals becoming chronically infected.

In these patients, chronic hepatic inflammation and fibrosis persist over several decades. Depending on various risk factors, between 10% and 40% of patients with chronic HCV infection will develop cirrhosis. Death related to the complications of cirrhosis may occur at an incidence of approximately 4% per year; hepatocellular carcinoma (HCC) occurs in this population at an estimated incidence of 1% to 5% per year. Patients diagnosed with HCC have a 33% probability of death during the first year. In 2010, more than 0.5 million deaths worldwide were attributed to infection with HCV. In addition to liver-related morbidity and mortality, HCV infection is related to extrahepatic complications including cryoglobulinemia, renal disease, type 2 diabetes and cardiovascular complications.

2.1.4. Clinical presentation

Clinically, the infection is generally asymptomatic but it may present with a wide variety of symptoms from nonspecific symptoms such as fatigue or malaise to symptoms characteristic of complications from advanced or decompensated liver disease related to synthetic dysfunction and portal hypertension. Other manifestations include cirrhosis, hepatocellular carcinoma, cryoglobulinemia and glomerulonephritis, as described above.

2.1.5. Management

Successful eradication of HCV has been shown to significantly reduce the risk of disease progression and related mortality as well as the development of HCC. Sustained virological response (SVR) is also associated with reduced occurrence of the extrahepatic complications diabetes mellitus, end-stage renal disease (ESRD) and cardiovascular events and a decrease in all-cause mortality.

Treatment of HCV infection has progressed considerably within the last years thanks to the development of several specifically-targeted antiviral drugs, directed against essential HCV proteins (direct-acting agents, DAAs). Several IFN-free DAA regimens are currently available in Europe and allows high rate of virological cure (>90%) with generally 12 weeks of treatment in a convenient fixed dose combination.

However, the approved and recommended regimens are not equally potent across all HCV genotypes and subpopulations. Notably, efficacy is reduced in patients with baseline viral variants resistant to NS5A inhibitors, especially in patients with GT1a or GT3. Despite the high SVR rates achieved with current DAA regimens, the infection is not eliminated from a substantial number of patients (1-9% in GT1 and even more in GT3 cirrhotics who represent nowadays the most difficult to treat population) and there is currently limited retreatment options for patients who have failed IFN-free treatment regimens. Additional limitations of several current regimens include the requirement of ribavirin for certain populations, significant drug to drug interactions, limited options for subjects with renal insufficiency.

Overall, beyond the need for an improved option for GT3 patients having pejorative factors at baseline (baseline NS5A RAS, cirrhosis), there remains a true unmet medical need in some situation of retreatment, notably in patients with genotype 3 and prior NS5A failure (with Y93H quasi universally selected in case of failure compromising response to subsequent lines of therapy). Moreover, as sofosbuvir is not recommended in patients with severe renal disease and as grazoprevir/elbasvir was approved for severe renal disease patients with infections due to HCV GT1 and GT4 only, the situation of patients with GT2, GT3 and GT5-6 with CKD stage 4 and 5, including those on dialysis, is currently not covered. There is also a need for salvage therapy that does not contain sofosbuvir for the small subset of patients with DAA-failure and CKD stage 4-5.

About the product

Maviret is a fixed dose combination (FDC) of two next generation DAAs: glecaprevir, (GLE, ABT-493), an inhibitor of HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein and pibrentasvir (PIB, ABT-530), an inhibitor of HCV NS5A, showing potent pan-genotypic activity *in vitro* with limited cross-resistance with earlier DAAs, and minimal renal elimination.

The GLE/PIB registrational program included a broad subject population across all genotypes : treatment-naive and treatment-experienced (to (peg)IFN, ribavirin, sofosbuvir) patients with or without (compensated) cirrhosis, patients with CKD stage 4-5, HIV-HCV co-infected patients and DAA-experienced patients to NS5A inhibitor and/or NS3/4A PI.

The FDC is to be taken orally once daily with food with the following regimen:

Recommended treatment duration for patients without prior HCV therapy

Patient Population	Recommended treatment duration	
	No cirrhosis	Cirrhosis
All HCV genotypes	8 weeks	12 weeks

Recommended treatment duration for patients who failed prior therapy with peg-IFN + ribavirin +/- sofosbuvir, or sofosbuvir + ribavirin

Patient population	Recommended treatment duration	
	No cirrhosis	Cirrhosis
GT 1, 2, 4-6	8 weeks	12 weeks
GT 3	16 weeks	16 weeks

Type of Application and aspects on development

CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on its potent pan-genotypic activity *in vitro* with limited cross-resistance with earlier DAAs and on its minimal renal elimination, which was seen as conferring added value to respond to the unmet medical need. CHMP agreed that the above constitute an important therapeutic innovation compared to previously available NS5A inhibitors.

Overall, the fact that Maviret could be used in patients with CKD was welcomed. Based on PK data, including a PK study in patients with renal impairment and on the data from the dedicated phase III study in patients with CKD stage 4 and 5, including patents on haemodialysis, CHMP considered Maviret to represent an additional option for patients with severe renal impairment and that it would address an unmet medical need.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets, containing 100 mg of glecaprevir and 40 mg of pibrentasvir as the active substances.

Other ingredients of the core tablets are copovidone (Type K 28), vitamin E (tocopherol) polyethylene glycol succinate, colloidal anhydrous silica, croscarmellose sodium, sodium stearyl fumarate, propylene glycol monocaprylate (Type II). The film coating is composed of hypromellose 2910 (E464), lactose monohydrate, titanium dioxide, macrogol 3350 and iron oxide red (E172).

The product is available in PVC/PE/PCTFE polymer and aluminium foil blister packs as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Glecaprevir

General information

The chemical name of glecaprevir is (3aR,7S,10S,12R,21E,24aR)-7-tert-butyl-N-{(1R,2R)-2-(difluoromethyl)-1-[(1-methylcyclopropane-1-sulfonyl)carbamoyl]cyclopropyl}-20,20-difluoro-5,8-dioxo-2,3,3a,5,6,7,8,11,12,20,23,24a-dodecahydro-1H,10H-9,12-methanocyclopenta[18,19][1,10,17,3,6]-trioxadiazacyclononadecino-[11,12-b]quinoxaline-10-carboxamide hydrate corresponding to the molecular formula $C_{38}H_{46}F_4N_6O_9S$ (anhydrate) and $C_{38}H_{46}F_4N_6O_9S \bullet xH_2O$ (hydrate). It has a relative molecular mass 838.87 g/mol (anhydrate) and has the following structure:

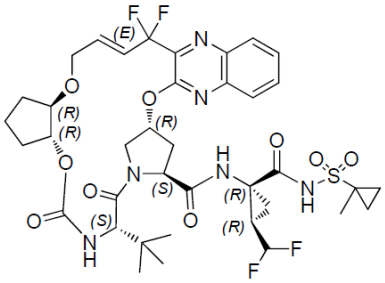


Figure 1 - Structure of glecaprevir

The structure of the active substance was elucidated by a combination of mass spectrometry (MS), infrared (IR) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy. Glecaprevir is sufficiently characterised and its structure is adequately elucidated.

Glecaprevir appears as a white to off-white crystalline powder. It shows pH dependent solubility in aqueous media, being practically insoluble at pH 2.1 and 5.1 and very slightly soluble at pH 6.6. Its pka values were found to be 4.0 and 11.7 and the partition coefficient (Log P) 2.5 at pH 7.4.

Glecaprevir has seven stereogenic centers and is manufactured as a single stereoisomer and its chiral purity is controlled through in-process controls and specifications for starting materials and intermediates. The molecule does also contain a double bond with E (*trans*) configuration.

The active substance exhibits polymorphism. A number of crystalline forms of glecaprevir have been identified but it has been demonstrated that the manufacturing process consistently produces the same crystalline form, which has been shown that it does not change during the proposed re-test period. It is characterized and controlled by X-ray powder diffraction (XRPD) analysis.

Glecaprevir active substance is qualified as a new active substance in itself as it has been demonstrated that it is not a constituent of a medicinal product previously authorised within the European Union.

Manufacture, characterisation and process controls

The synthesis of glecaprevir comprises five steps using four starting materials. All starting materials are controlled by suitable specifications. The intermediates have been defined. The proposed limits and specifications for the isolated intermediates have been acceptably justified based on the development studies along with supportive batch data and these are considered sufficient to guarantee the quality of the final drug substance.

Critical and non-critical process steps and parameters have been identified and adequate in-process controls are applied during the synthesis of the active substance. The characterisation of the active

substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The potential impurities are controlled in the active substance by validated test methods. It has been demonstrated that the impurities are generally adequately controlled during manufacturing of the active substance. The proposed tests and acceptance criteria for glecaprevir active substance are considered acceptable and justified.

Glecaprevir is packaged in double low density polyethylene (LDPE) bags, placed in high density polyethylene (HDPE) or fiber drums (secondary packaging). The LDPE bags used as primary packaging material are food grade and comply with the requirements of Ph. Eur. and European Directive 10/2011 as amended.

Specification

The glecaprevir specification includes appropriate tests and limits for appearance (visual), solution (Ph. Eur.), identification (IR, HPLC), polymorphism (XRPD), particle size distribution, assay, impurities, residual solvents, sulfated ash (Ph. Eur.), water content (Ph. Eur.), microbiological quality (Ph. Eur.) and acetamide (GC).

The origin, fate and control of mutagenic or potentially mutagenic impurities have been described in detail including adequate spiking experiments as applicable and the results thereof. The provided data is considered sufficient and the proposed control strategy, which is in line with the recommendations and principles outlined in the ICH M7 guideline, is acceptable.

However, particularly with regard to the levels of a particular impurity, in order to obtain further confirmation that the control limit will be consistently met the CHMP has requested results from a sufficient number of commercial batches of glecaprevir analysis to demonstrate consistent compliance with the control limit (post authorisation recommendation).

The control strategy for solvents is considered acceptable and appropriate limits for residual solvents are included in the glecaprevir specification. In addition, residual solvent data on 10 batches of glecaprevir are provided. For those residual solvents that results were below 10% of the ICH Q3C option 1 limit or 10% of the claimed PDEs no control test is deemed necessary.

Omission of testing for certain metals (used in the synthesis of starting materials) and elemental impurities has been sufficiently justified in line with ICH Q3D.

Sufficient evidence has been provided regarding the control of chiral purity.

The analytical procedures used in the control of the active substance have generally been satisfactorily described and validated in accordance with the ICH guidelines. Information regarding the reference standards used in the analytical testing is satisfactory.

Batch analysis data from nine production scale batches of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process from batch to batch.

Stability

Stability data on three pilot scale batches of glecaprevir from the clinical manufacturing site, stored in the intended commercial package for up to 12 months under long term conditions at 30°C / 75% RH, and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The planned length of study is 48 months. Supplemental stability data provided include data for three batches up to commercial scale from the proposed manufacturing site. These studies have been

initiated for all three batches and data is available for two batches through 9 months and one batch through 6 months under long term conditions (30 °C / 75 % RH) and for up to 6 months under accelerated conditions (40 °C / 75 % RH).

Samples were tested for appearance, assay, impurities, water content, crystal form and microbial quality. The test methods were the same as for release and are stability indicating. No significant changes were observed over the course of the stability studies apart from an upward trend show in water content which remain within the specification. This trend is attributed to the intrinsic nature of the active substance which is a non-stoichiometric, labile hydrate. No impact of water content increase on degradation and crystalline form is evidenced.

Photostability testing on two pilot scale batches following the ICH guideline Q1B was also conducted and results confirmed that the active substance is sensitive to light. Therefore, glecaprevir active substance must be packaged in its secondary storage container, to ensure adequate protection from exposure to high intensity light.

Additionally, results on temperature excursion and temperature cycling stability studies performed in one of the primary stability study on drug substance batches were provided. All stability data obtained after these studies met the requirements of the shelf-life specification. No adverse results were observed for all parameters tested besides an increase in water content remaining however within specification. Temperature excursion studies are also included supporting temperature excursions during shipping of up to 50°C for 1 month.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months of glecaprevir stored at or below 30°C in the proposed container closure system.

Pibrentasvir

General information

The chemical name of pibrentasvir is methyl {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1H-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2yl}carbamate corresponding to the molecular formula $C_{57}H_{65}F_5N_{10}O_8$. It has a relative molecular mass of 1113.18 g/mol and the following structure:

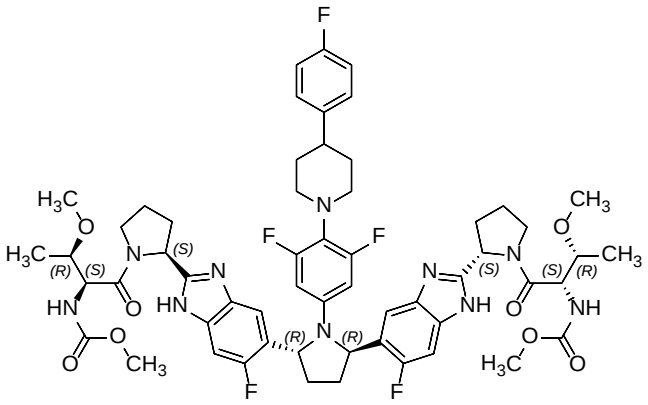


Figure 2 - Structure of pibrentasvir

The structure of the active substance was elucidated by a combination of mass spectrometry (MS), infrared (IR) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy. Pibrentasvir is sufficiently characterised and its structure is adequately elucidated.

Pibrentasvir active substance is a white to off-white to light yellow non-hygroscopic crystalline powder, practically insoluble in water, freely soluble in ethanol. It shows pH dependant solubility in aqueous media, being very slightly soluble at pH 1.1 and practically insoluble at and above pH 2.1. It also shows low passive permeability. Its pKa values were found to be 3.5, 4.1 and 11.6 and the partition coefficient (logP) is 7.5.

Pibrentasvir has eight stereogenic centres and is manufactured as a single isomer. The optical purity of the chiral centres is controlled in the starting materials. Epimerisation of all eight chiral centers during the manufacturing process to form the enantiomer of pibrentasvir is not possible. The stereoisomeric purity of the active substance is controlled through the starting material specifications and the design of the manufacturing process. The determination of the stereochemistry in the starting materials in combination with confirmation of the relative stereochemistry of pibrentasvir and stereochemical controls on process materials provides unequivocal proof of the stereochemistry of pibrentasvir.

Pibrentasvir molecule exhibits polymorphism and a number of crystalline forms have been identified as solvates but it has been demonstrated that the manufacturing process consistently produces the same crystalline form. The crystalline form of the active substance does not change during the proposed re-test period. The crystalline form is characterized and controlled by X-ray powder diffraction (XRPD) analysis.

Pibrentasvir active substance is qualified as a new active substance in itself as it has been demonstrated that it is not a constituent of a medicinal product previously authorised within the European Union.

Manufacture, characterisation and process controls

Pibrentasvir active substance is manufactured by a six-stage process from four starting materials which are well-defined and controlled by acceptable specifications.

The tests and acceptance criteria for the starting materials, in process controls and isolated intermediates are complete and sufficiently justified by purge studies.

Adequate in-process controls and critical process parameters have been identified and applied during the synthesis.

The potential impurities are controlled in the active substance by validated test methods. It has been demonstrated that the impurities are generally adequately controlled during manufacturing of the active substance. The proposed tests and acceptance criteria for pibrentasvir active substance are considered acceptable and justified.

Purging of non-mutagenic and mutagenic impurities originating from the starting materials has been adequately demonstrated. Some of the non-mutagenic impurities persist through the manufacturing process. However, these impurities are controlled in the starting materials with acceptance criteria justified by the purge experiments and the corresponding daughter impurities are additionally individually controlled in the active substance. The formation, fate and purging of impurities are adequately discussed and appropriate controls are generally proposed. However, particularly with regard to the levels of a particular impurity, in order to obtain further confirmation that the control limit will be consistently met the CHMP has requested results from a sufficient number of commercial batches of pibrentasvir analysis to demonstrate consistent compliance with the control limit (post authorisation recommendation).

Pibrentasvir is packaged in double low density polyethylene (LDPE) bags, placed in a high-density polyethylene (HDPE) or fibre drum. The polythene bags used as primary packaging material are food grade and comply with the requirements of Ph. Eur. and European Directive 10/2011 as amended.

Specification

The active substance specification includes appropriate tests and limits for appearance (visual), clarity and colour of solution (Ph. Eur.), identification (IR, HPLC), crystal form (XRPD), particle size (laser diffraction), assay (HPLC), impurities (HPLC), elemental impurities (ICP-OES), residual solvents (GS), sulfated ash (Ph. Eur.), water content, (Ph. Eur.), microbiologic quality (Ph. Eur.) and acetamide (GC).

The specifications are based on batch analyses of several batches of the drug substance prepared by the commercial process, and batches used for clinical and toxicological and stability data. The proposed specification is acceptable and adequately justified.

The analytical methods used have been adequately described, validated and are suitable for the quality control of pibrentasvir drug substance. Information regarding the reference standards used in the analytical testing is satisfactory.

Batch analysis data from 17 pilot scale and 1 commercial scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three pilot scale batches of active substance from the site for clinical manufacture stored in the intended commercial packaging for up to 18 months under long term conditions (30 °C / 75 % RH) and for up to 6 months under accelerated conditions (40 °C / 75 % RH) was provided according to the ICH guidelines. The planned length of study is 48 months. Supplemental stability data include data for three batches up to commercial scale from the proposed manufacturing site. These studies have been initiated for all three batches and data is available for two batches through 9 months and one batch through 3 months under long term conditions (30 °C / 75 % RH) and for up to 6 months and 3 months, respectively, under accelerated conditions (40 °C / 75 % RH).

Samples were tested for appearance, assay, impurities, water content, microbiological quality and polymorphism. The test methods were the same as for release and are stability indicating. No significant changes to any of the measured parameters were observed under long term and accelerated conditions and all remained within specification.

Photostability testing on one pilot scale following the ICH guideline Q1B was provided and confirm that the active substance is photosensitive. The results also demonstrate that the primary storage container provides sufficient light protection. Pibrentasvir must be stored in its secondary storage container to ensure adequate protection from exposure to high intensity light.

Stress testing during analytical method validation (temperature degradation, hydrolysis, acid and base exposure, photo-degradation and oxidation) was also performed. No degradation was observed under the conditions tested. Stress testing of pibrentasvir was also performed by subjecting pibrentasvir active substance to thermal cycling and thermal excursions. The data generated support temperature excursions during shipping of up to 50°C for 1 month.

The stability results justify the proposed retest period of 24 months when stored at or below 30°C in the commercial packaging. Stability data for production site-specific batches are comparable to the primary stability batch data.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description of the product and Pharmaceutical development

The finished product is an immediate release film coated tablet containing 100 mg of glecaprevir and 40 mg of pibrentasvir. The film-coated tablets are pink, oblong, biconvex, with “NXT” debossed on one side, the other side being plain intended for oral administration. The list of excipients is included in section 6.1 of the SmPC.

The aim of the pharmaceutical development work was to develop a stable formulation containing 100 mg of glecaprevir and 40 mg of pibrentasvir. A systematic approach was taken to develop the tablet formulation and manufacturing process. The quality target product profile (QTPP) was defined as follows: an oral dosage form containing 100 mg of glecaprevir and 40 mg of pibrentasvir of acceptable appearance, meeting the relevant compendial requirements for this pharmaceutical form, comprised of known excipients and stable in different climatic zones. An initial list of product critical quality attributes (CQAs) was generated based on the QTPP. Subsequently, a systematic evaluation, understanding, and refinement of the manufacturing process were carried out using design of experiments, statistical analysis, simulations, and mathematical models were undertaken to define the relationship of the material attributes and process parameters to the product CQAs. After determining the CQAs, critical process parameters (CPPs), and in-process controls (IPCs), the control strategy was defined to ensure final product quality. A final risk assessment was then completed to demonstrate risks previously identified are mitigated using the proposed control strategy.

Both active substances, glecaprevir and pibrentasvir, are poorly water soluble compounds. The solubility of both glecaprevir and pibrentasvir in aqueous media at 25 °C is a function of pH. Glecaprevir’s, solubility is not measurable at pH 2.0 and increases to 843 µg/mL at pH 6.8. Pibrentasvir’s solubility was not measurable at pH ≥ 3.3 at 25°C. It increased to 1.5 µg/mL at pH 2.6 and to ~0.4 mg/mL at pH 1.0. Based on their biopharmaceutical properties they are individually formulated as amorphous solid dispersions to increase the apparent aqueous solubility and obtain adequate *in vivo* absorption. Several particle sizes distribution (PSD) of glecaprevir and pibrentasvir active substances were evaluated in the blending and amorphous solid dispersion processes and appropriate PSD specifications were set to meet the finished product critical quality attributes (CQAs).

The choice and amount of excipients have been based on the evaluation of product manufacturability and performance. Vitamin E (tocopherol) polyethylene glycol succinate (TPGS) and propylene glycol monocaprylate (PGMC II) quantities in the final dose of Glecaprevir/Pibrentasvir film-coated tablets comply with tolerable upper intake level established by the European Food Safety Authority (EFSA) and the acceptable daily intake (ADI) determined by the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives respectively. All the tablet core excipients comply with Ph. Eur. or NF monographs. The coating agent powder is non-compendial but itis components are of Ph. Eur. or NF (iron oxide) quality. The compatibility between the active substances and the excipients is demonstrated by the finished product stability studies.

The Phase 1 first in human clinical studies were conducted with formulated tablets (formulations of individual glecaprevir and pibrentasvir tablets) at strengths of 2.5 and 25 mg for glecaprevir tablets and 1.5 and 15 mg for pibrentasvir tablets. The majority of Phase 1 and Phase 2 clinical studies were conducted with formulated tablets at strengths of 100 mg for glecaprevir tablets and 40 mg for

pibrentasvir tablets. The individual tablets were co-administered in the clinical studies. The commercial formulation was used in all Phase 2 extension and Phase 3 clinical studies and stability studies.
The manufacturing of amorphous solid dispersions was optimised to achieve the QTTP requirements, ensure stability of the active substances and intermediates and manufacturability.

Film-coated tablets

A co-formulated tablet composed of the two intermediates was chosen. The dosage form allows both glecaprevir and pibrentasvir to be formulated in the same tablet. Human PK studies were conducted to compare the *in vivo* performance of the uncoated fixed dose combination formulation with the single dose tablets containing 100 mg glecaprevir and 40 mg pibrentasvir used in phase II. The exposures of glecaprevir and pibrentasvir released from the uncoated tablet are stated to be comparable.

The film-coating is non-functional and dissolution is similar between uncoated and coated tablets indicating that there is no relevant impact of film-coating on drug release over the ranges examined.

The dissolution test method has been selected based on the physicochemical properties of the active substances, dissolution profiles of various amorphous formulations, dissolution performance at different conditions (media, apparatus, speed) and discriminating capability with respect to composition and manufacturing parameters.

Different types and amounts of surfactants have been evaluated. The concentration of the surfactant has been justified mainly based on solubility considerations. The rotation speed has been sufficiently justified. The chosen medium has been selected based on the aqueous solubility of both substances and the fact that similar dissolution profiles could be obtained for both substances.

The dissolution method has been shown discriminating with respect to certain formulation changes and process parameters. The evaluation of the dissolution profiles has been done by comparison of f1 and f2 values.

Regarding manufacturing process development, it was guided by a combination of univariate and multivariate experiments.

The interaction of critical process parameters (CPPs) was assessed for the glecaprevir and pibrentasvir intermediates by applying design of experiments (DOE) to both the blending and amorphous solid dispersion unit operations. The proposed CPPS ranges were suitably demonstrated through multivariate experiments and interactions between the process parameters and material attributes were addressed. In addition the proposed process parameter ranges are also adequately supported by the experience gained during development and manufacture of clinical and stability batches.

The container closure system of Glecaprevir/Pibrentasvir film-coated tablets, 100 mg/40 mg is a blister made of clear polyvinyl chloride / polyethylene/ polychorotrifluoroethene (PVC/PE/PCTFE) polymer and aluminium foil with vinyl heat seal coating. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process can be divided in two steps. The first step of the process comprises preparation of the glecaprevir and pibrentasvir intermediates and the second step of the process includes tableting and film-coating.

The manufacturing process of both intermediates and the film-coated tablets has been described in sufficient detail and is considered a standard process for solid oral dosage forms taking also into

consideration the manufacturer's prior knowledge and experience gained through the development and commercial manufacture of similar products marketed.

The critical process parameters (CPPs) have been thoroughly justified in the dossier.

The critical process parameters and their acceptable ranges as well the in-process controls (IPCs) during the manufacturing process have been presented and are adequately justified. No critical process parameters have been identified for the amorphous solid dispersion unit operations. The control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all release specifications.

The manufacturing process for the film-coated tablets will be validated prior to marketing according to an acceptable process validation scheme which has been provided. Process validation will be performed on at least three commercial scale batches of the respective intermediates and film-coated tablets, which is acceptable. Additional sampling will be performed during the manufacturing of the intermediates and tablet manufacture.

In conclusion, it is considered that the manufacturing process is sufficiently robust to provide assurance that film-coated tablets of consistent quality, complying with the designated specification, are produced.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), identification of glecaprevir and pibrentasvir (HPLC, UV), assay of glecaprevir and pibrentasvir (HPLC), uniformity of dosage units (Ph. Eur.), degradation products of glecaprevir and pibrentasvir (HPLC), dissolution of glecaprevir and pibrentasvir (HPLC), water content (Ph. Eur.) and microbiological quality (Ph. Eur.).

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Absence of crystallinity is controlled at the intermediate level and it is not considered necessary to include the test in the finished product specification. With respect to the absence of crystallinity the products are stable and no crystallisation has been observed during the manufacture of the product or in stability studies. The control strategy for minimizing crystallinity has been described in detail and is considered acceptable.

Regarding dissolution, since the release of both active substances occurs over a period exceeding 60 minutes, a two-point specification for both glecaprevir and pibrentasvir is proposed to provide a better control of the dissolution profile.

A risk assessment according to ICH Q3D option 2b has been performed for the product considering all potential sources. The estimated maximum daily exposure levels of all potential elemental impurities were less than the control threshold level (30% of the PDE). In addition, seven production scale batches have been screened for ICH Q3D Class 1 and Class 2 elements. In every batch, the levels were well below 30% of the oral PDE. Therefore no testing of elemental impurities will be performed on the finished product.

Batch analysis data for 3 production scale batches, 6 intermediate scale batches and 3 primary stability batches have been presented. All batches were manufactured at the commercial manufacturing site. The results show that the finished product can be manufactured with consistent quality and meeting its specifications.

Stability of the product

Three primary stability batches of film-coated tablets manufactured at the proposed manufacturer (at about 40% of commercial batch scale) and stored in the package proposed for marketing have been studied under long term conditions (30°C/75% RH) for up to 18 months and under accelerated conditions (40°C/75% RH) for 6 months according to the ICH Stability Guidelines. Samples were tested for appearance, assay, degradation products, water content, dissolution, water activity, crystallinity and microbial quality. The analytical methods are the same as for release testing and are stability indicating. No meaningful change is observed in any attribute studied at long-term and accelerated storage condition. All data reported comply with the proposed specifications and no trends were observed. Stability data of clinical batches showed absence of crystallinity by XPRD for all batches investigated, even when water content levels reached 11.0%.

Stability of bulk film-coated tablets when stored in the proposed container closure system (heat-sealed laminated foil (aluminium) bags) has also been investigated. A holding time of 12 months is considered adequately supported by presented data. It has been confirmed that the manufacturing date is established as the date of first mixing of an excipient with drug substance.

A photostability study was carried out on the primary batches according to ICH Q1B Guideline. The results indicate that the film-coated tablets are not sensitive to light therefore storage restrictions are not considered necessary.

Additional stability data on the primary stability batches include temperature excursion studies (-20°C for 0.5 months, 5°C for 12 months, 50°C/75%RH for 0.5 months), temperature cycling studies (9 months at 30°C/75%RH then cycling from -20°C to 50°C/75% RH over 35 days followed by 30°C/75% RH). Stability was assessed for description, assay, degradation products, dissolution, water content and crystallinity. No meaningful change was observed. These studies support exposure of the drug product to short periods of freezing or high temperatures that may be encountered during shipping.

Based on the provided stability data, the proposed shelf life of 30 months without any special storage conditions as stated in the SmPC (section 6.3 and 6.4) is acceptable.

Adventitious agents

There are no materials of human or animal origin used in the manufacture of the finished product.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the

CHMP recommends the following points for investigation:

- Results from a sufficient number of commercial batches of glecaprevir and pibrentasvir acetamide analysis to demonstrate consistent compliance with the control limit.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

Glecaprevir was evaluated in both HCV NS3/4A protease cleavage enzyme assays and HCV subgenomic replicon cell-based assays for inhibition of HCV. Glecaprevir displays low nanomolar (IC50 = 3.5 – 11.3 nM) activity against HCV genotypes 1 - 6 in enzymatic assays and was active against the genotype 1a, 1b, 2a, 2b, 3a, 4a and 6a (EC50 = 0.85 to 4.6 nM) replicons in vitro. Glecaprevir was more than 10000-fold more selective for inhibition of human HCV NS3/4A protease compared to representative human/mammalian polymerases.

In the *in vitro* replicon transient transfection assay, pibrentasvir retained its activity against a panel of 74 clinical samples from HCV genotypes 1-6 infected subjects, with an EC50 median value of 1.1 pM (range 0.27 to 3.5 pM).

Glecaprevir and pibrentasvir did not exhibit antiviral activity against HIV-1 or HBV.

Secondary pharmacodynamic studies

Receptor screening:
Glecaprevir (10 µM) displaced control-specific binding by greater than 50% only at the chloride (Cl-) channel, (IC50 11 µM), and has a weak effect on AT1, A1, BZD, CCK1, NK2 and 5-HT1b. These effects are not likely to be of clinical significance considering that the in vitro screening was performed at 10 µM and that the reported Cmax plasma level of GLE is 1.4 µM and considering the high binding to plasma proteins.

Pibrentasvir (10 µM) did not displace control-specific binding by greater than 50% at any receptors, ion channels, or transporters. Minor effect observed for BZD (-33%), CCK1 (-20%), ETa (-19%), H1 (-22%), Y2 (-23%), 5-HT1b (-20%); 5HT2a (-19%), σ (-21%) at 10µM. These effects are not likely to be of clinical significance considering that the in vitro screening was performed at 10 µM and that the reported Cmax plasma level of PIB is 0.09 µM and considering the high binding to plasma proteins.

Safety pharmacology programme

Central nervous system: GLE and PIB did not give any CNS/neurobehavioral effects in rats or mouse respectively at doses up to 100 mg/kg.

Cardiovascular: The IC50 for inhibition of hERG tail current was 85.6 µg/mL for GLE, higher than the reported Cmax plasma level (1.11 µg/ml).

Glecaprevir produced no major cardiovascular effects up to 100 mg/kg oral in conscious dogs and up to 0.553 µg/kg/min IV in anaesthetised dogs.

Pibrentasvir produced no significant block (<2%) of hERG tail current at 1.11 µg/ml, higher than the reported Cmax plasma level (0.1 µg/ml), and no major cardiovascular effects up to 100 mg/kg oral in conscious dog, or up to 19 µg/kg/min IV in anesthetized dog.

Respiratory: Glecaprevir and pibrentasvir produced no major respiratory effects up to 60 mg/kg oral in rats or 100 mg/kg oral in mouse, respectively.

Pharmacodynamic drug interactions

See section 2.4.3.

2.3.3. Pharmacokinetics

Methods of analysis

Glecaprevir and pibrentasvir were quantified by high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) in plasma samples of mouse, rat, rabbit, dog and monkey. Metabolites in plasma, urine, faeces, bile, hepatocyte and liver microsomal incubations from mouse, rat and dog ADME (absorption, distribution, metabolism and excretion) studies were separated by HPLC, detected by on-line radioflow detection, identified and structurally elucidated by MS/MS. The bioanalytical methods are considered adequate by CHMP.

Absorption
GLE is rapidly absorbed with Tmax <1h in all species but monkeys (Tmax: 2.8h), with a bioavailability of >90% in rodents, and lower for dogs (44%) and monkeys (26%) and quickly eliminated with a half–life of 1.7-4.3 hours in all species tested (mice, rat, dog, monkey), as compared to 6.6 h in humans. Glecaprevir plasma concentrations in fasted dogs were slightly higher than those obtained in fed animals (solution formulation). No major difference is observed between genders.

PIB is slowly absorbed with Tmax of 3.7-9h in all species, with a bioavailability of <10% in rodents, and slightly higher for dogs (29.8%) and monkeys (14.1%), and quickly eliminated with a half–life of 5.7-12.9 hours in all species tested (mice, rat, dog, monkey), as compared to 14.9h in humans.

Due to the species differences in exposures in rodents, mice have been chosen for multiple dose toxicity studies. After multiple doses, no difference is observed between genders in all species.

Plasma protein binding and blood-plasma ratios
GLE and PIB are highly bound to plasma proteins. Mean blood-to-plasma concentration ratios were 0.64, 0.60, 0.55, 0.75 and 0.57 in mouse, rat, dog, monkey and human, respectively for GLE. Concerning PIB, blood-to-plasma concentration ratios were 0.59, 0.57, 0.66, 0.60 and 0.62 in mouse, rat, dog, monkey and human, respectively.

Tissue distribution
GLE was widely distributed in most tissues with peak levels at 0.5-2 hours, and radioactivity declined to below the limit of quantification at 24h, except in liver (highly distributed: ratio tissue / blood up to 269, and persist up to 96h post dose), large and small intestine. GLE is present in the brain only at 0.5h post dose at very low concentrations, and in eye uveal tract and skin up to 8h post dose even if the radioactivity is low. No major affinity has been observed for tissues containing melanin.

PIB was widely distributed in most tissues with a peak levels at 4-8 hours. Highest concentrations are in bile, adrenal gland, liver and small intestine. Radioactivity declined to below the limit of quantification at 24h, except in the Harderian gland, preputial gland, prostate gland, salivary gland, stomach, thymus,

urinary bladder, cecum/large intestine. PIB is not present in the brain and eye. No major affinity has been observed for tissues containing melanin.

Metabolism / Excretion
GLE is the major component and all metabolites observed in all species are minor. GLE was cleared primarily through the biliary/faecal route in rat, dog and human, with minimal excretion in urine.

PIB is scarcely metabolized in all species, and is eliminated in faeces as unchanged parent drug.

2.3.4. Toxicology

The toxicological profiles of glecaprevir and pibrentasvir have been evaluated in a comprehensive set of non-clinical studies where the compounds have been evaluated separately. The performed studies include repeat-dose toxicity studies up to 6 months in rodents and 9 months in dogs, in vitro and in vivo genotoxicity, male and female fertility and early embryonic development in rodents, embryo-foetal development toxicity in rodents and rabbits, peri- and post-natal development studies in rodents, phototoxicity studies and impurity qualifying studies. In addition, one combination repeat-dose study has also been performed.

The main species for toxicological evaluation were rat and dog for glecaprevir and mouse and dog for pibrentasvir. The test species were justified as the rodent and non-rodent species with the highest systemic exposure. All selected species are considered as relevant from a metabolite perspective.

Both glecaprevir and pibrentasvir are lipophilic, with minimal aqueous solubility and the effect of formulation and dose defined the maximum feasible exposures in all toxicology species.

Single dose toxicity

No single dose toxicity studies were conducted with glecaprevir. One pharmacokinetic study with intravenous administration in rabbits was conducted with pibrentasvir.

Mortality was observed in two rabbits after intravenous administration of pibrentasvir at 50 mg/kg, while a dose of 5 mg/kg was well tolerated. The Applicant appreciated that the pibrentasvir plasma concentrations following the 50 mg/kg dose likely exceeded the 40 µg/mL solubility limit for pibrentasvir in plasma and this may have contributed to the observed mortality.

Repeat dose toxicity

The species selected for the definitive toxicology studies are rats and dogs for glecaprevir and mouse and dogs for pibrentasvir on the basis of similarities in their pharmacokinetic and metabolic profiles to human.

Concerning GLE, repeat-dose toxicity studies were conducted in mice, rats and dogs for up to 4, 26 and 39 weeks, respectively. 8 unscheduled deaths (3, 1, 1, 3 rats in the control group, 10, 40, and 120 mg/kg respectively) have been observed in the 26-weeks rats study.

The toxicological profile of GLE was mainly characterized by gastrointestinal (GI) toxicity associating clinical signs and histological lesions of the stomach (neutrophilic infiltration, ulceration / necrosis) at very high doses in rat (>120 mg/kg from 2 week study), hyperplasia and inflammation with degeneration muscle of oesophagus in mice treated for 4 weeks.

Gastro-intestinal toxicity (faecal effect, infiltration in stomach in some dogs, necrosis muscle in oesophagus in one dog) was also observed in dogs, with gallbladder oedema after 2 and 13 weeks of treatment.

GLE was also characterized by hematologic changes in all species.

GLE has also an impact on AST/ALT and/or GGT in dogs without major histopathologic correlates. No major hepatic findings have been observed in rats but focal mild necrosis of the liver correlating with increased liver enzymes (AST (+9.0-fold) and ALT (+7.7-fold)) in one female treated at the mid dose for 26 weeks in rats, and necrosis in 2 rats at the high dose after 13 weeks.

Concerning PIB, repeat-dose toxicity studies were conducted in mice, rats and dogs for up to 26, 13 and 39 weeks, respectively. Deaths have been observed in all study in mice but the 7-day study.

No major adverse effects have been identified at maximal feasible exposures (8 µg•hr/mL in rat, 123 µg•hr/mL in mouse and 25 µg•hr/mL in dog).

Decreases in absolute reticulocytes (-25% to -62%) in the 39-week study in dog were noted, without concurrent decrease in RBC mass; this was reversible.

Moreover, PIB induced lung adenoma in one male at high dose in 1 month mice study, a benign hepatocellular adenoma in liver and benign bronchiolar-alveolar adenoma in lung in one male at high dose in 26-weeks mice study, mammary adenocarcinoma in one female at high dose in 13-weeks rats study. However, these effects are interpreted as being incidental as they are common background findings in these species.

Due to cardiovascular issues observed with other products indicated for the treatment of HCV, cardiotoxicity with GLE and PIB has been investigated. CHMP noted that neither GLE nor PIB did induce major findings in safety pharmacology studies.

CHMP also noted that some cardiac toxicities have been observed in repeat dose toxicity studies with both substances:

- increase of minimal infiltration mononuclear cell in heart in rats treated for 13-weeks with GLE at the high dose (5M at 120 mg/kg/d versus 3M in control);
- higher incidence of cardiomyopathy in female in rats treated for 26-weeks with GLE at the high dose (9F at 60 versus 4F in control)
- papillary fronds in heart in dogs (1F) treated for 2 weeks with GLE at the low dose
- hyperplasia (1M at 20 mg/kg, 1M 1F at 60mg/kg) and infiltration 1F at 60 mg/kg in heart in dogs treated for 13 weeks with GLE at lower doses.
- higher incidence of sinus bradycardia and Second degree AV block in dogs treated for 39 weeks with GLE at high doses. Moreover potassium level have been decreased by GLE in rat treated for 26 weeks (-15% to -16% in M), and in 4-weeks study with the combination GLE/PIB (-19% in M).
- cardiomyopathy in mouse treated for 14 days with PIB at the high dose (1M);
- cardiomyopathy in a mouse treated for 26weeks with PIB at the high dose (1M). It could be noted that this mouse died with unknown cause and likely associated with oral gavage and/or animal handling procedures according the applicant). Moreover, another mouse in this study was euthanized due to dosing injury with foreign material, bacterial colonies, adhesion/inflammation/fibrosis in heart.
- fibrosis in heart in rat treated for 13 weeks with PIB at the high dose (2M)
- ectopic tissue in dog treated for 13 weeks with PIB at the high dose (1M)
- hyperplasia in dog treated for 39 weeks with PIB at the low dose (1F)

Due to the low incidence of each of these effects, not always dose responsive, no significant signal is raised and clinical data will be scrutinized.

Oral administration of a combination of GLE/PIB at 12.5/20 mg/kg/day for 1 month was well tolerated in rats and did not result in any signs of toxicity, especially major concerns about hematologic risk.

Genotoxicity

Glecaprevir and pibrentasvir genotoxicity was negative in *in vitro* (gene mutations in bacteria and mammalian chromosome aberration assays) and *in vivo* (micronucleus assay) GLP genotoxicity studies. CHMP concluded that both glecaprevir and pibrentasvir are non-genotoxic.

Carcinogenicity

Because the duration of treatment with glecaprevir/pibrentasvir is less than 6 months, and because genotoxicity studies and repeat-dose toxicity did not reveal any concern, no carcinogenicity study has been performed.

As per the Maviret SmPC, the maximal treatment duration is 16 weeks. Maviret is not recommended for the re-treatment of patients with prior exposure to NS3/4A- and/or NS5A-inhibitors.

Reproduction and developmental toxicity

In rats, GLE did not affect fertility or early embryonal development at up to 120 mg/kg/day (137x or 63x the 300mg human clinical exposure based on AUC in HCV-infected subjects without cirrhosis or HCV-infected subjects with cirrhosis respectively).

In mice, PIB did not affect fertility or early embryonal development at up to 100 mg/kg/day (100x the 120 mg human clinical exposure based on AUC in HCV-infected subjects without and with cirrhosis) but an increase of Pre (2.1-2.6% versus 0.4% in control) and post (5.9-8% versus 2% in control) implantation loss in all treated animals. However these implantation losses are within the range of historical data.

GLE was shown to be devoid of embryo-foetotoxic or teratogenic potential in rats at up to 120 mg/kg/d [safety margin of 116x or 53x the 300mg human clinical exposure based on AUC in HCV-infected subjects without cirrhosis or HCV-infected subjects with cirrhosis respectively]. However, in rabbit maternal toxicity [clinical findings (abnormal faecal findings, decreased and discoloured urine, anogenital hair discoloured brown, and thin body appearance), lower body weights] and embryofoetotoxicity [early delivery, 1 animal with all resorbed foetuses and an increase of post-implantation loss (early, late, and combined), Mean foetal body weights decreases (13% to 21% less)] have been observed at an estimated mean AUC (the only toxicokinetic sample collection conducted was on GD 7 due to excessive toxicity) lower than the 300 mg human clinical exposure. In the main study in rabbit, only 2 doses (20 and 60 mg/kg) have been studied due to toxicity observed in the previous study. The applicant concluded that GLE was not teratogenic at the dose levels evaluated due to the fact that visceral/skeletal malformations / variations observed in the treated groups were observed at a low incidence, not dose responsive, similar incidence in control or/and were within recent historical control data for this laboratory.

However, this conclusion was considered questionable by CHMP due to the fact that the exposure at the high dose tested is lower than the 300mg human clinical exposure.

Moreover, some variations have been observed only at the high dose: Caudal vertebra - Centra hemicentric in 2 foetuses (1.3% foetuses; 12.5% litters) and no such variation has been observed in historical data.

It could also be noted that despite the variations/malformations are within historical data, sternum misaligned, ribs fused, skull nasal bone (Additional ossification), thoracic vertebra (centra fused), gallbladder smaller than normal, kidney (increased renal pelvic cavitation), kidney (malpositioned, malrotated), aortic arch dilatated in thoracic cavity are observed in several foetuses only at high doses (and none in control).

Despite the fact that variation/malformation concerned only 1 animal/group, some variation/malformation have been observed only at treated animals and at a higher proportion of that seen on historical data (caudal vertebra- vertebra(e), hemivertebra(e); cervical neural arch(es), additional ossification centre; thoracic vertebra(e)- neural arch(es) misshapen; skull- frontal bone, Additional ossification centre). Therefore the embryofoetal toxicity risk cannot be fully characterized, but the Maviret SmPC takes into account the low exposure of GLE in rabbit as explained by the CHMP scientific advice in 2015, and the embryofoetotoxicity observed on DRF and main studies (post-implantation loss and variation / malformation).

PIB was shown to be devoid of embryo-foetotoxic or teratogenic potential in mouse at dose up to 100 mg/kg [safety margin of 50x the 120 mg human clinical exposure based on AUC in HCV-infected subjects with and without cirrhosis].

In the main study in rabbit, the applicant concluded that PIB was not teratogenic at the dose levels evaluated due to the fact that Visceral/skeletal malformations / variations observed in the treated groups were observed at a low incidence, not dose responsive, similar incidence in control or/and were within recent historical control data for this laboratory.

For PIB, exposures in embryofoetal development studies were sufficient to characterize the embryofoetal risk.

No major effect has been observed in rats treated with GLE in the prenatal and postnatal development studies in rats. Concerning PIB, it could be noted that viability index was decreased at the mid dose (10 mg/kg) for litter of F0, and the percentage of post-implantation loss was increased at high dose for litter of F1. However, it is noted that the increase of pre- (2.1-2.6% versus 0.4% in control) and post- (5.9-8% versus 2% in control) implantation loss observed in all treated animals in fertility study in mice were within the range of historical data. Therefore it could be concluded by CHMP that no major effect has been observed in mice treated with PIB.

Toxicokinetic data

Toxicokinetic assessment of glecaprevir and pibrentasvir was included in all toxicology studies conducted in mice, rats, dogs and rabbits. Toxicokinetic parameters (AUC, Cmax and Tmax) were determined in pivotal GLP-compliant repeated dose toxicity studies using validated analytical methods. Adequate plasma exposure for glecaprevir and pibrentasvir was reached in all species used for evaluation of general toxicity.

Local Tolerance

No separate local tolerance studies were conducted with GLE/PIB. Since the intended therapeutic route is oral, local tolerance can be evaluated within the frame of general toxicity studies. In repeat dose toxicity studies with GLE, erosions/ulcerations and inflammation in the stomach occurred in rats, most likely reflecting high local concentrations of the test compound with associated local irritative effects. No risk has been identified for PIB.

Immunotoxicity

Based on the lack of GLE or PIB-related changes in haematology, immune organ weights or histopathology, serum globulins or increased incidence of infections, the weight of evidence from repeated dose toxicology studies of up to 26 weeks' duration in mice / rats or 39 weeks' duration in dogs do not indicate an effect of GLE and PIB on the immune system.

Impurities

The initial assessment risk concerning acetamide, a product of hydrolysis of acetonitrile used in chemical syntheses of GLE and PIB and considered as possibly carcinogenic to humans (Group 2B) by IARC was not acknowledged. In the response to the CHMP concern, the applicant committed to control acetamide levels. CHMP agreed with the Applicant's proposal, but requested a confirmation of compliance with this limit through a post-authorisation measure.

Other toxicity studies

Glecaprevir absorbed light in the range of 290 to 350 nm and exhibits photo instability to UV-visible light in aqueous solutions at neutral pH. Despite the fact that GLE is not very well distributed to the skin and eye (tissue/plasma ratios for skin and eye <1), phototoxicity test have been performed. Glecaprevir was positive in the in vitro 3T3 test, but was considered by the applicant as negative in an in vivo assay in pigmented rats. However, it could be noted that focal retinopathy and corneal dystrophy in one or both eyes have been observed in all groups but the comparator article (8-MOP). Moreover corneal dystrophy appears in animals regardless of UVR exposure. The applicant explained these effects as a known occurrence, related to the UVR exposure process for retinopathy, and not an adverse response to GLE administration and UVR exposure due to the low distribution in eye, the absorb light below 400 nm and the diffuse corneal oedema in rats treated with positive control that could prevent detection of regions of corneal dystrophy / retinopathy.

PIB absorbed light in the range of 254 to 289 nm, was negative in the *in vitro* 3T3 test, and therefore has not a potential for phototoxicity.

CHMP agreed that no juvenile animal data were needed, as the product will be indicated in adults only.

2.3.5. Ecotoxicity / environmental risk assessment

Table 7 Summary of main study results

Substance (INN / Invented Name): GLE			
CAS-number (if available): 1838572-01-2 (hydrate)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or … shake-flask method	The n-octanol-buffer distribution coefficient, logD, at pH 7.4 and 25°C: 2.48	Potential PBT: No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	na	B/not B
	BCF	na	B/not B
Persistence	DT50 or ready biodegradability	Na	P/not P
Toxicity	NOEC or CMR	na	T/not T
PBT-statement :	The compound is not considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined		1.5 µg/L	> 0.01 threshold

(e.g. prevalence, literature)					
Other concerns (e.g. chemical class)		pKas : 4.0 ± 0.0 (ionization of the sulfonamide) 11.7 ± 0.0 (ionization of the carbamate nitrogen) Water solubility : 343 ± 12 µg/mL			
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Koc values for soil ranged from 1,243 to 2,506 L/kg The Koc values determined for sludge in this study ranged from 211 to 605 L/kg.			Tier B terrestrial studies were not triggered for GLE.
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	The GLE outcomes from Brandywine Creek were: # GLE - Whole system DT50: 42.1d (20°C) # GLE - Water phase DT50: 25.5d (20°C) # GLE - AR% in water: 77.4% (d0) to 1.4% (d100). # GLE - AR% in sediment: 18.7% (d0) to 65.1% (d100). # GLE - AR% in gas trap (CO2): <1.1% (d100). # MRT45 - AR% in water: < LOD (d0) to peak 6.6% at (d50) and then <LOD (d100). # MRT45 - AR% in sediment: < LOD (d0) to 17.3% (d100). The GLE outcomes from Choptank River were: # GLE - Whole system DT50: 52.5d (20°C) # GLE - Water phase DT50: 39.5d (20°C) # GLE - Total AR% in water: 71.9% (d0) to 9.3% (d100). # GLE - Total AR% in sediment: 21.2% (d3) to 71.7% (d100). # GLE - Total AR% in gas trap (CO2) after d100: <1.1%. # MRT45 - Total AR% in water: < LOD (d0) to peak 5.8% (d50) and then 5.1% (d100). # MRT45 - Total AR% in sediment: < LOD (d0) to 12.3% (d100). # MRT43 - Total AR% in water: < LOD (d0) to 7.1% (d100). # MRT43 - Total AR% in sediment: < LOD (d0) to 6.7% (d100).			**The applicant has not corrected the DT50 estimates for the recommended temperature (12°C) and is therefore requested to do so post-approval.**
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC for average growth rate NOEC yield	40.6	mg/L	PECsw/PNECw (daphnia) = 0.0031 (<1) No further study

			16.9		needed
Daphnia sp. Reproduction Test	OECD 211	NOEC (Survival) NOEC (Reproduction) NOEC (Growth) LOEC (Survival) LOEC (Reproduction) LOEC (Growth) EC50 (Survival) EC50 (Reproduction) EC50 (Growth)	4.91 4.91 4.91 9.98 > 4.91 > 4.91 > 9.98 > 9.98 > 9.98	mg/L	PECsw/PNECw (daphnia) = 0.0031 (<1) No further study needed
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	10.2	mg/L	PECsw/PNECfish =0.001 (<1) No further study needed
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>1,000	µg/L	PEC/PNECsludge = 0.000015 (<0.1) No further study needed
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism		NOEC		mg/kg	Species
Sediment-Water Chironomid Toxicity Test Using Spiked Sediment	OECD 218				**Study ongoing.**

Substance (INN/Invented Name): PIB			
CAS-number (if available): 1353900-92-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or … shake-flask method	logD at pH 7.4 and 25°C: 7.47 using the shake-flask method	Potential PBT: Yes
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	Ongoing		
Phase I			

Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)		0.6 µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)		pKa : 3.5 ± 0.1 (ionization of benzimidazole rings) 4.1 ± 0.2 (ionization of benzimidazole rings) 11.6 ± 0.2 (ionization of carbamate nitrogen)			
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Kd: ranged from 123 to 577 for the soils Kd: ranged from 6813 and 21522 for the sewage sludge. Koc values ranging from 3325 to 12168 for the soils and were 13990 and 48040 for the sewage sludge.			The Koc values indicate that PIB has a high or very high potential for binding to the solids tested
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308				**Study ongoing.**
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella Subcapitata*	OECD 201	NOEC	0.0044	Mg/L	PECsw/PNECw = 0.8 (<1) No further study needed
Daphnia sp. Reproduction Test	OECD 211				**Study ongoing.**
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210				**Study ongoing.**
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>1,000	mg/L	PEC/PNECsludge = 0.000006 (<0.1) No further study needed
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	Scheduled Study
Aerobic and anaerobic transformation in soil	OECD 307	DT50 %CO_2			Scheduled Study
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	Scheduled Study
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	Scheduled Study
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	Scheduled Study
Collembola, Reproduction Test	OECD 232	NOEC		mg/kg	Scheduled Study
Sediment dwelling organism		NOEC		mg/kg	
Sediment-Water Chironomid Toxicity Test Using Spiked Sediment	OECD 218				Study ongoing.

The available data did not allow CHMP to conclude definitively on the potential risk of GLE and PIB to the environment and the final data need to be submitted post-approval.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation to be addressed and the following final data to be submitted:

Glecaprevir:

- sediment-water chironomid toxicity test using spiked sediment OECD 218

The OECD TG308 issue remains to be fully resolved until the DT50 estimated have been temperature corrected in the study report and/or ERA.

Pibrentasvir:

- Aerobic Transformation in Aquatic Sediment Systems OECD 308

- Daphnia magna Reproduction Test OECD 211

- Fish, Early-Life Stage Toxicity Test OECD 210

- Bioaccumulation in Fish: Aqueous and Dietary Exposure OECD 305

- sediment-water chironomid toxicity test using spiked sediment OECD 218,

- Aerobic and Anaerobic Transformation in Soil OECD 307

- Soil Microorganisms: Nitrogen Transformation Test OECD 216

- Terrestrial Plant Test: Seedling Emergence and Seedling Growth Test OECD 208

- Earthworm, Acute Toxicity Tests OECD 207

- Collembolan Reproduction Test in Soil OECD 232

CHMP clarified that, depending on the results of these studies and as per the current guideline, other tests may need to be requested in the future.

2.3.6. Discussion on non-clinical aspects

Pharmacology

Pharmacological characterisation of glecaprevir, an NS3/4A protease inhibitor, and pibrentasvir, an NS5A inhibitor, has shown potent activity in the low nanomolar or picomolar range, respectively against all major HCV genotypes (GT1-6). No secondary pharmacological targets were identified in the *in vitro* screening for off-target activity and there were no safety issues identified in the non-clinical safety pharmacology studies. Consequently, no additional non-clinical investigations are considered necessary by CHMP.

Pharmacokinetics

The non-clinical pharmacokinetic profiles of glecaprevir and pibrentasvir are in general considered to have been adequately characterized. Rats and dogs were chosen by the Applicant as target species for the toxicology studies of glecaprevir whereas mice and dogs were chosen as target species for the toxicology studies of pibrentasvir due to similar elimination and metabolic profiles as in humans. There are essentially no metabolites present in human plasma after treatment with glecaprevir or pibrentasvir (none of the metabolites were over 10% of total drug related material and were classified as minor metabolites in accordance with relevant guidelines), i.e. there is no need for qualification of metabolites in non-clinical toxicity studies. No rabbit specific metabolites of glecaprevir or pibrentasvir were detected in rabbit liver microsomes justifying the use of rabbit for the embryo-foetal developmental.

Toxicology

The toxicology documentation for glecaprevir and pibrentasvir was considered comprehensive by CHMP, and studies in general have been conducted in accordance with relevant guidelines and GLP. It was noted

that the Applicant had sought scientific advice for the non-clinical program, and followed the recommendations received. In the repeat-dose toxicity studies with each compound, no target organs of toxicity were identified. The combination study did not reveal any new or additive toxicity at AUC exposures corresponding approximately to the intended clinical exposure. For glecaprevir, maximum achieved plasma exposures in the longest duration studies were 735 and 1440 µg·hr/mL for the rat and dog, respectively. These AUC exposures correspond to 153/70-fold and 300/137-fold the clinical AUC exposure in non-cirrhotic/cirrhotic patients, respectively. For pibrentasvir, maximum achieved plasma exposures in the longest duration studies were 123 and 25 µg·hr/mL for the CD-1 mouse and dog, respectively. These AUC exposures correspond to 85-fold and 17-fold the clinical AUC exposure in patients, respectively.

Reproductive toxicity

In the reproductive and developmental toxicology program, there were no test item-related findings in any of the fertility studies with glecaprevir and pibrentasvir at 137/63-fold the clinical AUC exposure in non-cirrhotic/cirrhotic patients for glecaprevir and 100-fold the clinical AUC exposure for pibrentasvir.

In animals reproduction studies, no adverse developmental effects were observed when the components of glecaprevir/pibrentasvir were administered separately during organogenesis at exposures up to 53 times (rats; glecaprevir) or 50 times (mice; pibrentasvir) higher than the human exposures at the recommended dose of glecaprevir/pibrentasvir. In rabbit, due to maternal toxicity, even though adequate doses were tested, maximal exposure could not be achieved to fully characterize the reproductive toxicity of pibrentasvir and of glecaprevir at clinical exposures (0.07 times for glecaprevir and 1.5 times for pibrentasvir). Moreover, embryo-foetal loss has been observed in the rabbit with glecaprevir, which precluded evaluation of glecaprevir at clinical exposures in this species. For PIB, exposures in embryofoetal development studies were sufficient to characterize the embryofoetal risk. *Overall,* while the systemic exposure in the GLE rabbit EFD studies was low, it is acknowledged that studies in rabbits and rats with GLE do not indicate direct significant harmful effects with respect to reproductive toxicity. Finally there was no significant harmful effect with either compound in rodent peri-/postnatal developmental studies in which maternal systemic exposures (AUC) to glecaprevir and pibrentasvir were approximately 47 and 74 times higher, respectively, than the exposure in humans at the recommended dose. Overall, given that there was some degree of uncertainty on the rabbit data for GLE, as a precautionary measure CHMP agreed that Maviret is not recommended to be used in pregnancy. This information is considered adequately reflected in the Maviret SmPC.

Genotoxicity/carcinogenicity

Glecaprevir and pibrentasvir genotoxicity was negative in *in vitro* (Gene mutations in bacteria and mammalian chromosome aberration assays) and *in vivo* (micronucleus assay) GLP genotoxicity studies. The applicant argued that taking into account the fact that the duration of treatment with glecaprevir/pibrentasvir is less than 6 months, and that genotoxicity studies and repeat-dose toxicity did not reveal any concern, no carcinogenicity study was required and therefore no carcinogenicity was performed. CHMP acknowledged that the maximal duration will be 16 weeks, Maviret is not recommended for the re-treatment of patients with prior exposure to NS3/4A- and/or NS5A-inhibitors. This has been reflected in the Maviret SmPC.

Ecotoxicology

Some data on the ERA were provided by the applicant, however, due to several missing studies (which have been requested to be submitted post-approval), a full environmental risk assessment of glecaprevir and pibrentasvir is not possible at the present time.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical dossier is considered comprehensive and studies in general have been conducted in accordance with relevant guidelines and GLP. The Applicant has sought scientific advice for the non-clinical program, and followed the recommendations received.

The non-clinical part of the dossier is considered to be sufficient. No major deficiencies have been identified. CHMP nevertheless agreed that the outstanding issues regarding the environmental risk assessment need to be addressed post-approval by the applicant for both compounds.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study	Description
ADME Studies	
M13-890	ADME study (GLE, PIB)
Ascending Dose Studies	
M13-356	SAD, MAD, food-effect, and ritonavir DDI study (GLE)
M13-355	SAD, MAD, food-effect, and ritonavir DDI study (PIB)
M13-586	GLE and PIB coadministration DDI study; PIB and paritaprevir/ritonavir DDI study
M14-716	GLE and PIB coadministration
Bioavailability Studies	
M14-711	GLE/PIB Phase 3 tablet food-effect study
Intrinsic Factor Studies	
M15-432	GLE 100 to 300 mg and PIB 80 to 120 mg coadministration in Han Chinese, Japanese, and Caucasian subjects
M14-066	GLE 700 mg and PIB 160 mg coadministration in Han Chinese, Japanese, and Caucasian subjects
M13-604	Hepatic impairment study
M13-600	Renal impairment study
Mechanism-Based Drug-Drug Interaction Studies	
M13-605, Arm 1	CYP1A2 (caffeine), CYP2D6 (dextromethorphan), CYP3A (midazolam), CYP2C19 (omeprazole) and CYP2C9 (tolbutamide) cocktail DDI study with GLE 300 mg + PIB 120 mg
M14-380	CYP1A2 (caffeine), CYP2D6 (dextromethorphan), CYP3A (midazolam), CYP2C19 (omeprazole) and CYP2C9 (tolbutamide) cocktail DDI study with GLE 700 mg + PIB 160 mg
M13-582	P-gp substrate (digoxin)

M13-585	P-gp substrate (dabigatran etexilate); UGT1A4 substrate (lamotrigine)
M14-724	P-gp/CYP3A inducer (carbamazepine)
M14-723	P-gp/CYP3A inducer and OATP inhibitor (rifampin)
Drug-Drug Interaction Studies with Commonly Coadministered Drugs	
Calcium Channel Blockers	
M13-578	Felodipine; amlodipine
Angiotensin Receptor-II Blockers	
M13-599	Losartan; valsartan
Oral Contraceptives	
M13-598	Ethinyl estradiol (EE)/norgestimate; norethindrone; EE/levonorgestrel
Statins	
M13-579	Pravastatin; rosuvastatin; atorvastatin
M14-721	Simvastatin; lovastatin
Acid-Reducing Agents	
M14-715	Omeprazole

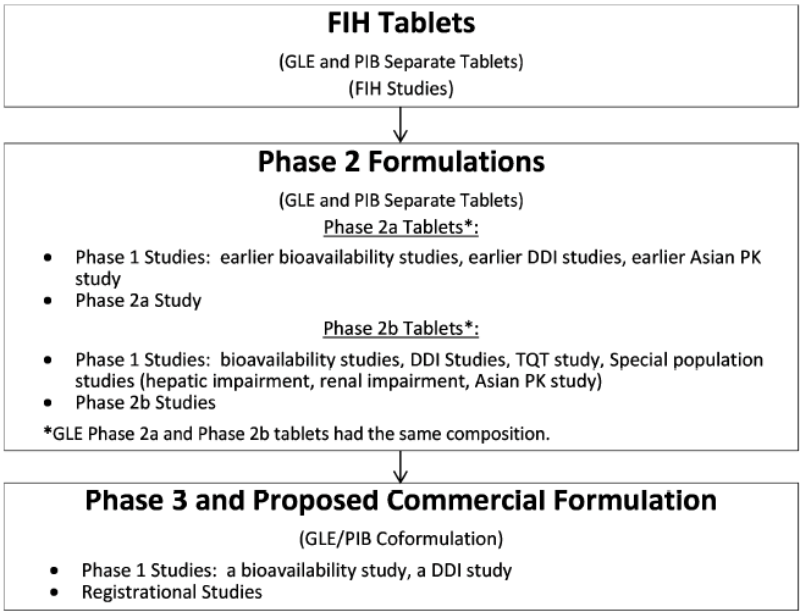
Study	Description
Opioid Replacement Therapy	
M13-602	Methadone; buprenorphine/naloxone
Immunosuppressants	
M13-584	Cyclosporine (Cyclosporine A [CsA]) 100 mg
M13-605, Arm 2	CsA 400 mg
M13-592	Tacrolimus
Human Immunodeficiency Virus (HIV) Drugs	
M13-593	Raltegravir
M13-577	Darunavir and ritonavir; rilpivirine
M13-587	Lopinavir/ritonavir
M13-603	Atazanavir and ritonavir
M13-597	Efavirenz/emtricitabine/tenofovir disoproxil fumarate
M15-584	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; abacavir/dolutegravir/lamivudine
HCV Drugs	
M14-532	Sofosbuvir
Pharmacodynamic Study	
M15-543	Thorough QT

2.4.2. Pharmacokinetics

2.4.2.1. PK properties

Chemical considerations

Several formulations of GLE and PIB (as separated or combined tablets) were used during the clinical development of GLE/PIB: the FIH formulation, Phase 2a and Phase 2b separated tablets of GLE and PIB, and the combined Phase 3 tablet of GLE/PIB 100/40 mg (used in the all Phase 3 studies).



Furthermore, additional GLE and PIB formulations were evaluated in bioavailability and ADME studies, but were not developed further.

Given the low permeability and solubility in aqueous media of GLE and PIB (both BCS Class 4), no parenteral formulations were developed.

GLE and PIB exhibit several asymmetric carbons are both enantiomers and a unique enantiomer was selected (for each active entity) for clinical development.

Absorption

Several formulations of GLE and PIB (as separated or combined tablets) were used during the clinical development of GLE/PIB. As regards to the absorption properties of the fixed dose combination GLE/PIB (corresponding to the tablet used in all the Phase 3 studies and submitted within this MAA procedure), it could be noted that this tablet should be administered with food to maximize GLE and PIB exposures and reach plasmatic concentrations equivalent to those measured with separated tablets of GLE and PIB used in phase 2 studies under fasting condition. Overall, food increased exposures of both GLE and PIB. Following moderate and high-fat breakfast, GLE exposures increased to 1.8- to 3.2-fold, and PIB exposures were increased to 1.4- to 2.1-fold of those under fasting conditions. Fat or calorie content had limited impact on exposures of GLE and PIB.

After single oral doses of GLE/PIB 300 mg/120 mg co-formulated Phase 3 tablets in the non-fasting state, GLE and PIB Tmax in plasma was around 5.0 hours.

GLE is a substrate and inhibitor of P-gp, BCRP, OATP1B1, and OATP1B3, greater than dose-proportional increases in GLE exposure may relate to GLE mediated inhibition of these transporters. PIB is a substrate for efflux transporters P-gp and/or BCRP. When GLE 300 mg QD and PIB 120 mg QD are coadministered, the GLE exposure remains similar (17% difference). However, the coadministration of PIB with GLE saturates intestinal P-gp and BCRP transporters and increases the bioavailability of PIB, leading to an increasing PIB exposure approximately three times that of PIB alone.

Distribution

GLE and PIB are mainly bound to human plasma proteins (respectively 97.5% and >99.9%) regardless of their concentrations (ranging from 0.1 to 30 µM). The unbound fraction of GLE and PIB in human plasma was similar between HCV-negative subjects with different degrees of renal and hepatic impairment and healthy subjects, except for subjects with severe hepatic impairment where the unbound glecaprevir fraction was significantly increased relative to healthy subjects.

GLE and PIB were not preferentially distributed into red blood cells with a mean human blood-to-plasma ratio of 0.57 and 0.62, respectively.

Elimination

Metabolism

In vitro, GLE exhibited limited metabolism, predominantly by CYP3A4/5 and to a much less extent by CYP2D6, 2C9, and 2C8. PIB is not significantly metabolized in vitro. In healthy male subjects, unchanged GLE and PIB were the only radiochemical component of drug related materials in plasma following administration of [14C]GLE and [14C]PIB. Overall, GLE and PIB are not significantly metabolized and exposure to metabolites is marginal, with no major metabolite (>10% of total drug) identified.

Excretion

The majority (>90%) of the plasmatic unchanged GLE and PIB is excreted in faeces. The renal clearance of GLE and PIB is negligible, with no PIB and <1% of GLE detected in urine.

The t1/2 of GLE 300 mg coadministered with PIB 120 mg following multiple QD doses was 6 to 9 hours.

The t1/2 of PIB 120 mg coadministered with GLE 300 mg following multiple QD doses was 23 to 29 hours.

Dose proportionality and time dependencies

Linearity

Following single and multiple doses in healthy subjects, GLE and PIB exposure exhibited greater than dose-proportional increase:

Table 8 GLE multiple dose pharmacokinetics (study M13-356)

Pharmacokinetic Parameters (units)	GLE Regimens, Day 10 Geometric Mean (Mean, %CV)		
	200 mg QD (N = 8)	400 mg QD (N = 8)	800 mg QD (N = 8)
C_{max} (ng/mL)	137 (148, 44)	1810 (2610, 100)	14100 (17200, 52)
T_{max}[a] (h)	3.0 (1.0 – 5.0)	4.0 (3.0 – 5.0)	4.0 (3.0 – 5.0)
C_{trough} (ng/mL)	1.04 (1.14, 39)	4.98 (7.88, 130)	40.9 (58.2, 80)
AUC_{24} (ng•h/mL)	556 (565, 19)	5980 (8840, 113)	64100 (80400, 54)
C_{max}/Dose (ng/mL/mg)	0.68 (0.74, 44)	4.53 (6.52, 100)	17.6 (21.5, 52)
AUC_{24}/Dose (ng•h/mL/mg)	2.78 (2.83, 19)	15.0 (22.1, 113)	80.1 (100, 54)
AUC R_{ac}[b]	0.95 [0.88 – 1.30]	1.14 [0.76 – 1.31]	1.81 [0.72 – 3.66]

a. Median (minimum through maximum).

b. R_{ac} = Accumulation ratio (calculated as the ratio of AUC_{24} on Study Day 10 to Study Day 1). Median and range are presented.

Table 9 PIB multiple dose pharmacokinetics (study M13-355)

Pharmacokinetic Parameters (units)	PIB Regimens, Day 10 Geometric Mean (Mean, %CV)			
	30 mg QD (N = 7)	60 mg QD (N = 7)	180 mg QD (N = 8)	600 mg QD (N = 8)
C_{max} (ng/mL)	9.17 (9.68, 34)	27.0 (31.0, 56)	115 (123, 38)	312 (324, 26)
T_{max} [a] (h)	5.0 (1.0 – 5.0)	5.0 (2.0 – 5.0)	5.0 (3.0 – 5.0)	5.0 (4.0 – 5.0)
C_{trough} (ng/mL)	0.64 (0.68, 32)	2.31 (2.47, 40)	9.97 (12.9, 84)	26.5 (27.6, 28)
AUC_{24} (ng•h/mL)	52.1 (54.5, 33)	162 (180, 49)	786 (881, 52)	2090 (2170, 27)
C_{max}/Dose (ng/mL/mg)	0.31 (0.32, 34)	0.45 (0.52, 56)	0.64 (0.69, 38)	0.52 (0.54, 26)
AUC_{24}/Dose (ng•h/mL/mg)	1.74 (1.82, 33)	2.70 (3.00, 49)	4.37 (4.89, 52)	3.48 (3.61, 27)
AUC R_{ac} [b]	1.53 [0.98 – 2.46]	1.32 [0.73 – 2.61]	1.38 [1.15 – 1.98]	1.33 [1.11 – 1.68]

a. Median (minimum through maximum).

b. R_{ac} = Accumulation ratio (calculated as the ratio on Study Day 10 to Study Day 1); mean and range (minimum to maximum) are presented.

Time dependency

When coadministered, both GLE and PIB reached steady-state within 5-6 days. With the GLE 400 mg QD + PIB 120 mg QD combination, after seventh day of dosing relative to the first, GLE Cmax and AUC24 were similar (≤ 23% difference) and C24 was higher (↑ 49%), and PIB exposures were higher (↑ 27% AUC24, ↑ 113% C24).

Variability

GLE has high variability in Cmax and AUC (ranged from 54% – 98% and 49% – 77%, respectively). PIB has moderate to high variability in Cmax and AUC (ranged from 25% – 60% and 26% – 64%, respectively). Presence of food has minimal impact on the variability of GLE and PIB exposure. Intra-individual variability was not discussed by the Applicant.

2.4.2.2. Population PK analysis

GLE and PIB PK profiles were mainly characterized in healthy subjects with the separated tablet formulations. In HCV patients, PK data were collected by sparse sampling from four phase 2 and six phase 3 studies and analysed using a population PK (PPK) approach. In total, 21866 plasma concentrations for GLE (from 2710 subjects) and 22013 plasma concentrations for PIB (from 2704 subjects) were included in the PopPK analysis. The majority of the subjects (89%) included in the pharmacokinetic analysis received GLE 300 mg and PIB 120 mg dose.

With regard to the population PK analysis, GLE and PIB plasma concentration-time data were described by a two-compartment model with first-order absorption and elimination and inter-individual variability in key pharmacokinetic parameters CL/F (GLE and PIB) and V2/F (PIB only). The base models accounted for dose and presence of cirrhosis on GLE, and the effect of coadministration with GLE on PIB. Final models that included intrinsic and extrinsic covariates are as follows:

Table 10 Population PK model: Effect of Covariates

DAA	Parameter (Unit)	Parameter Estimate (95% CI)	Covariate Effect(s)
GLE	CL/F (L/day)	1150 (1060, 1260)	Moderate and severe renal impairment: ↓ 29% End-stage renal impairment: ↓ 47% Female: ↓ 19% Presence of cirrhosis: ↓ 24% Age 55 ± 10 years: ↓ 5% Opioid usage: ↓ 10%
	V2/F (L)	130 (115, 144)	--
	F1	1[a]	Presence of cirrhosis: ↑ 54% Phase 3-formulation: ↓ 26% PPI high dose: ↓ 42%
	Ka (1/day)	8.63 (8.13, 9.16)	--
PIB	CL/F (L/day)	6340 (6000, 6680)	Moderate and severe renal impairment: ↓ 8% End-stage renal impairment: ↓ 35% Female: ↓ 22% Asian Race: ↓ 19% Presence of cirrhosis: ↓ 9% Age 55 ± 10 year: ↓ 2%
	V2/F (L)	1380 (1260, 1500)	Body weight 80 ± 10 kg: ↑ 7%
	F1	1[a]	GLE coadministration: ↑ ~3-fold Phase 3-formulation: ↓ 16% BCRP inhibitors: ↑ 13%
	Ka (1/day)	6.13 (5.77, 6.50)	--

a. Relative bioavailability (F1) fixed to 1 for reference doses of GLE 300 mg or PIB 120 mg.

Based on the individual model-predicted AUC24,ss for subjects receiving the proposed GLE/PIB 300 mg/120 mg regimen, impacts of covariate on GLE and PIB exposures are as follows:

Table 11 Impact of covariates on GLE and PIB pharmacokinetic exposures

DAA	Covariate	Covariate Effect on $AUC_{24,ss}$
GLE	Bodyweight, BMI and BSA:	No significant impact.
	Age:	32% higher exposures for 10-year increase in age (65 years versus 55 years).
	Sex:	39% higher exposures in females.
	Race:	No significant impact.
	Cirrhosis status:	2.2-fold exposure in subjects with cirrhosis.
	Renal function:	55% higher exposure in moderate or severe renal impairment, and 86% higher exposure in end stage renal disease. Dialysis has no impact on GLE pharmacokinetics.
	Co-medications:	5% lower exposure in subjects who took high dose PPIs (omeprazole 40 mg QD equivalent or higher). 16% higher exposure in subjects who took opioid medications.
PIB	Bodyweight, BMI and BSA:	3% decreased exposures for 10-kg increase in bodyweight (90 kg versus 80 kg).
	Age:	13% higher exposures for 10-year increase in age (65 years versus 55 years).
	Sex:	37% higher exposures in females.
	Race:	26% higher exposures in Asians.
	Cirrhosis status:	7% higher exposure in subjects with cirrhosis.
	Renal function:	13% higher exposure with moderate or severe renal impairment, and 54% higher exposure with end stage renal disease. Dialysis has no impact on PIB pharmacokinetics.
	Co-medications:	27% higher exposure in subjects who took BCRP inhibitors.

The estimated exposures in HCV-infected subjects with or without cirrhosis are as follows:

Table 12 GLE 300 mg QD and PIB 120 mg QD multiple dose exposures in healthy and HCV-infected subjects without cirrhosis

DAA	Pharmacokinetic Parameters (unit)	Healthy Subjects[a] (N = 230)	HCV-Infected Subjects Without Cirrhosis (N = 1804)[b]	HCV-Infected Subjects with Cirrhosis (N = 280)[b]
GLE	C_{max} (ng/mL)	1230 (598 to 3550)	597 (150)	1110 (78)
	$AUC_{24,ss}$ (ng•h/mL)	4380 (2380 to 12100)	4800 (198)	10500 (93)
PIB	C_{max} (ng/mL)	295 (193 to 457)	110 (49)	111 (44)
	$AUC_{24,ss}$ (ng•h/mL)	2170 (1450 to 3980)	1430 (63)	1530 (54)

a. Overall geometric mean and range of geometric from individual studies or study arms.

b. Geometric mean (CV%) of individual subject-estimated C_{max} and AUC values.

Finally, the fact GLE and PIB are mutually interacting and that their PK is not linear raises some issues on the level of confidence derived from the PKPOP analyses.

2.4.2.3. Intrinsic factors

Body weight

The effect of weight on GLE and PIB exposure in HCV-infected subjects was evaluated using the population PK analysis. In the final model, weight was identified as significant covariate for PIB PK parameters: Increased weight was associated with increased PIB distribution volume (↑ 7% per 10 kg), resulting in lower exposure (approximately 3% decreased exposure per 10 kg). This was not considered clinically significant by CHMP. Weight was not a significant covariate for GLE PK parameters.

Sex

Effect of sex on GLE and PIB exposure in HCV-infected subjects was evaluated using PPK analysis. In the final model, sex was identified as significant covariate for GLE and PIB PK parameters: females had lower apparent clearance of GLE (↓ 19%) and PIB (↓ 22%) compared to males, resulting in higher exposure of GLE (↑ 39%) and PIB (↑ 37%) in females. However, this was not considered clinically significant by CHMP.

Age

Effect of age on GLE and PIB exposure in HCV-infected subjects was evaluated using PPK analysis. In the final model, age was identified as significant covariate for PIB PK parameters: Increased age was associated with a lower apparent clearance of GLE (↓ 5% per 10 years) and PIB (↓ 2% per 10 years), resulting in higher exposure of GLE (↑ 32% per 10 years) and PIB (↑ 13% per 10 years). However, this was not considered clinically significant by CHMP.

Race

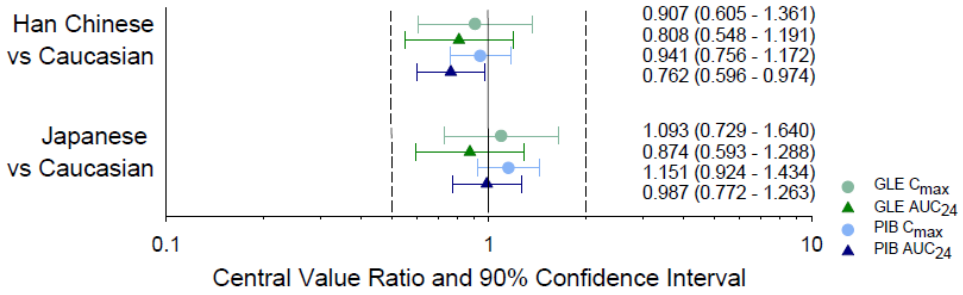
Two studies (M15-432 and M14-066) were performed to assess the PK and safety of GLE and PIB between Asian and Caucasian subjects.

- Study M15-432 included 135 male and female adults (45 Han Chinese, 45 Japanese and 45 Caucasian) randomly assigned in equal ratios to 5 cohorts:

	Days 1 to 7	Days 8 to 14
Cohort 1	GLE 200 mg QD	GLE 200 mg QD + PIB 120 mg QD
Cohort 2	GLE 300 mg QD	GLE 300 mg QD + PIB 120 mg QD
Cohort 3	PIB 120 mg QD	GLE 300 mg QD + PIB 120 mg QD
Cohort 4	PIB 80 mg QD	GLE 200 mg QD + PIB 80 mg QD
Cohort 5	GLE 100 mg QD	GLE 100 mg QD + PIB 120 mg QD

Formulations: GLE Phase 2b tablets; PIB Phase 2b tablets

The results with the combination of GLE 300 mg QD + PIB 120 mg QD are as follows:



Cohorts 2 and 3: GLE 300 mg QD + PIB 120 mg QD (Day 14)

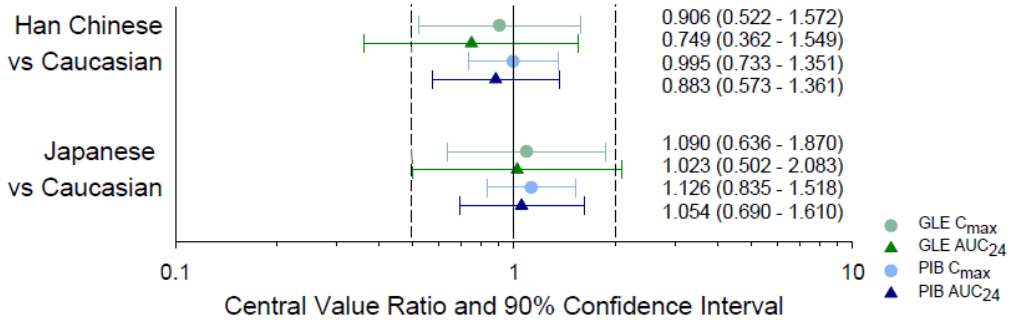
Figure 3 - Relative bioavailability of GLE and PIB in Han Chinese or Japanese versus Caucasian subjects (study M15-432)

- Study M14-066 included 35 healthy male and female adults (11 Han Chinese, 12 Japanese and 12 Caucasian) randomly assigned in equal ratios to 2 cohorts:

	Days 1 to 7	Days 8 to 14
Cohort I	GLE 700 mg QD	GLE 700 mg QD + PIB 160 mg QD
Cohort II	PIB 160 mg QD	GLE 700 mg QD + PIB 160 mg QD

Formulations: GLE Phase 2a tablets; PIB Phase 2a tablets

The results are as follows:



Cohorts 1 and 2: GLE 700 mg QD + PIB 160 mg QD (Day 14)

Figure 4 - Relative bioavailability of GLE and PIB in Han Chinese or Japanese versus Caucasian subjects (study M14-066)

Overall, there is a trend for lower GLE and PIB exposures in Chinese subjects as compared to Caucasian in the studies, but these differences are minor and not clinically significant.

Renal impairment

Study M13-600 is a Phase 1 open-label study assessing the PK and safety of a single dose of GLE 300 mg + PIB 120 mg under non-fasting conditions in subjects with mild, moderate and severe renal impairment and in subjects with end-stage renal disease with or without dialysis. 46 adult male and female subjects were enrolled:

	Group	N	eGFR (mL/min/1.73m^2)	Regimens
Sub-Study 1	Normal Renal Function	8	≥ 90	GLE 300 mg + PIB 120 mg
	Mild Renal Impairment	8	60 – 89	
	Moderate Renal Impairment	8	30 – 59	
	Severe Renal Impairment	8	15 – 29	
	ESRD Not on Dialysis	6	< 15	
Sub-Study 2	ESRD	8	Dialysis required	GLE 300 mg + PIB 120 mg; on Dialysis and Non-dialysis Days[a]

Formulations: GLE Ph2b tablets, PIB Ph2b tablets

a. Single doses were administered 3 hours before the start of hemodialysis (Dialysis Day) and on the day prior to a planned dialysis session (Non-dialysis Day). A washout interval of ≥ 7-day separated doses.

The results are as follows:

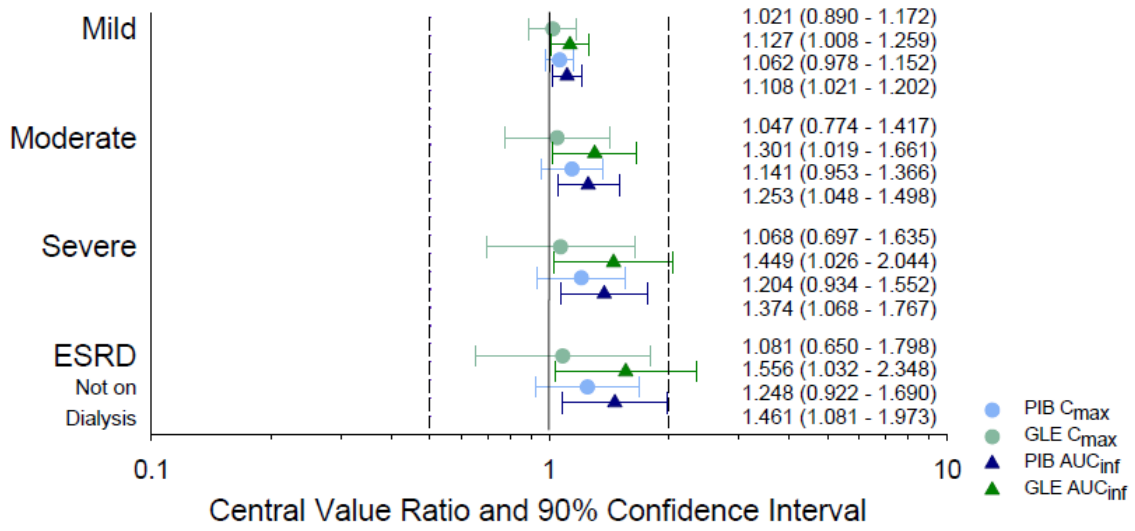
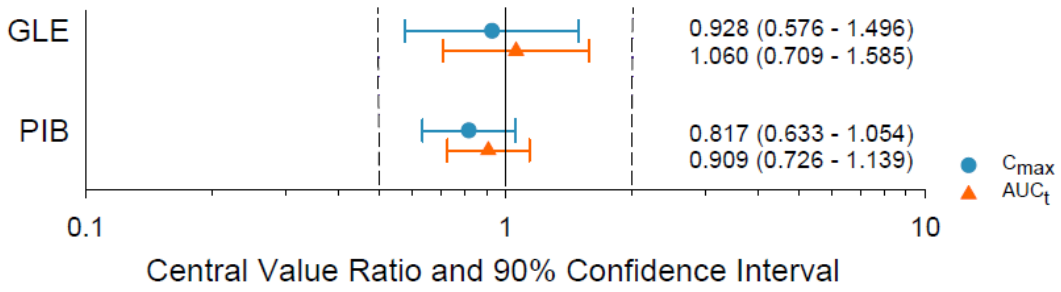


Figure 5 - Relative bioavailability of GLE and PIB in subjects with renal impairment versus subjects with normal renal function (study M13-600)



GLE, PIB: Period 1 Day 1 (Day of Dialysis)/Period 2 Day 1 (Non-dialysis Day)

Figure 6 - Effect of haemodialysis on GLE and PIB in dialysis-dependent ESRD subjects (study M13-600)

The percentage of unchanged GLE or PIB excreted in urine was minimal across groups (≤ 0.28%) and was not clinically relevant. Protein binding for GLE and PIB was not significantly different in mild, moderate, severe, or ESRD (not on dialysis) groups compared to the normal group.

Overall, renal impairment, with or without dialysis, was not determined to have a clinically significant effect on GLE or PIB exposures in non-HCV infected subjects or in patients with HCV. No dose adjustment is recommended when GLE/PIB is administered in subjects with renal impairment.

Hepatic impairment

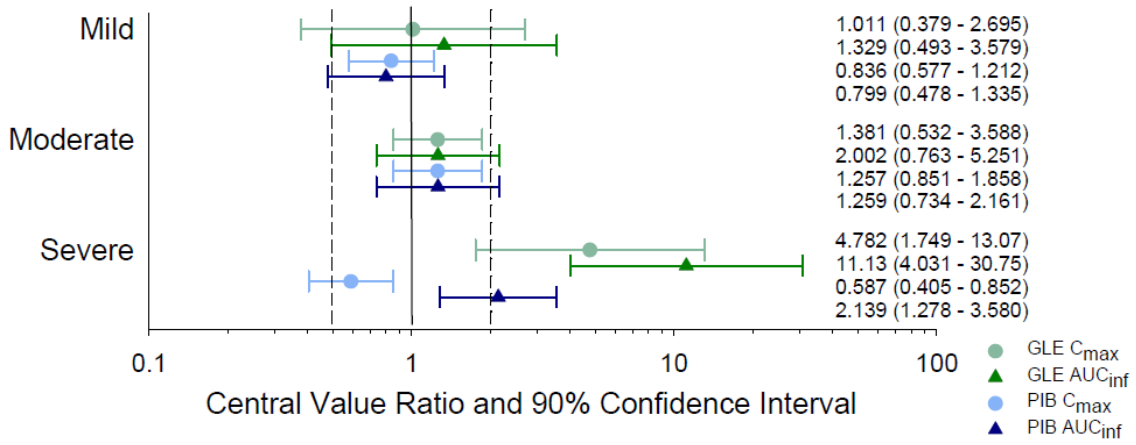
Study M13-604 is a Phase 1 open-label study assessing the PK and safety of a single dose of GLE + PIB under non-fasting conditions in non-HCV subjects with mild, moderate and severe hepatic impairment compared to subjects with normal hepatic function. 27 adult male and female subjects were enrolled. In each groups, subjects received 2 or 3 different dosing regimen of PIB +/- GLE (with at least a 14-day washout between each dosing regimen).

Subject Group	Period 1	Period 2	Period 3
Mild Hepatic Impairment (CP-A)	PIB 120 mg	GLE 200 mg + PIB 120 mg	GLE 300 mg + PIB 120 mg
Moderate Hepatic Impairment (CP-B)	PIB 120 mg	GLE 200 mg + PIB 120 mg	GLE 300 mg + PIB 120 mg
Severe Hepatic Impairment (CP-C)	PIB 120 mg	GLE 300 mg + PIB 120 mg	--
Normal hepatic function	PIB 120 mg	GLE 200 mg + PIB 120 mg	GLE 300 mg + PIB 120 mg

All study drugs were administered as single doses in each period. Dosing between periods was separated by a minimum 14-day washout interval.

Formulations: GLE Ph2b tablets, PIB Ph2b tablets

The results with GLE 300 mg + PIB 120 mg are as follows:



GLE 300 mg + PIB 120 mg; Period 3 (CP-A, CP-B, and normal hepatic function) or in Period 2 (CP-C)

Figure 7 - Relative bioavailability of GLE and PIB in subjects with hepatic impairment versus subjects with normal hepatic function (study M13-604)

The fraction unbound of GLE in plasma from subjects with mild or moderate impairment and of PIB in all hepatic impairment groups was not significantly different from normal subjects, but was significantly higher for GLE in subjects with severe hepatic impairment ($p < 0.05$).

The percentage of GLE bound to plasma proteins in subjects with mild or moderate impairment (97% to 98%) was not significantly different than in normal subjects, but was significantly lower for GLE in subjects with severe hepatic impairment (95%). The percentage of PIB bound to plasma proteins in all impairment groups (≥ 99.99%) was not significantly different than in normal subjects.

Overall, the use of GLE/PIB is not recommended in HCV subjects with CP-B hepatic impairment given the 2-fold increase of GLE exposure observed in this study and the greater than predicted effect of CP-A hepatic impairment in HCV-infected subjects relative to non-HCV infected subjects. In subjects with CP-C, GLE/PIB is contraindicated given the large increases in GLE exposure (increase to 11-fold).

Pharmacokinetic interaction studies

- **In vitro**

Based on in vitro data on the GLE/PIB metabolism, the effect of any CYP inhibitors or inducers on PIB pharmacokinetics is not expected to be significant and clinically relevant.

GLE inhibits CYP2C8, CYP2C9 and CYP3A4. PIB has not shown any CYP inhibition at concentration up to 30µM. GLE and PIB does not exhibit any CYP2B6 inhibition. Besides, it is agreed that neither GLE nor PIB are time-dependent inhibitors of the studied CYP450.

Based on data from in vitro studies, it cannot be excluded that GLE and PIB induce CYP3A4 at the intestinal level.

GLE and PIB inhibited in vitro UGT1A1 and UGT1A4 but did not show inhibition of UGT1A6, UGT1A9 or UGT2B7 (IC50 >50 µM) in human liver microsomes.

Table 1 - In vitro enzyme and transporter inhibition potency of GLE and PIB
(1 and 0 represents negative and positive signal, respectively)

Enzymes	GLE IC50 or Ki* (µM)	GLE Systemic/ Intestine	PIB IC50 or Ki* (µM)	PIB Systemic/ Intestine	Total Systemic/ intestine
CYP1A2	>500	0	>0.7[3]	0	0
CYP2B6	>500	0	>0.7[3]	0	0
CYP2C8	7.5	0	0.65[3]	0	0
CYP2C9	74[1]	0	>30[1]	0	0
CYP2C19	>200[1]	0	>30[1]	0	0
CYP2D6	>200[1]	0	>30	0	0
UGT1A1	7.31[1]	0/1	1.3[3]	0/1	0/1
UGT1A4	6.20[1]	0/1	0.014[3]	1/1	1/1
UGT1A6	>50[1]	0/0	>1.9[3]	0	0
UGT1A9	>50[1]	0/0	>1.9[3]	0	0
UGT2B7	114	1/1	Activation	-	1/1
CYP3A	28.3	0/1	>0.7[3]	0	0/1
Transporters					
P-gp	0.165	1/1	0.036	1/1	1/1
BCRP	1.15	1/1	14	0/1	1/1
OATP1B1	0.0085	1	1.3	1	1
OATP1B3	0.032	1	>30[2]	0	1
OAT1	>100	0	>30[2]	0	0
OAT3	>100	0	>30[2]	0	0
OCT2	>100	0	>30[2]	0	0
Transporters (optional)					
OCT1	>30	0	>30[2]	0	0
MATE1	>30	0	>30[2]	0	0
MATE2-K	>30	0	>30[2]	0	0
BSEP	0.0485	1	39	0	1

*Ki for enzymes, IC50/2 for transporters, Concentrations with > means that this was the highest concentration studied.
[1] May be an underestimation of the inhibition potential. In vitro methods questioned. [2] Inhibition was less than 50% at 30 µM [3]. Not compensated for fumic [3] Corrected for fumic

However knowing that UGT2B7 is also located at intestinal level, it is unknown whether GLE may inhibit this enzyme considering its worst estimated concentration at this level i.e. 143.2 µM. Based on the data provided, the recalculation of the AUC ratio using ka=0,1 min^{-1}, as the worst-case estimate (EU Guideline on the investigation of Drug Interaction, January 2013) predicts a R value= 1,63 (values <1,25 are not expected to have DDI).

GLE and PIB are both substrates of the efflux transporters P-gp, and/or BCRP. GLE is a substrate of the uptake transporter OATP1B1 and 1B3 but not PIB. Neither GLE nor PIB is an OCT-1 substrate.

The liability for GLE and PIB to be substrate of BSEP (bile salt export pump) has not been investigated.

However CHMP agreed that this is not a concern because BSEP has a narrow substrate specificity mainly transporting conjugated bile salts and structurally similar compounds (2013 ITC Whitepaper). Hence BSEP is unlikely to have a role in the disposition of NMEs.

Furthermore, the impact of any polymorphism of P-gp BCRP, and OATP1B1/3 has been clarified as part of the D106 assessment and no effect on the efficacy/safety of GLE/PIB is expected.

GLE and PIB are P-gp and BCRP, BSEP and OATP1B1 inhibitors. GLE also inhibits OATP1B3. Inhibition of OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2K by GLE and PIB has not been identified up to 30µM.

The results of the investigations of stability and adsorptions issues in the in vitro transporter inhibition studies were not found. Data supporting the presence of actual concentration for GLE and PIB during the incubation have been submitted.

The transporter studies with OCT2, OAT1, OAT3, MATE1 and MATE2 were performed in HEK cells where target concentrations were confirmed investigating the effect on OCT-1. Regarding PIB, stating solubility in incubation buffer is not considered adequate and the applicant should provide data on stability/adsorption of PIB in the assays on OCT1, OATP1B3, OCT2, OAT1, OAT3, MATE1 or MATE2K inhibition for the data to be is considered reliable. CHMP recommended that these data are submitted ***as a post-authorisation measure*** by end of March 2018.

In vivo

Twenty-two clinical interaction studies were conducted in healthy volunteers to assess the magnitude of the potential interactions with GLE/PIB. Because the FDC was not available before phase III studies, most of DDI studies used individual tablets of GLE and PIB.

As part of the D106 Q/R assessment, clarifications was made on which situations and exposure increases and decreases in GLE and PIB exposures that should lead to a contraindication and which should lead to a "not recommended" statement (notably as regards carbamazepine or other strong/moderate P-gp/CYP3A inducers.

Drugs that increase exposures of GLE/PIB: No upper exposure level of GLE that would result in a contraindication has been defined. However, due to limited data in this high exposure range, drug interactions resulting in exposures greater than 6-fold of the HCV non-cirrhotic population are "not recommended." And, a further 3-fold increase due to drug interactions in subjects with cirrhosis will result in GLE exposures 6-fold of non-cirrhotic subjects. Thus the maximum increase in GLE exposure allowed due to drug interactions for all subjects was established at 3-fold. For PIB no safety problems have been observed making GLE the limiting factors. This is agreed on.

Drugs that decrease exposures of GLE/PIB: An exposure-response (SVR_{12}) evaluation of PIB was further discussed in Q105. No ER relationship was found for GLE. The results for PIB show that even patients with low PIB concentrations experience response rates over 95%. Further, the Applicant states that a reduction of PIB exposure by 70% is expected to decrease the SVR12 response rate in TN GT3 patients below 90% which is considered clinically meaningful.

Consequently the combination of GLE/PIB with strong inducers should be contra-indicated and with moderate inducers not recommended.

GLE and PIB combination

The effect of GLE on PIB and reciprocally has been assessed as part of the study M13-586, Arm 1. Results show that that GLE (400 mg/day) significantly raises PIB exposure about 3.5-fold probably due to P-gp and BCRP inhibition. Additionally, based on results obtained as part of the study (cohort 2 and 3), GLE (300 mg, multiple doses) is expected to increase about 3-fold PIB exposure whereas no clinically relevant

effect is observed of PIB (120 mg multiple doses) on GLE exposure (AUC ratio= 1,7 with a 90%CI [1,053-1,309]).

PIB increases GLE exposure, but this is not expected to be clinically relevant.

Effect of GLE/PIB on the pharmacokinetics of other drugs

Effect of GLE and PIB on CYP450 enzymes

GLE/PIB significantly affects the exposure of the probe CYP1A2, CYP3A4 CYP2C19 and CYP2D6 substrates caffeine, midazolam, omeprazole and dextromethorphan (DMX), but in a different way. Indeed, the GLE and PIB combination increases caffeine and midazolam AUC, about 37% and 27%, respectively, whereas it decreases dextromethorphan and omeprazole exposure about 25% and 21%. These effects are driven by GLE and not fully clear as regards CYP1A2, CYP2D6 and CYP2C19 since in vitro GLE is not expected to inhibit these enzymes at therapeutic concentrations.

However, except for omeprazole at a dose higher than 20 mg, although uncertainties remain on the mechanism behind the observed changes, this is not expected to be clinically relevant. As regards omeprazole at dose higher than 20 mg, the risk of reduced efficacy if allowing concomitant 40 mg qd treatment is considered unnecessary. Therefore the co-administration of Maviret with omeprazole 40 mg qd is not recommended.

Felodipine and amlodipine are sensitive CYP3A substrates. GLE increases felodipine and amlodipine AUC about 31% and 21%, respectively. These results are consistent with the weak CYP3A4 inhibition observed with midazolam the exposure of which increasing lesser than 2 -fold. Even though these changes are statistically significant, they are not expected to be clinically relevant. The effects of felodipine and amlodipine on GLE and PIB PK have also been studied and no pharmacokinetic interaction has been identified. No dose adjustment is recommended when GLE/PIB is combined with felodipine or amlodipine.

Effect of GLE and PIB on UGT1A1 and UGT1A4

Raltegravir is metabolised by UGT1A1. Results from the study M13-593 show a significant increase of raltegravir $C_{max\ and}$ AUC, about 1.34- and 1.47-fold respectively. RAL C_{min} increases about 2-fold with a 90%CI [1.42-4.9], this variation may be attributed to RAL variability and food intake. The large therapeutic margin and the safety profile of RAL allow this effect to not be considered clinically relevant. Therefore, RAL can be combined with GLE/PIB without dose adjustment**.**

Levothyroxine has been identified as an UGT1A1 substrate (Williams J.A and al. Drug metabolism and disposition, 2004). However, currently data on DDI with levothyroxine bring on a risk of loss of efficacy rather than on an increased risk of toxicity. Therefore if the interaction is not ruled out between GLE/PIB and levothyroxine, due to UGT1A1 inhibition by the FDC, its clinical relevance is questionable. Therefore, this combination should be in the list of risk that should be monitored and add in the RMP**.**

No significant change has been observed on lamotrigine, an UGT1A4 substrate, when it is combined with GLE and PIB. No clinically relevant changes are observed on GLE and PIB exposures.

P-gp inhibition

GLE and PIB increase the exposure of digoxin about 48% and its C_{max} about 72%. No significant effect on the PK of both GLE and PIB is observed. The Applicant therefore recommends the decrease of the dose of digoxin to about half. This is not supported by CHMP. As a matter of fact, this effect could be more pronounced in the clinical setting notably, in women patients in whom the therapeutic margin of digoxin is narrower than in men, and in patients with an altered renal function. This study does not sufficiently reflect the clinical conditions to decide of any dose recommendations. Then, only the measure of

digoxinemia allows an adequate dose adjustment to be made. This has been reflected in the Maviret SmPC.

Likewise, with GLE and PIB, dabigatran AUC and C_{max} increase about 2.4-fold and 2-fold, respectively. The magnitude of this interaction is similar to the one observed with dronedarone, a P-gp inhibitor, with which the combination of dabigatran is strictly contra-indicated. Therefore the proposed SmPC warning to not recommend dabigatran with the FDC is not supported. Dabigatran with GLE/PIB must be contra-indicated. This is reflected in the Maviret SmPC.

OATP1B1 and OATP1B3 inhibition

- Losartan and valsartan

Losartan is a P-gp and an OATP2B1 substrate and not an OATP1B1 and 1B3 substrate. GLE and PIB, significantly increase losartan and its active metabolite C_{max}, by 2.5-fold and 2.2-fold. This is driven by P-gp inhibition. Besides, their AUC modestly increase about 1.14-fold and 1.56-fold. This is not expected to be clinically meaningful.

Valsartan is an OATP1B1- and OATP1B3 substrate. With GLE and PIB, valsartan exposure increases about 1.3-fold translating the moderate impact of GLE and PIB on valsartan disposition. According to these results, and considering the safety margin of valsartan, no dose adjustment is needed with GLE/PIB.

- HMG Co-A reductase inhibitors (statins)

Pravastatin is not metabolised but is taken up by OAT1B1 and 1B3 into the hepatocytes. With GLE/PIB, its AUC increases about 2.3-fold due to inhibition of these uptake transporters by GLE. The Applicant recommends to decrease about 50% the dose of pravastatin. This proposal is not supported. Pravastatin is a well-tolerated statin and a doubling of its exposure is not expected to be clinically relevant. Furthermore, current recommendations in the pravastatin EU SmPC is to initiate the treatment with a low dose, 10 mg day, in case of unfavorable factors (DDI, hepatic impairment) and to adjust the dose according to the impact on lipids. There is no data that authorized to claim a half dose of pravastatin may lead to an optimal efficacy on lipids-lowering. The dose of pravastatin should not exceed 20 mg/day. This was reflected in the Maviret SmPC.

Rosuvastatin is an OATP1B1 and also a BCRP substrate, the exposure of which is expected to increase when combined with an inhibitor of these transporters as GLE and PIB. The study M13-579 shows a substantial increase in rosuvastatin C_{max} about 5.6-fold and a 2-fold increase in its AUC. Therefore a low daily-dose of rosuvastatin (5 mg/day) should be used. This was reflected in the Maviret SmPC.

Atorvastatin is OATP1B1 and 1B3 substrate and also a P-gp, BCRP substrate. The substantial increase its C_{max} and AUC, about 22-fold and 8-fold, respectively, requires to contra-indicate this statin with GLE/PIB. This is reflected in the Maviret SmPC.

Simvastatin is an OATP1B1 and 1B3 substrate and also a P-gp, BCRP substrate. In the study M14-721, GLE and PIB increase the C_{max} and AUC of both simvastatin and simvastatin hydroxy acid (its active metabolite) by 2-fold and 2.3-fold, and 11-fold and 4.5-fold, respectively. These results are consistent with the PK features of simvastatin and the active hydroxy acid metabolite. The C_{max} of the latter translates the inhibitory effect at the biliary level of GLE and PIB on P-gp and BCRP. CHMP agreed that this co-administration should be contraindicated. This is reflected in the Maviret SmPC.

Lovastatin is an OATP1B1 and 1B3 substrate and also a P-gp substrate. As simvastatin and its hydroxyl acid metabolite, AUC and C_{max} of the parent compound and acid lovastatin (active metabolite) significantly increase with GLE/PIB about 1.7-fold and 1.1 fold, and 4.1-fold and 5.7-fold, respectively.

Therefore, their co-administration is not recommended. However, some guidance will be specified in case this co-administration is unavoidable.

Pitavastatin and fluvastatin share the same feature towards OATP1B1 and 1B3 as pravastatin but this has not been studied. This is reflected in the Maviret SmPC.

Effect of GLE and PIB on Ethinyl Estradiol (EE)/Norgestimate (NGM), Norethindrone (NET), or EE/Levonorgestrel (LNG) Based Oral Contraceptives

Oral contraceptive agents undergo metabolism by multiple pathways as CYP450 and UGT. **EE** is also a substrate of OATP1B1 and 2B1. With GLE and PIB, plasma exposures of EE, norgestrel, norgestromin and levonorgestrel increase about 28% and 40 %, 63%, 44%, and 68% respectively. Usually, these changes are not expected to be clinically relevant. Nevertheless the onset of asymptomatic grade 1 (n=3), 2 (n=1) and 3 (n=1) ALT elevation in 5 healthy women is compelling and foreshadow that these events, actually, may be more pronounced and symptomatic in the target population intended to be treated by GLE/PIB. The Applicant proposes to not recommend the combination of this DAA with EE containing regimen. This recommendation is not supported.

As a matter of fact, as part of the DDI study M12-205 (R& D 13-949) with the FDC ombitasvir, paritaprevir, ritonavir, the event of transaminase elevation was reported in five subjects and were assessed as moderate in severity. Of note 3 of these 5 healthy women discontinued prematurely the study. Additionally these events occurred without any significant increase of EE AUC. During clinical trials with another FDC containing the DAA, ombitasvir/paritaprevir/ritonavir, transient elevations of ALT to greater than 5 times the upper limit of normal occurred in 1% of subjects, these elevations were significantly more frequent in the subgroup of subjects who were using EE as combined oral contraceptive or contraceptive vaginal rings. Consequently, it has been decided that the combination of EE with ombitasvir/paritaprevir ritonavir is strictly contra-indicated.

Presently in GLE/PIB case, specific recommendations have been given as part of the pivotal clinical trials that any treatment by EE must be stopped 2 weeks before starting the DAA and only restarted 30 days after the end of the DAA treatment. Then, one cannot preclude that in the clinical setting the magnitude of the ALT elevations will be more pronounced and clinically relevant. Consequently, the combination of GLE/PIB and EE should be contra-indicated.

No significant PK change is observed with norethindrone then no dose adjustment is recommended.

No clinically significant interactions were observed between GLE and PIB with progestin-only contraceptives.

Opioid Replacement

The study M13-602 shows that no clinically relevant interaction is expected with buprenorphine or methadone. Consequently, no dose adjustment is needed with GLE/PIB.

Effect of other drugs on GLE/PIB pharmacokinetics

Transporters/enzyme inducers: carbamazepine and rifampicin

Rifampicin is a strong enzyme and transporter inducer but also exhibits OATP inhibitory effect that can be evidenced only after a single oral dose. In the study M14-723, a single rifampicin dose increased GLE exposure (↑ 6.5-fold C_{max}, ↑ 8.6-fold AUC_{inf}), but had no effect on PIB exposure (≤ 9% change). Multiple doses of rifampicin slightly increased GLE (↑ 40% C_{max}), but PIB exposures were decreased (↓ 79% C_{max}, ↓ 83% AUC_{inf}). When GLE and PIB were administered 24 hours after the last dose of rifampicin, exposures

were decreased for both GLE (↓ 86% C_{max}, ↓ 88% AUC_{inf}) and PIB (↓ 83% C_{max}, ↓ 87% AUC_{inf}). Therefore, GLE/PIB is contra-indicated with rifampicin.

Repeated doses of carbamazepine significantly decreases GLE and PIB AUC, about 66% and 50%, respectively (Study M14-724) using 200 mg BID. Doses up to 400 mg could be used in clinical practice. Based on these GLE/PIB should be contraindicated with carbamazepine, as well as all strong inducers.

For moderate inducers the combination with GLE/PIB should be not recommended. This is reflected in the Maviret SmPC.

Acid-Reducing Agents

Omeprazole was used as a prototypical proton-pump inhibitor to evaluate the effect of acid-reducing agents on the pharmacokinetics of GLE and PIB. Omeprazole was administered in the morning approximately 1 hour before starting breakfast (QD regimen) or in the evening without food (QPM regimen).

GLE exposure was slightly lower (↓ 22% C_{max}, ↓ 29% AUC_{inf}) when GLE and PIB were coadministered with omeprazole 20 mg QD compared to GLE and PIB alone; PIB exposure was similar (≤ 3% difference).

GLE exposure was lower (↓ 64% C_{max}, ↓ 51% AUC_{inf}) when GLE and PIB were coadministered with omeprazole 40 mg QD compared to GLE and PIB alone; PIB exposure was similar (≤ 15% difference).

GLE exposure was lower (↓ 46% C_{max}, ↓ 49% AUC_{inf}) when GLE and PIB were coadministered with omeprazole 40 mg QPM compared to GLE and PIB alone; PIB exposure was similar (≤ 7% difference).

The Applicant suggests no dose adjustment with GLE/PIB. This is not supported by CHMP since results with OMP 40 mg are close to those observed with carbamazepine. However, GLE/PIB can be used with omeprazole at a dosage that does not exceed 20 mg QD and according to the conclusion drawn as part of the D106 Q/R assessment, omeprazole 40 mg QD is not recommended due to the risk of loss of GLE/PIB efficacy. This is reflected in the Maviret SmPC.

Immunosuppressant

With ciclosporin 100 mg/day, GLE and PIB exposure (AUC) increase about 14%, 37% and 22%. On the contrary, with ciclosporin 400 mg, GLE and PIB exposure raises about 5- and 1.9- fold, respectively, whereas ciclosporin exposure falls within the 90%CI of [0.8-1,25].

These difference can be explain by the balance between the three compounds towards P-gp, BCRP and OATP and their affinity/inhibition for these transporters whereas at 400 mg day, ciclosporin inhibitory effect counterbalances this state and inhibition of GLE and PIB efflux and uptake (only with GLE) transport by ciclosporin prevails over.

As part of the D106 Q/R assessment, the Applicant finally suggests to not recommend the use of ciclosporin doses >100 mg per day with GLE/PIB face to uncertainties as regards the safety profile of the combination. However, since ciclosporin + GLE/PIB is not contra-indicated, an additional recommendation is added for patients eligible for GLE/PIB and receiving ciclosporin dose >100 mg/day. This is reflected in the Maviret SmPC.

DDI with other drugs for HIV Treatment:

HIV protease inhibitors (atazanavir, darunavir, lopinavir, ritonavir)

Darunavir/ritonavir strongly inhibits CYP3A, P-gp, BCRP and OATP this effect is mainly driven by ritonavir. When GLE/PIB is combined with this PI, GLE exposures substantially increases about 5-fold, 3-fold and 8-fold for AUC C_{max} and C_{min}, respectively. This is related to the inhibition of multiple pathways

involved in GLE disposition as the uptake and efflux transport by OATP1B1/B3, P-gp and BCRP at the hepatocyte and enterocyte level.

PIB AUC and Cmin increase but weakly and this is not considered clinically relevant. These results finally show the modest impact on PIB exposure of P-gp and BCRP inhibition on its elimination. Moreover the estimated boosting effect of GLE on PIB exposure, that is an increase about 3-fold of PIB AUC, is also not evidenced.

DRV/RTV exposures are also increased but this is not considered clinically relevant. The Applicant suggests that the combination of GLE/PIB and DRV/RTV is not recommended. Considering the 90%CI of GMR for GLE AUC, [3.615-6.842], that does not discard an increase AUC more than 6-fold, contra-indicate the combination of DRV/RTV with GLE/PIB is then raised. As a matter of fact, with ATV/RTV, GLE AUC mean ratio increases about 6.5-fold, with a 90% CI [5.23-8.1] a total of 10/24 subjects report ALT elevations. The Applicant links this adverse event to ATV and proposes to contra-indicate ATV/RTV combination with GLE. The applicant has proposed a differential approach for LPV/RTV and DRV/RTV (not recommended) as compared to ATV/RTV (contra-indicated). Indeed, although PK parameters of GLE and PIB were significantly affected in presence of LPV/RTV and DRV/RTV, the concern on increased transaminases were mainly derived from the findings with ATV/RTV. After discussion through the procedure this approach was endorsed by CHMP, but with a close scrutiny to be maintained in post marketing.

Non-nucleoside reverse transcriptase inhibitors (rilpivirine, efavirenz):

Rilpivirine is mainly metabolised by CYP3A4. With GLE/PIB, its AUC increases about 1.8-fold. The magnitude of the interaction is lesser than observed with DRV/RTV with which no dose adjustment is currently recommended in rilpivirine SPC. Therefore, no dose adjustment is needed with GLE/PIB.

Efavirenz (EFV)/Emtricitabine (FTC)/Tenofovir Disoproxil Fumarate (TDF)

GLE/PIB does not significantly alter the exposure of **efavirenz and emtricitabine**. **Tenofovir** AUC, C_{max} and C_{min} increase about 29%, 22%, and 38% and is probably related to P-gp inhibition by GLE/PIB. These changes are similar to those observed with ATV/RTV or DRV/RTV. Therefore, no dose adjustment is recommended but the observed increased in tenofovir exposure could potentiate tenofovir associated adverse events, including renal disorders.

As regards the effect of efavirenz on GLE and PIB exposure, the Applicant estimated a 70% decrease in GLE/PIB exposure based on the results obtained in other healthy subjects. Efavirenz is a known moderate to strong inducer and CHMP agreed that its combination with GLE/PIB should be not recommended.

Elvitegravir (EVG)/Cobicistat (c)/Emtricitabine (FTC)/Tenofovir Alafenamide (TAF; Arm 1) or Abacavir (ABC)/Dolutegravir (DTG)/Lamivudine

Elvitegravir AUC increases about 46%, cobicistat AUC increases about 42% but it can be agreed that no dose adjustment is needed. Scrutiny will be exercised in post marketing. Emtricitabine and TAF changes are not considered clinically relevant.

As regards abacavir, dolutegravir, lamivudine, no clinically relevant interaction is expected likewise the observed changes in GLE/PIB PK do not need any dose adjustment to be made. This is reflected in the Maviret SmPC.

Drugs for HCV Treatment

GLE and PIB increased exposure of sofosbuvir via inhibition of P-gp and BCRP, but did not affect exposure of GS-331007 metabolite. No clinically significant interactions were observed between GLE and PIB with sofosbuvir.

Other DDI

According to the pharmacokinetic profile of the following drugs, a discussion on the drug-drug interaction risk with GLE/PIB has been requested:

- voriconazole, a CYP3A,2C substrate and inhibitor

- dronédarone, a P-gp inhibitor

- colchicine, a P-gp/CYP3A substrate

- repaglinide, an OATP1B/B3 and CYP3A/2C8 substrate

- gemfibrozil, an OATP1B1/1B3 inhibitor

- methotrexate (MTX), paclitaxel, mitoxantrone, irinotecan: BCRP substrates

As part of the D106 AR, clarifications have been provided by the Applicant. However the lack of data on the ability of these drugs to be substrates or inhibitors of transporters notably OATP1B1 and 1B3, made the predictability of the net effect quite difficult. As an illustration, MTX is a MRP4 substrate but the effect by GLE/PIB on MRP4 is unknown.

Besides, regarding, gemfibrozil and repaglinide, the Applicant is referring to a PBPK simulation for the prediction of GLE/PIB interaction. The applicant has not submitted qualifications supporting the use of CYP2C8 and OATP1B1/3 quantitatively. In addition as there is a lack of abundance data for OATP1B, there is not enough scientific support to make quantitative simulations. It is therefore not possible to use these simulations for dosing recommendations. However, even though a clinically relevant interaction cannot be completely ruled out in the absence of dedicated DDI studies, CHMP considered that scrutiny towards signals is warranted in the post marketing setting, rather than a statement in the Maviret SmPC.

2.4.3. Pharmacodynamics

Mechanism of action

Glecaprevir is an inhibitor of 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.

Pibrentasvir is an inhibitor of HCV NS5A which is essential for viral replication. In vitro resistance selection and data on cross-resistance support NS5A is the target of PIB.

Primary and Secondary pharmacology

Primary pharmacology – Resistance analysis

In vitro activity

In a biochemical assay, glecaprevir inhibited the activity of NS3/4A protease enzymes from HCV GT1-6 with IC_{50} values ranging from 3.5 to 11.3 nM. The EC_{50} values of glecaprevir and pibrentasvir against full-length or chimeric replicons encoding NS3 or NS5A from laboratory strains, and chimeric replicons

from clinical isolates are presented below. Pan-genotypic activity was shown in vitro. GLE had a median toxic dose (TD50) of 72,000 nM in the MTT cytotoxicity assay (yielding a therapeutic index that exceeded 10^4-fold).

Table 2 - Activity of GLE and PIB against HCV genotypes 1-6 replicon systems

HCV Subtype	Glecaprevir EC_{50}, nM (range)				Pibrentasvir EC_{50}, nM (N) (range)			
	Lab strains,	n	Clinical isolates,	n	Lab strains,	n	Clinical isolates,	n
1a	0.85	9	0.08 (0.05 – 0.12)	11	0.0018	10	0.0009 (0.0006 – 0.0017)	11
1b	0.94	8	0.29 (0.20 – 0.68)	9	0.0043	12	0.0027 (0.0014 – 0.0035)	8
2a	2.2	7	1.6 (0.66 – 1.9)	4	0.0023	4	0.0009 (0.0005 – 0.0019)	6
2b	4.6	8	2.2 (1.4 – 3.2)	4	0.0019	5	0.0013 (0.0011 – 0.0019)	11
3a	1.9	4	2.3 (0.71 – 3.8)	2	0.0021	5	0.0007 (0.0005 – 0.0017)	14
4a	2.8	4	0.41 (0.31 – 0.55)	6	0.0019	5	0.0005 (0.0003 – 0.0013)	8
4b	NA		NA		NA		0.0012 (0.0005 – 0.0018)	3
4d	NA		0.17 (0.13 – 0.25)	3	NA		0.0014 (0.0010 – 0.0018)	7
5a	NA		0.12	1	0.0014	5	0.0011	1
6a	0.86	4	NA		0.0028	5	0.0007 (0.0006 – 0.0010)	3
6e	NA		NA		NA		0.0008	1
6p	NA		NA		NA		0.0005	1

NA = not available

In the presence of 40% human plasma there was approximately 10-fold and 40-fold decrease in inhibitory potency against GT1a-H77 and GT1b-Con1 replicons for glecaprevir and pibrentasvir, respectively, reflecting the high degree of protein binding for both agents.

Glecaprevir: Replicon resistance selection studies were conducted in GT1a-H77, GT1b-Con1, GT2a-JFH-1, GT2b, GT3a, GT4a, and GT6a cell lines at 10-, 100- or 500-fold above the EC_{50} of GLE for the respective cell lines.

The major amino acid substitutions selected in NS3 by GLE in the GT1, 2 and 4 replicon cell lines were A156T and A156V. In GT3a replicon, most of the colonies selected contained A156G or Y56H + Q168R. Of note, the one baseline NS3 substitution (A166S) that was associated with a reduced clinical efficacy in genotype-3 infection was not selected in vitro, and does to our understanding not confer a reduced susceptibility in vitro. In GT6a replicon, GLE selected D168H and D168V.

Effects on phenotypic susceptibility of these substitutions and other single substitutions typical for the class are summarized in the next table. Of note, in GT1a, substitutions at position 80 had no impact on activity of GLE. In GT3a, Q80R reduced susceptibility by 21-fold; a substitution seemingly of overall low clinical importance (next section).

Table 3 - Levels of resistance conferred by NS3/4A single amino acid substitutions in HCV GT 1-4 and GT6 transient replicons to GLE

HCV Subtype	GLE Fold increase in EC_{50}		
	<5	5-100	>100
1a	V36A/L/M, Q41R, F43L, T54S, V55I, Y56H, V71A, Q80K/L/R, Q89R, A150V, R155K/M/S/T/V, A156G, D168A/E/H/N/V, I170T/V, P334S, S342P, E357K, V406A, V406I, T449I, V23A (NS4A)	D168F/Y	A156T
1b	T54A, V55A, Q80K/L, P89L, R155K, A156S, D168A/E/H/T/V/Y, V170A, E176G	D168F/K	A156T/V
2a	G15D, V55A/I, Y56F/H, D168A/E/H/V/Y		A156T/V
2b	Y56F, E79G, P146S, A150V, F154Y, A160T, D168A/E/F/H/S/V/Y, E173G, A178T/V	D168T	A156M/T/V
3a	R155K, S166T, Q168H	Q80R, Q168L/R	A156G
4a	P67S, R155C	G90R, D168H/V	A156T/V
4d	Y56H, D168V		
6a	M179T	D168A/V	D168G/H/Y

Pibrentasvir: Selection of resistant substitutions within NS5A were conducted in GT1a, GT1b, GT2a, GT2b, GT3a, GT4a, and GT6a cell lines at 10-, 100- or 1000-fold above the EC_{50} of PIB for the respective cell lines. None of the cells survived selection with 100- or 1000-fold over the EC_{50} value of PIB in any cell line with the exception of GT1a-H77 (colony survival at 100-fold EC_{50} was 0.0002%). There were no surviving colonies with selection at 10-fold over the EC_{50} value of PIB in the GT1b-Con1, GT2b, GT4a, GT5a and GT6a replicon cell lines. PIB had a TD50 of > 32,000,000 pM in the MTT cytotoxicity assay (yielding a therapeutic index that exceeded 106-fold).

The major substitution selected in GT1a-H77 was Y93H in NS5A at 10-fold over the EC_{50} value. This substitution (not selected with genotype 1b virus), yielded a fold change of 7. At 100 fold change above EC50, substitutions Q30D (fold change 95), Y93D (FC not available), Q30 deletion (FC not available), or H58D + Y93H (FC 2000) were detected in 1 colony each. Substitutions selected at 100-fold over the EC_{50} value required a 2 – 3 nucleotide change.

In the GT2a cell line, only three colonies survived selection at 10-fold over the EC_{50} value of PIB; F28S+M31I (FC 15,000) was present in two colonies while P29S+K30G (FC 2.3) was present in one colony. In the GT3a cell line, three colonies containing Y93H (FC 1) were selected at fold change 10 over EC50. The one baseline NS5A substitution (A30K) that was associated with a reduced clinical efficacy in genotype-3 infection was not selected in vitro.

The impact on in vitro susceptibility by a large number of single, double and triple substitutions, were studied in transient replicons for genotypes 1-6. No single substitutions conferred a relevant fold change to PIB (all genotypes). Certain (but far from all) double and triple mutants conferred high fold changes to genotype 1a and genotype 3a virus. For genotype 2a one double mutant studied yielded high level resistance (clinical relevance likely very low). Combinations of substitutions that did confer resistance are shown in the next table. The table also highlights the absence of substitutions conferring in vitro

resistance in genotype 1b-virus. Indeed, for genotype 1b, 2b, 4a, 4d, 5a and 6a none of the double/triple mutants studied conferred a relevant FC to PIB.

Table 4 - Activity of PIB against <u>certain</u> NS5A amino acid substitutions in the HCV GT 1a-H77 transient replicon

Substitution	N	Mean EC50 pM (+/- SD)	Mean EC90 pM (+/- SD)	FC in EC50	Replicative capacity %
GT1a					
M28G + Q30R	3	15713 ± 5580	113030 ± 34567	21824	66
Q30K + H58D	6	170 ± 40.7	1249 ± 283	235	166
Q30K + Y93H	3	1286 ± 353	7584 ± 1641	1786	14
Q30R + H58D	6	91.0 ± 37.0	604 ± 280	126	50
Q30R + Y93H	3	187 ± 110	661 ± 331	260	21
Q30R + Y93N	3	94.6 ± 15.5	647 ± 120	131	3.6
L31M + Y93N	3	140 ± 34.2	748 ± 202	195	31
P32L + Y93C	4	124 ± 27.8	755 ± 144	172	0.5
H58D + Y93C	4	168 ± 32.3	2392 ± 399	233	13
H58D + Y93H	4	1612 ± 272	7764 ± 2077	2238	13
H58D + Y93N	3	1418 ± 279	7773 ± 1700	1969	21
H58D + Y93S	4	1058 ± 457	8701 ± 2752	1469	2.1
M28G + Q30R + H58C	3	679 ± 115	7268 ± 3891	942	63
Q30H + H58D + Y93H	3	6737 ± 1085	30913 ± 8712	9357	16
Q30K + H58D + E62A	3	99.5 ± 3.9	543 ± 30.9	138	90
Q30R + L31M + H58D	3	1227 ± 277	7298 ± 2203	1704	77
GT1b					
L28M + Y93H	3	2.2 ± 0.23	5.1 ± 0.17	1.2	104
R30Q + Y93H	3	2.3 ± 0.15	4.8 ± 0.40	1.2	60
L31F + Q54H	3	4.5 ± 0.87	9.2 ± 1.8	2.4	99
L31F + A92E	3	1.2 ± 0.15	3.5 ± 0.49	0.6	36
L31F + Y93H	3	2.8 ± 0.17	8.4 ± 2.1	1.5	35
L31M + Y93H	3	1.3 ± 0.24	4.3 ± 0.41	0.7	11
L31V + Y93H	3	1.7 ± 0.31	4.5 ± 0.38	0.9	24
Q54H + A92E	3	1.7 ± 0.28	4.3 ± 0.31	0.9	62
Q54H + Y93H	3	1.7 ± 0.31	4.5 ± 0.68	0.9	35
Q54Y + Y93H	3	2.0 ± 0.33	7.0 ± 0.56	1.0	34
P58S + Y93H	3	1.5 ± 0.45	5.7 ± 2.5	0.8	34
A92V + Y93H	3	0.68 ± 0.29	2.6 ± 0.98	0.4	2.5
L28M + R30Q + Y93H	3	1.0 ± 0.24	3.2 ± 0.29	0.5	28
L31F + Q54H + A92E	3	3.2 ± 0.57	8.2 ± 1.3	1.7	70
Q54H + A92V + Y93H	3	1.8 ± 0.70	5.2 ± 0.68	1.0	1.4
GT2a					
T24A + M31L	3	0.80 ± 0.30	5.8 ± 2.3	0.8	
T24A + C92S	3	1.7 ± 0.23	5.1 ± 1.1	1.7	
T24S + F28C	3	1.4 ± 0.17	6.0 ± 2.8	1.4	
F28S + M31I	3	14303 ± 2722	39977 ± 10415	14448	
F28S + Y93H	3	NA	NA	-	

P29S + K30G	4	2.3 ± 0.36	12.9 ± 1.7	2.3
GT2b				
L28F + L31I	3	1.3 ± 0.29	6.1 ± 2.4	1.1
L28F + L31M	5	1.4 ± 0.27	8.4 ± 4.0	1.2
L28F + L31V	3	NA	NA	-
L31M + C92S	3	0.96 ± 0.19	5.8 ± 1.7	0.8
L31M + C92Y	3	0.80 ± 0.15	4.6 ± 1.3	0.7
L31V + C92S	3	0.59 ± 0.03	2.9 ± 0.28	0.5
L28F + L31M + C92S	3	2.0 ± 0.54	14.3 ± 4.1	1.6
L28F + L31M + C92Y	3	NA	NA	-
GT3a				
S24F + M28K	3	173 ± 65.1	865 ± 82.2	267
S24F + A30K	3	2.1 ± 0.14	4.4 ± 0.03	3.3
M28K + A30K	3	NA	NA	-
A30K + L31I	3	2.4 ± 0.03	11.6 ± 2.3	3.6
A30K + Y93H	3	45.1 ± 2.3	180 ± 17.4	69
L31F + Y93H	3	NA	NA	-
L31I + Y93H	3	9.6 ± 1.5	58.3 ± 13.3	15
S24F + M28K + A30K	3	8932 ± 1517	38547 ± 3825	13742
A30K + L31I + Y93H	3	2770 ± 353	9134 ± 1118	4262
Subtypes 4a, 4d, 5a and 6a: Tested single and double mutants did not confer any FC (FC ranging from 0.8-2, mostly being around 1)				

Note: Large numbers of mutants tested without any effects on FC (for example double mutants for genotype 1a virus) are not shown in this table.

The Applicant did a comparison of effects by various NS5A RAVs on PIB and the presently approved NS5AS inhibitors (DVC, LDV, VEL, OBV, ELB). In summary, the resistance barrier seems higher for PIB than for other approved agents of the class (see following table).

Table 5 - Comparison of fold change in EC_{50} by NS5A amino acid substitutions for various NS5A inhibitors

HCV Subtype	NS5A AA Substitutions	PIB	DCV	OBV	ELB	LDV	VEL
1a	M28A	2.0	-	-	61	-	-
	M28T	2	437	8965	15	61	7.5
	M28V	1.8	1.0	58	1	0.6	-
	Q30E	2.4	-	1326	-	5458	37
	Q30H	1.0	154	3	6	183	2.3
	Q30R	1.7	178	800	16	632	2.2
	L31M	1.1	140	2	10	554	16
	L31V	1.3	614	155	61	-	>100
	H58D	1.1	124	243	6	1127	7.3
	Y93C	1.7	383	1675	11	1602	11
	Y93H	6.7	2324	41383	220	1677	609
	Y93N	7.0	8641	66740	929	>14,706	2758
	Q30R+L31M	3.0	16785	504	-	-	198

	Q30R+Y93H	260	-	351081	-	-	>419
	L31M+H58D	23	-	-	-	-	>419
	L31M+Y93C	6.1	-	1973	-	-	5515
	H58D+Y93N	1969	-	-	-	-	>372
1b	L28M	1.0	1.2	2	2	-	-
	L31F	1.2	1.4	10	15	-	-
	L31M	1.5	1.4	0.9	1	-	-
	L31V	0.8	2.5	8	4	-	1
	Y93H	0.6	7.3	77	17	>1000	1.2
	L31V + Y93H	0.9	1225	12328	-	-	>100
2a	F28S	1.2	-	11618	-	-	91
3a	A30K	1.1	44	-	50	>10	-
	Y93H	2.3	2154	6728	485	>20	>100
	Y93S	-	-	-	-	-	>100
6a	L31V	1.0	-	68	-	-	>100

GLECAPREVIR/PIBRENTASVIR COMBINATION

Additive activity was documented for PIB and GLE. Moreover, combination resulted in enhanced suppression of resistant colony emergence indicating a higher genetic barrier to resistance when GLE and PIB are combined. Combination of each agent with sofosbuvir resulted in additive to synergic activity. Of note, combination of each agent with RBV also led to additive to synergistic inhibition of HCV replication.

CLINICAL VIROLOGY

Phase IIa Monotherapy Study (M13-595)

This was a Phase 2a, randomized, open-label, multicenter dose-ranging study that explored the safety, tolerability, pharmacokinetics, and antiviral activity of GLE and PIB administered as monotherapy for 3 days in HCV GT1-infected treatment-naïve adults with and without compensated cirrhosis. GLE was dosed 100 to 700 mg QD, and PIB dosed 15-240 mg (15, 40, 120 or 240 mg) QD. Following monotherapy patients received Viekirax + Exviera + RBV for 12 weeks.

An immediate and substantial decline in HCV viral load was observed on study day 1 for all doses of ABT-493 (100 mg to 700 mg QD), with slightly slower onset with the 100 mg dose. A ~4 log10 decline (range: –3.7 to –4.2 log10 IU/mL) in mean HCV viral load was observed in all GLE (ABT-493) dose groups after 3 days, irrespective of cirrhosis status.

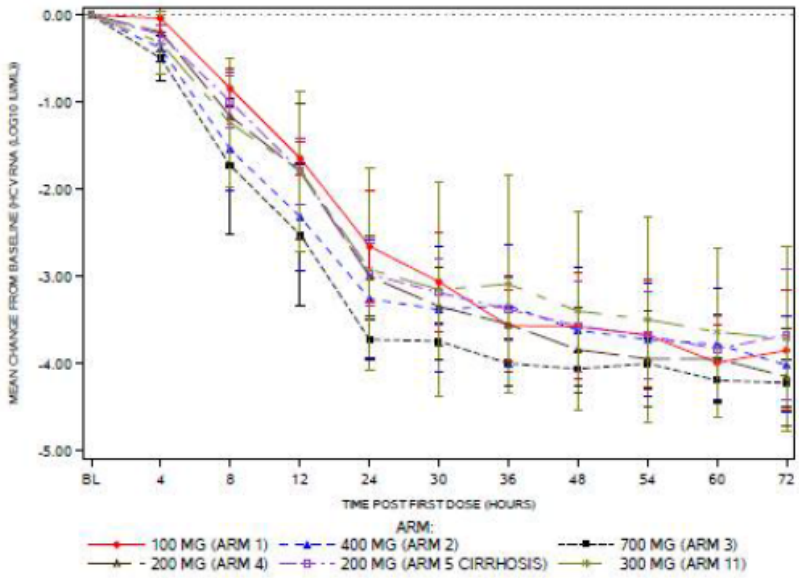


Figure 8 - Mean change in HCV RNA from baseline to each time point during ABT-493 monotherapy

An immediate and substantial decline in HCV viral load was also observed on Study Day 1 for the 40 mg, 120 mg, and 400 mg doses of ABT-530. A ~4 log10 decline (range: –3.8 to –4.3 log10 IU/mL) in mean HCV viral load was observed in these PIB (ABT-530) dose groups after 3 days, irrespective of cirrhosis status. The 15 mg dose has been found to result in statistically lower maximal mean HCV RNA decrease (–3.38 log10 IU/mL at 3 days, P < 0.01 for each dose comparison).

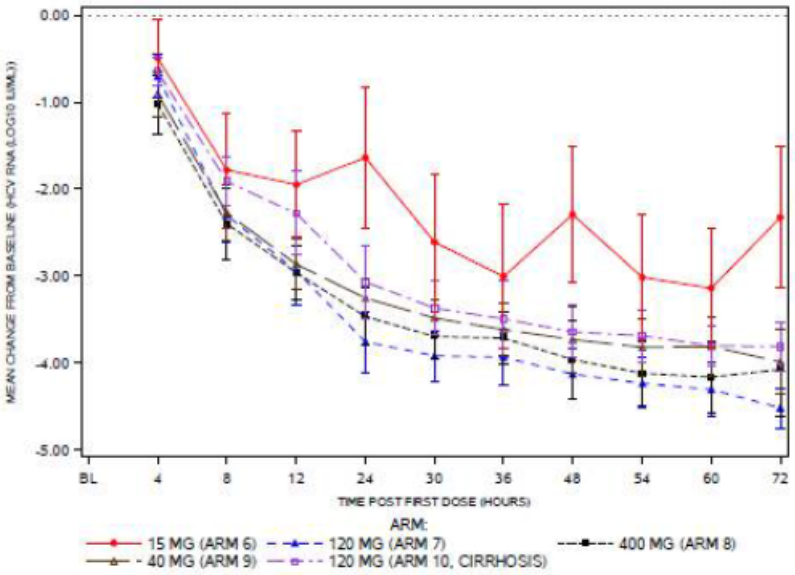


Figure 9 - Mean change in HCV RNA from baseline to each time point during ABT-530 monotherapy

Resistance analysis in monotherapy study

Resistance analysis was conducted on all baseline samples from subjects receiving GLE) or PIB and at post-baseline time points in samples with HCV RNA ≥ 1000 IU/mL.

Among the 30 genotype 1a- and 5 genotype 1b-infected subjects with post-baseline sequence data during the ABT-493 monotherapy period, 1 genotype 1a-infected subject (with Q80K pre-existing at baseline) had a treatment-emergent A156T variant in NS3. The patient was in the 700 mg dose group.

Among the 33 genotype 1a- and 7 genotype 1b-infected subjects who received ABT-530 and had baseline sequencing data, 3 genotype 1a-infected subjects with pre-existing variants in NS5A at baseline had multiple treatment-emergent variants in NS5A during monotherapy. All 3 subjects had preexisting variants that as single variants do not confer resistance to ABT-530, but acquired additional variants at resistance-associated amino acid positions (30, 31, 32, 58, 92, and/or 93) during monotherapy.

2.4.3.1. QT study

Study M15-543 was performed in 48 healthy volunteers accordingly to the ICH E14 guideline. GLE and PIB were co-administered as single doses of 400 mg and 120 mg, respectively, or 600 mg and 240 mg, respectively. The active control was moxifloxacin.

The active control is positive, and the combination GLE + PIB at supra-therapeutic doses is negative.

While the GLE/PIB could have been further increased, the negative results of this study are reinforced by the absence of particular signal based on electrophysiological investigations and animal data.

2.4.3.2. PK/PD relationships

Efficacy

The exposure-efficacy relationships were evaluated for SVR12 and rapid virologic response (RVR), defined as an undetectable serum HCV RNA at Week 4 of treatment. Data were issued from 2635 subjects who received the GLE and PIB combination, with or without RBV, across 9 Phase 2 and 3 studies.

GLE exposure was not significantly associated with SVR12 rates across all evaluated populations at the proposed GLE/PIB dose and durations. PIB exposure was a statistically significant predictor of SVR12 ($p < 0.05$) in treatment-naïve and PRS-experienced non-GT3 subjects and treatment-naïve GT3 subjects. A 50% decrease in PIB AUC resulted in a 0.8% decrease in SVR12 (from 99.7% to 98.9%) for treatment-naïve and PRS-experienced non-GT3 subjects, and a 3.3% decrease in SVR12 (from 98.1 to 94.8%) for treatment-naïve GT3 subjects. Due to the low virologic failure rates, a 50% decrease in PIB exposure is not expected to have a clinical meaningful impact on SVR12 rates.

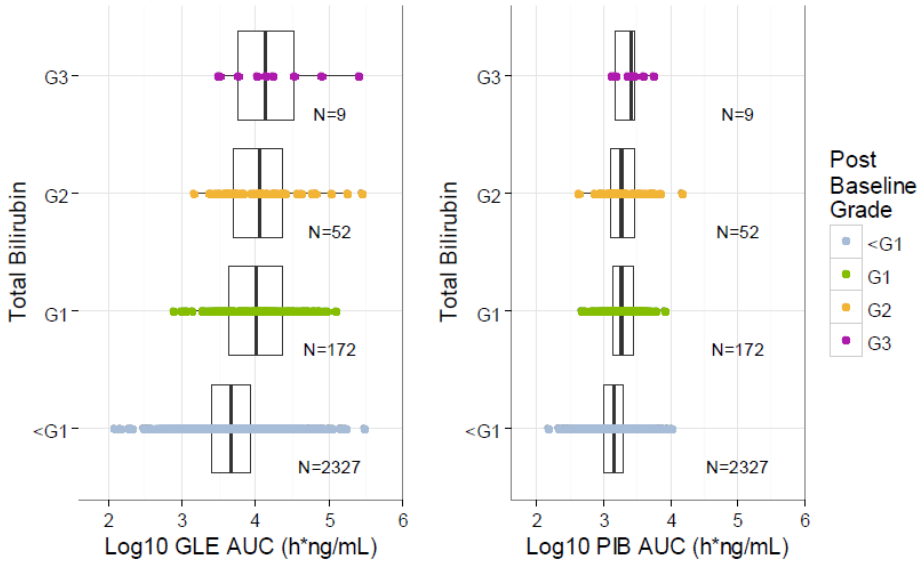
No apparent correlation was observed between RVR and GLE or PIB AUC from GT1 to GT5. Although a slight trend between RVR and GLE quartiles was observed for GT6-infected subjects, the overall RVR rate in GT6-infected subjects is comparable or higher than the RVR rates observed in other non GT6-infected subjects. The logistic regression analyses did not identify significant relationship between GLE/PIB exposure and RVR within the GLE and PIB exposure ranges evaluated in the analyses.

Similar relationships were observed when C_{trough} was used as a measure of exposure.

Safety

No positive exposure-response relationship was observed between PIB and GLE exposures and ALT elevations. Results were similar when using Cmax instead of AUC.

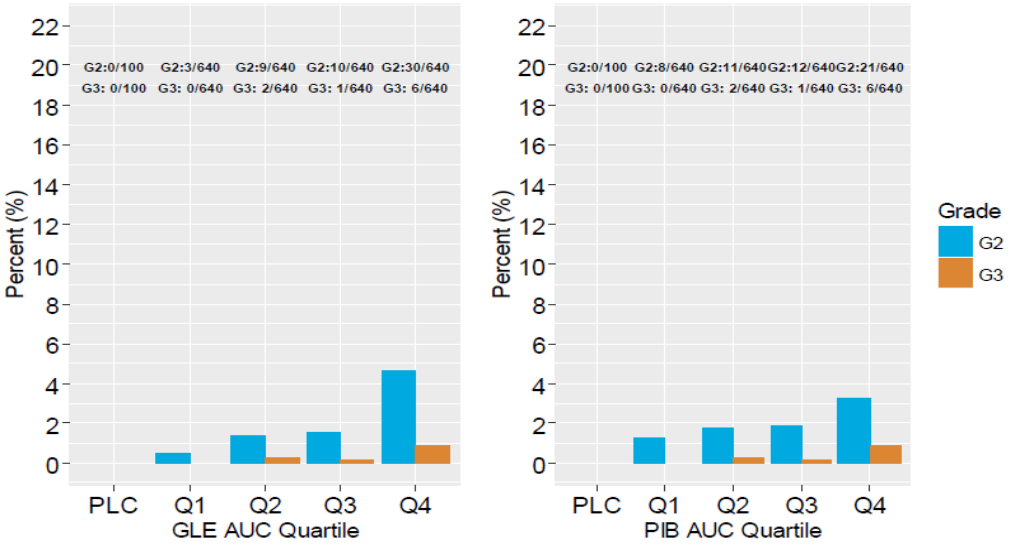
The frequency of ≥ Grade 2 post-baseline total bilirubin values increased with increasing GLE and PIB AUC values. Based on the logistic regression analyses, higher GLE AUCs are correlated with higher odds of post-baseline total bilirubin elevation ≥ Grade 2. PIB AUC values were not significantly associated with ≥ Grade 2 total bilirubin elevation. Results were similar when using Cmax instead of AUC:



Box = Interquartile range (IQR)

Figure 10 - Maximum post-baseline total bilirubin elevation in grade versus AUC values

The incidence and severity of post-baseline total bilirubin elevations appeared to increase with increasing GLE and PIB exposures. Increasing GLE exposure to 2-fold is predicted to increase the rate of post-baseline total bilirubin elevation ≥ Grade 2 from 2.38% to 3.71%, respectively, which is not considered to be clinically meaningful.



Note: The first bar represents incidence (%) of events in subjects receiving placebo. The other four bars show the incidences of events for each quartile of drug exposure. The numbers at the top of each bar give the number of events over the number of subjects.

Figure 11 - Percent of subjects with post-baseline total bilirubin elevation ≥ grade 2 versus AUC

GLE and PIB exposures in subjects with diarrhoea were comparable to the exposures observed in other subjects and their GLE and PIB exposures fell within the exposure ranges of subjects who did not have diarrhoea. The frequency of diarrhoea appears to be not associated with GLE or PIB AUC values. Logistic regression analyses did not identified association between diarrhoea and GLE or PIB exposures. Results were similar when using Cmax.

2.4.4. Discussion and conclusion on clinical pharmacology

Pharmacokinetic properties:

Several formulations of GLE and PIB (as separated or combined tablets) were used during the clinical development of GLE/PIB. As regards the absorption properties of the FDC GLE/PIB (corresponding to the tablet used in all the Phase 3 studies and submitted within this MAA procedure), it could be noted that this tablet should be administered with food to maximize GLE and PIB exposures and reach plasmatic concentrations equivalent to those measured with separated tablets of GLE and PIB used in Phase 2 studies without regard to food.

According to the results of the mass-balance study M13-890, GLE and PIB are both not significantly metabolized. The plasmatic unchanged GLE and PIB are mostly excreted in faeces and their renal clearance is negligible, with less than 1% of the products detected in urine. The study performed in renal impaired subjects shows that a maximum average increase of ≈50% for GLE and PIB exposure is observed in subjects with eGFR < 30 ml/min, with doubled exposures in some patients. Although this increase is not clinically relevant and could support the use of GLE/PIB in renal impaired subjects, such increase was not expected given renal elimination was not identified as a significant route of elimination. In the same way, the systemic exposure of GLE and PIB is significantly increased in moderate and severe hepatic impaired subjects, although oxidative metabolism was not identified as a significant route of elimination.

GLE and PIB PK profiles were mainly characterized in healthy subjects with the separated tablet formulations. In HCV patients, PK data were collected by sparse sampling in Phase 2 and Phase 3 studies

and analysed using a population PK (PPK) approach. As a result, the estimated exposure of PIB in HCV-infected subjects is lower than those measured in healthy subjects (AUC24 at 2170 ng.h/ml in healthy subjects vs 1430 ng.h/ml in HCV subjects without cirrhosis). Furthermore, GLE and PIB exhibited greater than dose-proportional increase of their exposure. This non-linear PK property of GLE and PIB was modelled based on the findings of dose-escalation studies conducted in healthy volunteers and introduced as a fixed effect in the PPK analysis where only HCV patients' data were included.

Interactions

In vitro

GLE is mainly cleared through the biliary and fecal route. Only 22,6 % of the administered dose represents the parent drug, about 42% was the sulphonamide hydrolysis product M6 yielded by gut microflora and 26% gather oxidative metabolites and their sulphonamide hydrolysis products.

PIB is mainly recovered as unchanged in feces about 98,5% of the total drug based on the results of the mass-balance study in healthy volunteers.

The effect of any CYP inhibitors or inducers on PIB pharmacokinetics is not expected to be significant and clinically relevant.

GLE inhibits CYP2C8, CYP2C9 and CYP3A4. PIB has not shown any CYP inhibition at concentration up to 30µM. GLE and PIB does not exhibit any CYP2B6 inhibition. Besides, it is agreed that neither GLE nor PIB are time-dependent inhibitors of the studied CYP450. It cannot be excluded that GLE and PIB, induce CYP3A4.

GLE and PIB inhibited in vitro UGT1A1 and UGT1A4 but did not show inhibition of UGT1A6, UGT1A9 or UGT2B7 (IC50 >50 µM) in human liver microsomes.

GLE and PIB are both substrates of the efflux transporters P-gp and/or BCRP. GLE is a substrate of the uptake transporter OATP1B1 and 1B3 but not PIB. Neither GLE nor PIB is an OCT-1 substrate.

The liability for GLE and PIB to be substrate of BSEP (bile salt export pump) has not been investigated.

GLE and PIB are P-gp and BCRP, BSEP and OATP1B1 inhibitors. GLE also inhibits OATP1B3. Inhibition of OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2K by GLE and PIB has not been identified up to 30µM.

In vivo

GLE and PIB combination

The effect of GLE on PIB and reciprocally has been assessed as part of the study M13-586, Arm 1. Results show that that GLE (400 mg/day) significantly raises PIB exposure about 3,5-fold probably due to P-gp and BCRP inhibition.

P-gp substrate

GLE and PIB increase the exposure of digoxin of about 48% with a 90% CI [1,4-1,57] and its Cmax of about 72% with a 90%CI [1,45-2,04]. The Applicant therefore recommends a decrease of about half the dose of digoxin. This is not supported by CHMP. As a matter of fact, this effect could be more pronounced in the clinical setting notably, in women patients in whom the therapeutic margin of digoxin is narrower than in men, and in patients with an altered renal function. This study does not sufficiently reflect the clinical conditions to decide of any dose recommendations. Caution and therapeutic concentration monitoring of digoxin is recommended.

Likewise, with GLE and PIB, dabigatran AUC and Cmax increase about 2,4-fold and 2-fold, respectively. The magnitude of this interaction is similar to the one observed with dronedarone, a P-gp inhibitor, with which the combination of dabigatran is strictly contra-indicated. Therefore the proposed SmPC warning to not recommend dabigatran with the FDC is not supported. Dabigatran with GLE/PIB is contra-indicated.

The combination with GLE/PIB led to increase statins exposure up to 8-fold. Therefore, GLE/PIB should be contra-indicated with atorvastatin and simvastatin, and not recommended with lovastatin. With pravastatin and rosuvastatin, a low dose should be used.

EE containing oral contraceptives

Oral contraceptive agents undergo metabolism by multiple pathways as CYP450 and UGT. EE is also a substrate of OATP1B1 and 2B1. With GLE and PIB, plasma exposures of EE, norgestrel, norgestromin and levonorgestrel increase about 28% and 40 %, 63%, 44%, and 68% respectively. Usually, these changes are not expected to be clinically relevant. Nevertheless the onset of asymptomatic grade 1 (n=3), 2 (n=1) and 3 (n=1) ALT elevation in 5 healthy women is compelling and foreshadow that these events, actually, may be more pronounced and symptomatic in the target population intended to be treated by GLE/PIB. The Applicant proposes to not recommend the combination of this DAA with EE containing regimen. This recommendation is not supported by CHMP, who agreed that this should be strengthened to a contra-indication.

Inducers: Carbamazepine and rifampicin

With rifampicin, GLE and PIB exposure decrease about 88% and 87%, respectively. With carbamazepine, this is about 66% and 50% respectively, but the 200 mg BID tested dose of carbamazepine being lower than the standard therapeutic dose, this warrants caution in the interpretation. Therefore, rifampicin and carbamazepine are contra-indicated with GLE/PIB.

Acid-reducing agents

GLE/PIB can be used with omeprazole at a dosage that does not exceed 20 mg QD.

Ciclosporin

With ciclosporin, 100 mg/day, GLE and PIB exposure (AUC) increase about 14%, 37% and 22%. On the contrary, with ciclosporin 400 mg, GLE and PIB exposure raises about 5- and 1,9- fold, respectively, whereas ciclosporin exposure falls within the 90%CI of [0,8-1,25].

These difference can be explained by the balance between the three compounds towards P-gp, BCRP and OATP and their affinity/inhibition for these transporters whereas at 400 mg day, ciclosporin inhibitory effect counterbalances this state and inhibition of GLE and PIB efflux and uptake (only with GLE) transport by ciclosporin prevails over.

GLE/PIB is not recommended for use in patients requiring stable ciclosporin doses > 100 mg per day. If the combination is unavoidable, use can be considered if the benefit outweighs the risk with a close clinical monitoring.

HIV boosted protease inhibitors: DRV/RTV, ATV/RTV and LPV/RTV

The applicant has proposed a differential approach for LPV/RTV and DRV/RTV (not recommended) as compared to ATV/RTV (contra-indicated). Indeed, although PK parameters of GLE and PIB were significantly affected in presence of LPV/RTV and DRV/RTV, the concern on increased transaminases were mainly derived from the findings with ATV/RTV. After discussion through the procedure CHMP agreed to maintain close scrutiny in the post marketing setting.

The combination of efavirenz with GLE/PIB is not recommended.

No clinically relevant interaction is expected with GLE/PIB and no dose adjustment is needed with amlodipine, felodipine, valsartan, losartan, buprenorphine/naloxone, methadone, abacavir, dolutegravir, emtricitabine, lamivudine, rilpivirine, raltegravir, lamotrigine, midazolam, caffeine, dextromethorphan, tolbutamide, norethindrone, levonorgestrel, norgestimate, tenofovir alefenamide.

Pharmacodynamics:

Glecaprevir/pibrentasvir is a fixed dose combination of 2 new generation pan-genotypic DAA.

Glecaprevir is an inhibitor of HCV NS3/4A protease with high pan-genotypic activity, with mean EC50 ranging from 0.8 to 4.6 nM across GT1-4 and GT6. In contrast to previous protease inhibitors, this new generation PI has important potency against HCV GT 2 and GT3, even though the activity is lower than against GT1 (2- to 5- fold the activity against genotype 1). The Applicant has explored its use in combination with pibrentasvir in all genotypes.

In vitro, glecaprevir showed optimized pharmacodynamics properties as compared to previous PIs. Indeed, apart from the poorly fit A156T resistance-associated substitution (RAS), glecaprevir activity is poorly affected (<5-fold loss of activity) by common GT1 RAS associated with virologic failure to other PIs, including single substitutions at key resistance-associated positions R155 or most but not all substitution at position D168.

In vitro selection experiments and studies on effects by various amino acid substitutions on the susceptibility to GLE and PIB showed that substitutions at positions A156 and D168 are key mutations for GLE across genotypes 1-6. These NS3/4A RAVs are typical for other approved agents of this class: telaprevir (R155, A156), boceprevir (156, 155), simeprevir (R155, D168), grazoprevir (D168, 156), paritaprevir (D168, R155). These RAVs have a low viral fitness, and as a consequence they are infrequently detected in viruses from the untreated patient. It was also previously shown that such RAVs, selected during failing HCV therapy (containing an HCV protease inhibitor), reverted to wild type within 1 year of follow-up in the majority of cases (e.g. Sullivan 2013). Provided that a certain time would elapse from a previous treatment failure with NS3/4A-containing therapy, such previously selected drug resistance may therefore not have a relevant impact on GLE antiviral activity in a subsequent re-treatment.
Naturally occurring NS3 polymorphisms seen in higher frequencies have a viral fitness close to that of wild type virus. For the NS3/4A class, Q80K, detected in 10-30% of untreated GT1a-infected patients, has been shown to lower treatment outcomes for some regimens (simeprevir, paritaprevir), despite a limited impact on genotypic susceptibility. This polymorphism has no impact on GLE in vitro susceptibility, or treatment outcomes. The one and only NS3 polymorphism with a negative impact on treatment outcomes with GLE/PIB, concerning genotype 3-infection, was substitution A166S, which was detected in the baseline virus of around 9% of genotype 3-infected patients. This clinical impact is not so clear from the in vitro results (not selected in vitro, and to our understanding with no impact on in vitro susceptibility) The applicant was requested to discuss this issue and has clarified that the apparent enrichment of A166S at baseline in the virologic failure subjects was most likely coincidental and does not contribute to virologic failure.
Pibrentasvir is an inhibitor of HCV NS5A with picomolar pan-genotypic activity across all genotypes (EC50 values of 1.4 pM to 5.0 pM in GT1-6). PIB appears similarly highly potent in all genotypes including GT1, GT2 and GT3, which contrast with other NS5A inhibitors and in the different subtypes tested (notably in GT4 and GT6). Moreover, in vitro activity does not seem to be significantly impacted by presence of common RAS (notably L31M in GT2a or Y93H, A30K in GT3).

In vitro, pibrentasvir retains activity against Y93H which confers to this drug a potential advantage over other NS5A.

While certain double and triple mutants conferred fold changes to genotype 1a and genotype 3a virus, most of the combinations studied did not. For the other geno/sub types, the double/triple mutants studied did not confer a seemingly relevant FC to PIB in vitro. In analogy with A166S and outcomes in genotype 3-infection, the one baseline NS5A substitution (A30K) that was associated with a reduced clinical efficacy (again in genotype-3 infection, detected in 6% of baseline samples) was not selected in vitro, and yielded no fold change. The applicant, in response to the day 90 LoQ, further underlines that A30K unlike Y93H requires at least two nucleotide changes from the WT sequence.

Additive activity was documented for PIB and GLE and combination of both drugs has been shown to increase the genetic barrier to resistance. There was additive to synergistic activity with sofosbuvir, with ribavirin.

Glecaprevir has been shown to have no specific activity against HIV and HBV. Moreover, GLE activity was not impacted in presence of common HIV PIs, lopinavir and darunavir, and vice versa.

As regards the salient aspect of the clinical virology, in monotherapy study in GT1, a ~4 log decline in viral load was documented after 3 days of each GLE or PIB monotherapy. Few patients developed RAS at key position in NS3 or NS5A. Unfortunately, the viral kinetic/resistance in monotherapy has not been explored in other GT, notably in GT3.

The applicant's choice in monotherapy design (only in GT1 patients) has limitation to adequately substantiate the genetic barrier in the key patient population of GT3 patients.

As regards the PK/PD relationships for safety aspects, a trend to higher incidence of total bilirubin elevation in subjects with higher GLE exposure was highlighted. This may be due to the inhibition of UGT1A1 by GLE/PIB. However, the clinical significance of such relationship seems limited.

Finally, based on the total amount of in vitro, in vivo data and the QTc study, this FDC does not raise particular issue on the risk of QT prolongation.

2.5. Clinical efficacy

2.5.1. Dose response studies

The GLE/PIB 300/120mg dose has been selected to maximize SVR and minimize selection of resistant variants while balancing the safety of this combination. This dose selection was made on the basis of the following studies:

- A Phase 2a monotherapy study in HCV GT1-infected patients (Study M13-595) that showed that GLE doses of 100 mg to 700 mg QD or for PIB doses of 40 mg to 400 mg QD led to similar decreases ~4 log in mean HCV plasma RNA viral load from baseline on day 3.

Table 6 - Maximal decrease in HCV GT-1 RNA with GLE or PIB monotherapy (ITT population)

	GLE Dose Groups					PIB Dose Groups			
Variable	100 mg	200 mg[a]	300 mg	400 mg	700 mg	15 mg	40 mg	120 mg[a]	400 mg
N	8	16	8	8	9	8	8	16	8
Mean Change[b]	–4.11	–4.06	–3.79	–4.02	–4.31	–3.38	–4.08	–4.21	–4.25

a. Subjects with cirrhosis and subjects without cirrhosis.

b. Least square mean maximum change from baseline expressed as $\log_{10}$ IU/mL.

- Further, GLE doses of 300 mg and 200 mg combined with PIB 120 mg or 40 mg for 12 weeks have been evaluated in Phase II dose ranging studies (Part I and II of SURVEYOR studies). Rates of virologic failure were examined across genotypes and suggest GLE/PIB dose of 300/120 will maximize SVR rate compared to lower dose-combinations. Notably, two virological breakthroughs were observed in GT3-infected patients receiving 200mg GLE (and PIB 40mg and 120mg respectively) while no GT3 infected subject receiving 300 mg GLE combined with 120 mg PIB experienced virologic breakthrough. In addition, in GT1, 1 patient had relapse in the 40mg PIB arm while all GT1 achieved SVR in the 120mg PIB arm (co-administered with the same dose of GLE).

Table 7 - Summary of virologic failures observed in dose-ranging studies M14-867 and M14-868 (part 1 and part 2)

	Studies M14-867 and M14-868 Part 1 and 2 (All Genotypes)	
DAA Regimens with 12-Week Duration	**Breakthrough**	**Relapse Before SVR_{12}**
All 200 mg GLE Arms	0.81% (2/246)	2.4% (6/246)
All 300 mg GLE Arms	0.35% (1/285)	1.1% (3/285)
All 40 mg PIB Arms	1.4% (1/69)	4.3% (3/69)
All 120 mg PIB Arms	0.43% (2/462)	1.3% (6/462)
200 mg GLE + 40 mg PIB	1.4% (1/69)	4.3% (3/69)
200 mg GLE + 120 mg PIB	0% (0/121)	2.5% (3/121)
200 mg GLE + 120 mg PIB + Ribavirin	1.8 % (1/56)	0% (0/56)
300 mg GLE + 120 mg PIB	0.39% (1/258)	1.2% (3/258)

Cross reference: Studies M14-867, M14-868

- Moreover modeling and simulations including simulations within difficult to treat populations or with 8 weeks treatment duration suggest that higher SVR rates can be achieved with a regimen of GLE/PIB dose of 300/120mg compared to lower dose combinations. Exposure-efficacy analyses as well as results from phase II studies (in non-cirrhotic patients) suggest that addition of ribavirin would not have a meaningful impact on SVR.
- Exposure safety analysis shows wide safety margins for GLE exposure (at least 6-fold) to ALT and total bilirubin elevations. Although GLE 300 mg increases PIB exposure at 120 mg by 4-fold, the PIB exposure was less than the exposures of PIB 600 mg QD for which favorable safety profile was reported in study M13-356.

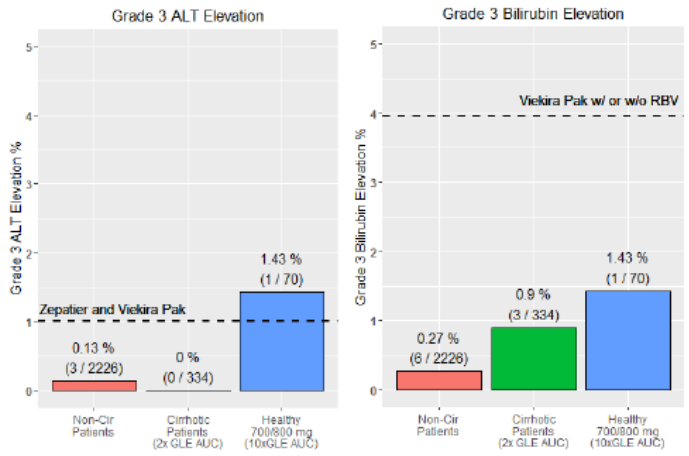


Figure 12 - Summary of the incidence rates in HCV-infected subjects who received the proposed GLE/PIB 300 mg/120 mg dose and healthy subjects who received 700 mg or 800 mg GLE

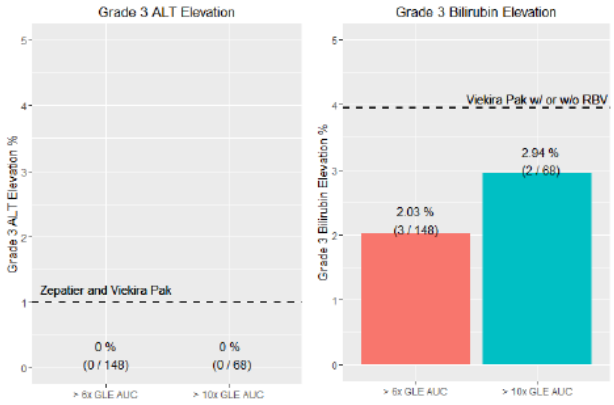


Figure 13 - Summary of the incidence rates in HCV-infected subjects who have high GLE exposures (6-fold and 10-fold higher than the geometric mean GLE exposure in subjects without cirrhosis)

2.5.2. Main studies

The clinical development program for GLE/PIB includes efficacy and safety data from 6 Phase III studies and 3 Phase 2 supportive studies that were conducted in various populations as illustrated in the following table:

Table 8 - Summary of the main studies

Clinical Study	Design	Study population		
		Genotype	Prior HCV treatment	Cirrhosis status
Phase III studies				
M13-590 ENDURANCE-1 N=703	GLE/PIB 300 mg/120 mg QD for 8 (n = 351) or 12 weeks (n = 352)	GT 1 HCV mono- or **HIV-coinfected**	TN or TE-PRS	None had cirrhosis
M15-464 **ENDURANCE-2** N = 202 **Placebo control**	GLE/PIB 300 mg/120 mg QD (n = 202) or placebo (n= 100) for 12 weeks	GT2	TN or TE-PRS	None had cirrhosis
M13-594 **ENDURANCE-3** N = 390 **Active control**	GLE/PIB 300 mg/120 mg QD for 8 (n = 157) or 12 weeks (n = 233) **or SOF 400 mg + DCV 60 mg QD** for 12 weeks (n = 115)	GT3	TN	None had cirrhosis
M13-583 ENDURANCE-4 N = 121	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 121)	GT4-GT6	TN or TE-PRS	None had cirrhosis
M14-172 **EXPEDITION-1** N = 146	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 146)	GT1, GT2, GT4-6	TN or TE-PRS	**All had compensated cirrhosis**
M15-462 **EXPEDITION-4** N = 104	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 104)	**GT1-6 and CKD stages 4 and 5**	TN or TE-PRS	20 (19%) had cirrhosis
Phase II supportive studies				
M14-867 Part 2	GLE 300 mg + PIB 120 mg	GT1, GT4-6	TN or TE-P/R	None had cirrhosis

SURVEYOR-I N = 66	QD for 8 weeks (N = 34 GT1) GLE 300 mg + PIB 120 mg QD for 12 weeks (N = 32 GT4-6)			
M14-868 **Part 1+2** **SURVEYOR-II** N = 190	GLE/PIB 300 mg/120 mg QD for 8, 12 or 16 weeks	GT2, GT3	TN or TE-P/R	**All (n=54 GT3) had cirrhosis in arm O and P**
M14-868 **Part 3** **SURVEYOR-II** N = 131	GLE/PIB for 12 weeks (N = 62 TE without cirrhosis or TN with cirrhosis) or 16 weeks (N = 69 TE with or without cirrhosis)	GT3	TN with cirrhosis TE-PRS with and without cirrhosis	**40 TN with cirrhosis** **47 TE with cirrhosis**
M14-868 Part 4 SURVEYOR-II N = 203	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 199) or 12 weeks (n = 25) for GT2 GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 58) for GT4,5,6	GT2, GT4,GT5, GT6	TN or TE-PRS	None had cirrhosis
M15-410 **MAGELLAN-1** N = 113	GLE/PIB 300 mg/120 mg QD for 12 (n = 66) or 16 weeks (n = 47)	GT1, GT4	**DAA-experienced to NS5A and/or PI**	26 (23%) had cirrhosis

As reflected in the above table, the main studies were conducted in non-cirrhotic treatment-naive patients or patients having failed previous treatment with PegIFN+ribavirin/PR (including some patients with PR+ Sofosbuvir)/PRS.

A small sample sized study was performed in DAA treatment experienced patients (almost exclusively GT1 and only 4 GT4), the MAGELLAN-1 (M15-410) study. Some HIV co-infected patients were included in the development programme and a dedicated study is ongoing in this population.

A dedicated study was performed in cirrhotic patients and in patients with CKD.

The studies shared some common features:

Inclusion/Exclusion criteria

Inclusion and exclusion criteria to define study populations were harmonized across the registrational studies; key inclusion and exclusion criteria in the majority of these studies are listed as follows:

Table 9 - Key Inclusion and Exclusion Criteria in the Pooled Phase 2 and Phase 3 Studies

Studies	Key Inclusion Criteria	Key Exclusion Criteria

M15-464[a]
M13-594[a]
M13-590[a]
M13-583[a]
M14-172[a]
M15-462[a]
M15-410 Part 1 Arm C[b] and Part 2[a]
M14-867 Part 2 Arms I and K[b]
M14-868 Parts 1 and 2 (Arms A, D, J, L, and O)[b], Part 3 (Arms Q and R)[a], and Part 4 (Arm S)[a]
	• Male or female, at least 18 years of age at time of screening
	• Subject had positive anti-HCV antibody and plasma HCV RNA viral load ≥ 1,000 IU/mL at screening
	• Chronic HCV infection defined as 1 of the following:
	  ○ Positive for anti-HCV antibody or HCV RNA at least 6 months before screening; or
	  ○ A liver biopsy consistent with chronic HCV infection; or
	  ○ Abnormal alanine aminotransferase levels for at least 6 months before screening
	• BMI is ≥ 18 kg/m^2 at the time of screening
	• Voluntarily signed and dated an informed consent form, approved by an Institutional Review Board/Independent Ethics Committee prior to the initiation of any screening or study specific procedures
	• Able to understand and adhere to the study visit schedule and all other protocol requirements
		• History of severe, life-threatening or other significant sensitivity to excipients of the study drug
		• Positive test result at screening for hepatitis B surface antigen (all studies) or anti-HIV-1 antibody (except Study M13-590)
		• Females who are pregnant or intending to become pregnant, or breastfeeding, and males with a female partner who was pregnant or is intending to become pregnant during the course of the study
		• HCV genotyping performed during screening indicating coinfection with more than 1 HCV genotype
		• Any cause of liver disease other than chronic HCV infection
		• Consideration by the investigator, for any reason, that the subject was an unsuitable candidate to receive GLE, PIB, or GLE/PIB
		• Child-Pugh B or C or history of liver decompensation.

BMI = body mass index; HCV = hepatitis C virus; GLE = glecaprevir; HIV-1 = human immunodeficiency virus 1; PIB = pibrentasvir; RNA = ribonucleic acid

a. Coformulated GLE/PIB.

b. Coadministered as GLE and PIB tablets, separately.

There were no upper limits for baseline body mass index (BMI) or age in the registrational studies and subjects were included regardless of any positive toxicology screen result.

Screening laboratory inclusion criteria were similar across all 9 studies, except for small differences in the Phase 2 supportive studies (and the study/parts in cirrhotic subjects or CKD Stage 4 or 5 subjects, as appropriate):

The following laboratory parameters must have been fulfilled at screening in the majority of these studies:

- Alanine aminotransferase and aspartate aminotransferase ≤ 10 × the upper limit of normal (ULN);
- Direct bilirubin ≤ ULN (for subjects without cirrhosis) or a total bilirubin ≤ 3 × ULN (for subjects with cirrhosis);
- Platelets ≥ 60,000/μL (≥ 40,000/μL in Study M15-462) and ≥ 90,000/μL in subjects with and without cirrhosis, respectively;
- Haemoglobin A1c indicating no uncontrolled diabetes (e.g., ≤ 8 or ≤ 8.5%);
- Haemoglobin ≥ the lower limit of normal;
- Albumin ≥ 2.8 g/dL or ≥ lower limit of normal in subjects with or without cirrhosis, respectively;
- International normalized ratio ≤ 2.3 or ≤ 1.5 in subjects with or without cirrhosis, respectively, unless subject had known haemophilia or was stable on an anticoagulant regimen affecting international normalized ratio.

The main differences between studies were related to HCV genotype, the presence or absence of severe renal impairment, and the presence or absence of cirrhosis.

Subjects with cirrhosis were allowed in 4 registrational studies (Study M14-172, Study M14-868 Part 3, Study M15-410 Part 2, and Study M15-462). A consistent definition for documenting the presence or absence of cirrhosis was employed:

An absence of cirrhosis was defined by documented evidence of:

- A liver biopsy within 24 months prior to or during screening, demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of ≤ 3, Ishak fibrosis score of ≤ 4; or
- A FibroScan® score of < 12.5 kPa within 6 months of screening or during the screening period; or
    - Subjects with an indeterminate FibroScan® score (12.5 ≤ score < 14.6) were to have a qualifying liver biopsy
- A screening FibroTest score of ≤ 0.48 and aspartate aminotransferase to platelet ratio index (APRI) < 1.
    - Subjects with an indeterminate FibroTest (0.48 < result < 0.75), or conflicting FibroTest and APRI results (e.g., FibroTest ≤ 0.48, but APRI ≥ 1) were to have a qualifying FibroScan® or qualifying liver biopsy

The presence of cirrhosis was defined by documented evidence of:

- Histologic diagnosis of cirrhosis on a liver biopsy e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of > 3 or Ishak fibrosis score of > 4; or
- FibroScan® score ≥ 14.6 kPa;
    - Subjects with an indeterminate FibroScan® score (12.5 ≤ score < 14.6) were to have a qualifying liver biopsy; or
- A screening FibroTest score of ≥ 0.75 and APRI > 2;
    - Subjects with an indeterminate FibroTest (0.48 < result < 0.75) or discordant FibroTest and APRI results (e.g., FibroTest ≥ 0.75, but APRI ≤ 2) were to have a qualifying FibroScan® or liver biopsy

Study designs:

All efficacy data through Post-Treatment Week 12 were included for the primary endpoint (sustained virologic response 12 weeks post dosing [SVR12]) and secondary endpoints of on-treatment virologic failure (OTVF) and post-treatment relapse. Comparisons to an active control, historical controls, and across arms with different treatment durations of GLE/PIB were conducted for the primary efficacy endpoint analyses.

The individual registrational studies employed different and complementary study designs, that is:

- Comparison to historical control: Studies M13-590, M15-464, and M14-868 Part 4 evaluated primary efficacy compared to a historical SVR12 rate for the current standard-of-care direct-acting antiviral agent (DAA) regimen at the time of study start. A -6% margin was used for non-inferiority to the historical rate in all of these comparisons.
- Duration controlled: Studies M13-590, M13-594, M14-868 (Part 3) and M15-410 (Part 2) each implemented a duration-controlled study design evaluating either 8 weeks versus 12 weeks with a -5% margin (Study M13-590), 8 weeks versus 12 weeks with a -6% margin (Study M13-594), or 12 weeks versus 16 weeks without hypothesis testing (Study M14-868 Part 3 and Study M15-410 Part 2) of GLE/PIB.
- Placebo-controlled: Study M15-464 was randomized, double-blind, and placebo-controlled, and enabled characterization of the GLE/PIB safety profile.
- Active-controlled: Study M13-594 randomized and compared 12 weeks GLE/PIB versus 12 weeks sofosbuvir (SOF) and daclatasvir (DCV) with a -6% non-inferiority margin.
- Open-label, single arm: Additional studies employed single-arm, open-label, assigned duration study designs among important subpopulations, including:

  (1) subjects with compensated (Child-Pugh Class A) cirrhosis (Study M14-172 and Study M14-868 Part 3),
  (2) subjects with CKD Stage 4 or 5 (Study M15-462), and
  (3) HCV GT2-, GT4-, GT5-, and GT6-infected subjects without cirrhosis (Study M13-583, 12-weeks of GLE/PIB in HCV GT4, GT5 or GT6; Study M14-868 Part 4: 8 weeks of GLE/PIB in HCV GT2, GT4, GT5, or GT6).

A single, active comparator or historical control could not be employed across the registrational studies since, at the time of study conduct, there was no single regimen that was approved across all HCV genotypes:

- Study M13-590: The first of the 3 ranked primary efficacy endpoints was a comparison of the SVR12 rate of the 12-week treatment duration (Arm A) in the intention-to-treat mono-infected HCV GT1 population excluding prior SOF + RBV ± pegylated interferon (pegIFN) failures (ITT-PS) to the historical SVR12 rate of 97% from ombitasvir/paritaprevir/r + dasabuvir ±RBV or SOF/LDV.

- Study M15-464 Arm A and Study M14-868 Part 4 Arm S GT2: Non-inferiority of the SVR12 rate of GLE/PIB 300 mg/120 mg QD for 12 weeks (Study M15-464) or 8 weeks (Study M14-868 Part 4 Arm S GT2), excluding prior SOF + RBV ± pegylated interferon (pegIFN) failures, to the historical SVR12 rate of 95% of SOF + RBV for 12 weeks was to be established.

- Study M13-594: Non-inferiority of the SVR12 rate for GT3-infected TN subjects without cirrhosis of GLE/PIB 300 mg/120 mg QD for 12 weeks (Arm A) could be achieved with respect to the active control arm.

During the conduct of the Phase 3 Study M15-464, treatment assignment remained blinded to the investigator, subject, study site personnel, and AbbVie throughout the 12-week Double-Blind Treatment Period for an unbiased comparison of safety. All other Phase 2 and 3 studies were open-label.

Randomization was utilized in Studies M15-464, M13-594, M13-590, M14-868, and M15-410. Studies M13-583, M14-172, and M15-462 were single-arm studies; therefore, no randomization was performed. Study M14-867 was not randomized.

Missing Data Imputation for SVR :

For analyses of SVR, subjects missing visit values will have backward imputation applied, if possible. For backward imputation, if the nearest HCV RNA value after the SVR window is unquantifiable or undetectable, then it will be used to impute the HCV RNA value in the SVR window. If a subject is missing an HCV RNA value within the appropriate SVR window after performing backward imputation, then this value will be imputed with an HCV RNA value from a local laboratory if present; otherwise, the HCV RNA value will be missing. Subjects with missing HCV RNA data in the analysis window, after imputations, will be imputed as a failure.

Phase 3 studies

A Randomized, Open-Label, Multicentre Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 1 Infection (ENDURANCE-1)

Methods

Phase 3, randomized, open-label, multicentre study to evaluate the efficacy and safety of the ABT-493/ABT-530 combination regimen in HCV treatment-naïve or prior treatment-experienced chronic HCV GT1-infected or HCV GT1/HIV-1 co-infected subjects without cirrhosis for 8- and 12-week treatment durations.

Prior treatment experience:

- interferon [IFN], or
- pegylated interferon [pegIFN] with or without RBV, or
- SOF plus RBV with or without pegIFN

Treatments

- Arm A: ABT-493/ABT-530 (300 mg/120 mg once daily [QD]) for 12 weeks;
- Arm B: ABT-493/ABT-530 (300 mg/120 mg QD) for 8 weeks.

Objectives

Primary objectives

- show non-inferiority of SVR12 rates among mono-infected HCV GT1 DAA-naïve subjects (the percentage of subjects achieving SVR12) of 12 weeks of treatment with ABT-493/ABT-530 to the historical SVR rate established by current approved standard of care (SOC) regimens for mono-infected HCV GT1 DAA-naïve subjects (OBV/PTV/r + DSV ± RBV or SOF/LDV for 12 weeks);
- show non-inferiority in SVR12 rates among mono-infected HCV GT1 DAA-naïve subjects of the ABT-493/ABT-530 regimen for 8 weeks versus 12 weeks of treatment;
- assess safety of 8 and 12 weeks of treatment with ABT-493/ABT-530.

Secondary objectives

- percentage of subjects with SVR12 among mono-infected HCV GT1 subjects
- percentage of subjects with SVR12 among all HCV GT1 subjects
- percentage of subjects with SVR12 among subjects with HCV GT1/ HIV-1 coinfection
- percentage of subjects with SVR12 among prior SOF treatment-experienced HCV GT1 subjects
- percentage of subjects with on-treatment virologic failure; and percentage of subjects with post-treatment relapse.

Outcomes/endpoints

Primary endpoint

primary efficacy variable: SVR12.

Secondary endpoints

- percentage of subjects with SVR12 in the ITT-MS population (ITT mono-infected HCV GT1 subjects);
- percentage of subjects with SVR12 in the ITT population;
- percentage of subjects with SVR12 among subjects with HCV GT1/HIV-1 coinfection;
- percentage of subjects with SVR12 among prior SOF-treatment experienced HCV GT1 subjects;
- percentage of subjects with on-treatment virologic failure (defined as confirmed increase of > 1 log10 IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment); and
- percentage of subjects with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment; excluding subjects who had been shown to be re-infected).

Sample size

Approx. 620 subjects

Randomisation

HCV GT1-infected TN or TE subjects without cirrhosis were randomized in a 1:1 ratio into 1 of 2 treatment arms (310 subjects per arm); randomisation was stratified by screening viral load (< or ≥ 6 million IU/mL) and by HCV GT1 subtype (1b or non-1b).

Blinding (masking)

Open-label

Statistical methods

Primary efficacy analysis

- Efficacy of the 12-week treatment duration (Arm A): lower bound of the 2-sided 95% confidence interval for the percentage of subjects in Arm A achieving SVR12 is greater than 91% in the ITT-PS population (the intention-to-treat [ITT] subset of HCV mono-infected DAA-naïve subjects).
- Non-inferiority of the 8-week treatment duration (Arm B) to Arm A in SVR12 using a non-inferiority margin of 5% in the per protocol (PP) ITT-PS population (ITT-PS-PP) (all randomized subjects in the ITT-PS population, with the exception of subjects who prematurely

discontinued prior to Week 8, subjects who experienced virologic failure prior to Week 8, and subjects who had no HCV RNA value in the SVR12 visit window or later).
- Non-inferiority of the 8-week treatment duration (Arm B) to Arm A in SVR12 using a non-inferiority margin of 5% in the ITT-PS population.

Numbers analysed

703 subjects (352 in Arm A and 351 in Arm B) were randomized and received at least 1 dose of study drug.

A Randomized, Double-Blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493 / ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 2 Infection (ENDURANCE-2)

Methods

Phase 3, randomized, double-blind (DB), placebo-controlled multicentre study to evaluate the efficacy and safety of ABT-493/ABT-530 in chronic HCV GT2-infected subjects without cirrhosis, who were either HCV treatment-naïve or prior treatment-experienced (i.e., with interferon [IFN] or pegIFN ± RBV or SOF + RBV ± pegIFN).

Treatments

- Arm A: ABT-493/ABT-530 300 mg/120 mg once daily (QD) for 12 weeks
- Arm B: Matching placebo QD for 12 weeks followed by open-label ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks

Objectives

Primary efficacy objectives

- assess the efficacy (SVR12) of treatment with ABT-493/ABT-530 compared to a historical SVR12 rate of treatment with sofosbuvir (SOF) + ribavirin (RBV)
- assess the safety of 12 weeks of treatment with the ABT-493/ABT-530 combination regimen compared to placebo in adults with chronic hepatitis C virus (HCV) genotype (GT) 2 infection without underlying cirrhosis.

Secondary efficacy objectives

- assess the percentage of subjects treated with ABT-493/ABT-530 with on-treatment virologic failure during the double-blind (DB) treatment period,
- assess the percentage of subjects treated with ABT-493/ABT-530 with post-treatment relapse following the DB treatment period,
- assess the efficacy (SVR12) of ABT-493/ABT-530 among subjects with prior SOF + RBV ± pegylated interferon alfa-2a or alfa-2b (pegIFN) failure.

Outcomes / endpoints

Primary efficacy endpoint

- percentage of subjects with SVR12 among subjects treated with ABT-493/ABT-530 in the DB treatment period (Arm A), excluding prior SOF + RBV ± pegIFN failures.

Secondary efficacy endpoints

- percentage of subjects in Arm A, excluding prior SOF + RBV ± pegIFN failures, with on treatment virologic failure during the DB treatment period;
- percentage of subjects in Arm A, excluding prior SOF + RBV ± pegIFN failures, with post-treatment relapse following the DB treatment period;
- percentage of subjects in Arm A with prior SOF + RBV ± pegIFN failure with SVR12.
- percentage of subjects with on-treatment virologic failure, the percentage of subjects with posttreatment relapse, and the percentage of subjects with SVR12 among the prior SOF + RBV ± pegIFN failures

Sample size

291 to 321 subjects were planned to be enrolled in a 2:1 ratio to the ABT-493 and ABT-530 treatment arm or placebo (194 to 214 subjects in Arm A and 97 to 107 subjects in Arm B). The 21 to 51 subjects (14 to 34 subjects in Arm A) with prior SOF + RBV ± pegIFN failure were not to be included in the primary endpoint; therefore, 180 subjects were to be available in Arm A for the primary endpoint (SVR12).

Randomisation

The study consisted of 3 periods:

- Double blind (DB) treatment period: subjects randomized in a 2:1 ratio to receive either 12 weeks of ABT-493/ABT-530 (Arm A) or 12 weeks of matching placebo (Arm B), respectively.
- Open-Label (OL) Treatment Period: subjects randomized to placebo in the DB Treatment Period received OL ABT-493/ABT-530 for 12 weeks.
- Post-Treatment Period: subjects randomized to active drug (Arm A) who completed or prematurely discontinued study drug during the DB treatment period and subjects randomized to placebo (Arm B) who completed the OL Treatment Period or prematurely discontinued study drug in the OL Treatment Period were followed for 24 weeks post-treatment to monitor HCV RNA levels and to evaluate safety, efficacy, and the emergence and persistence of resistant viral variants.

Randomization of subjects was stratified into 3 strata by type of previous treatment experience, i.e., HCV treatment-naïve or the last treatment regimen that the subject had received:

- IFN or
- pegIFN ± RBV or
- SOF + RBV ± pegIFN

Blinding (masking)

During the DB treatment period, the applicant, investigators, and subjects were blinded to drug assignment and virologic results.

Statistical methods

Primary efficacy analysis

Percentage of subjects treated with ABT-493/ABT-530 with SVR12 compared to the 95% SVR12 rate of the current standard-of-care (SOF + RBV for 12 weeks). Non-inferiority margin 6%.

Secondary efficacy analysis

The percentage of these subjects treated with ABT-493/ABT-530 with SVR12 would be superior to the 95% SVR12 rate of the current standard of care (SOF + RBV for 12 weeks) if the LCB of the 2-sided 95% CI of the percentage of subjects with SVR12 was > 95%.

Numbers analysed

304 subjects were randomized and 302 subjects received at least 1 dose of study drug.

A Randomized, Open-Label, Active-Controlled, Multicenter Study to Compare Efficacy and Safety of ABT-493/ABT-530 to Sofosbuvir Co-Administered with Daclatasvir in Adults with Chronic Hepatitis C Virus Genotype 3 Infection (ENDURANCE-3)

Methods

Phase 3, randomized, open-label, active-controlled multicentre study to compare efficacy and safety of ABT-493/ABT-530 to SOF and DCV in treatment-naïve chronic HCV GT3-infected subjects without cirrhosis.

Treatments

HCV GT3-infected treatment-naïve subjects without cirrhosis were enrolled into 1 of 3 treatment arms:

- Arm A: ABT-493/ABT-530 300 mg/120 mg once daily (QD) for 12 weeks
- Arm B: SOF 400 mg + DCV 60 mg QD for 12 weeks
- Arm C: ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks

Objectives

Primary objectives

- to show non-inferiority in the percentage of subjects achieving SVR12 after 12 weeks of treatment with ABT-493/ABT-530 to that of patients achieving SVR12 after 12 weeks of treatment with sofosbuvir (SOF) and daclatasvir (DCV),
- to show non-inferiority of 8 weeks of treatment with ABT-493/ABT-530, and to assess safety of ABT-493/ABT-530 compared to SOF and DCV in adults with chronic hepatitis C virus (HCV) genotype 3 (GT3) infection.

Secondary objectives

- assess superiority of 12 weeks of ABT-493/ABT-530 to SOF and DCV based on SVR12,
- calculate percentages of subjects with on-treatment virologic failure
- calculate percentages of subjects with post-treatment relapse.
- assess pharmacokinetics and emergence and persistence of viral variants in these treatment regimens.

Outcomes/endpoints

Primary efficacy endpoint

- percentage of subjects achieving SVR12 in the ITT population. To support the primary comparisons, the analyses were also conducted in per protocol populations.

Secondary efficacy endpoints

- percentage of subjects with on-treatment virologic failure; and
- percentage of subjects with post-treatment relapse.

Sample size

Approximately 460 subjects were planned to be enrolled (230 in Arm A, 115 in Arm B, and 115 in Arm C).

Randomisation

Subjects meeting all eligibility criteria were initially randomized in a 2:1 ratio to Arms A or B. After enrolment in Arms A and B was completed, subjects were to be assigned to Arm C.

Blinding (masking)

Open-label

Statistical methods

Primary efficacy analysis

Non-inferiority in the SVR12 rate of the 12-week regimen (Arm A) to the standard of care (SOF + DCV) was shown if the lower bound of the CI for the difference (Arm A minus Arm B) was above the non-inferiority margin of –6% or if the lower bound of the CI for the SVR12 rate within Arm A was greater than 92%. Non-inferiority of Arm C to Arm A was defined similarly.

Secondary efficacy analysis

Superiority of Arm A to Arm B would have been shown if the lower bound of the CI for the difference in SVR12 rates between arms (Arm A minus Arm B) would have been above 0%.

Numbers analysed

506 subjects were randomized and 505 subjects (233 subjects in Arm A, 115 subjects in Arm B, and 157 subjects in Arm C) received at least 1 dose of study drug.

A Single-Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 4, 5, or 6 Infection (ENDURANCE-4)

Methods

Phase 3, single arm, open-label, multicentre study to evaluate the efficacy and safety of ABT-493/ABT-530 in HCV GT4-, GT5-, or GT6-infected subjects without cirrhosis, who were either HCV treatment-naïve or treatment-experienced (i.e., had failed prior interferon [IFN] ± ribavirin [RBV], pegylated interferon [pegIFN] ± RBV, or sofosbuvir [SOF] + RBV ± pegIFN).

Treatments

ABT-493/ABT-530 300 mg/120 mg once daily (QD) for 12 weeks.

Objectives

Primary objectives

- percentage of subjects achieving SVR12 after 12 weeks of treatment with ABT-493/ABT-530
- evaluate safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus (HCV) genotype (GT) 4, 5, or 6 infection

Secondary objectives

- calculate the percentage of subjects with on-treatment virologic failure and post-treatment relapse.

- assess pharmacokinetics and emergence and persistence of viral variants in this treatment regimen.

Outcomes/endpoints

Primary efficacy endpoints

- SVR12.

Secondary efficacy endpoints

- percentage of subjects with on-treatment virologic failure
- percentage of subjects with post-treatment relapse

Sample size

Approximately 130 subjects

Blinding (masking)

Open-label study

Statistical methods

Primary efficacy analysis

No formal hypothesis was tested. The number and percentage of subjects in the ITT population achieving SVR12 were summarized with a 2-sided 95% confidence interval (CI).

Secondary efficacy analysis

The percentage of subjects meeting each secondary efficacy endpoint was summarized with 2-sided 95% Wilson score intervals.

Numbers analysed

Analysed: 121 subjects were enrolled and received at least 1 dose of study drug.

A Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis (EXPEDITION-1)

Methods

Phase 3, single-arm, open-label, multicentre study to evaluate the efficacy and safety of ABT-493/ABT-530 in chronic HCV GT1-, 2-, 4-, 5-, or 6-infected subjects with cirrhosis who were either HCV treatment-naïve or prior treatment-experienced, i.e. interferon [IFN] or pegylated interferon [pegIFN] ± ribavirin [RBV] or sofosbuvir [SOF] + RBV ± pegIFN).

Treatments

ABT-493/ABT-530 300 mg/120 mg once daily (QD) for 12 weeks.

Objectives

Primary objectives

- percentage of subjects achieving SVR12 following 12 weeks of treatment with ABT-493/ABT-530
- evaluate the safety of ABT-493/ABT-530 in adults with chronic HCV GT 1, 2, 4, 5, or 6 infection and compensated cirrhosis

Secondary objectives
- calculate the percentage of subjects with on-treatment virologic failure
- calculate the percentage of subjects with post-treatment relapse
- assess PK and the emergence and persistence of viral variants in this treatment regimen.

Outcomes/endpoints

Primary efficacy endpoint
- SVR12. The number and percentage of subjects in the intention-to-treat (ITT) population achieving SVR12 were summarized with a 2-sided 95% confidence interval (CI).

Secondary efficacy endpoints
- The percentage of subjects with on-treatment virologic failure
- The percentage of subjects with post-treatment relapse

Sample size

approximately 175 subjects

The number of subjects in this study was based on practical considerations in enrolling subjects with cirrhosis.

Blinding (masking)

open-label

Statistical methods

No formal hypothesis was tested. The percentage of subjects with on-treatment virologic failure and post-treatment relapse was summarized with 2-sided 95% Wilson score intervals

Numbers analysed

146 subjects were enrolled and received at least 1 dose of study drug.

A Single-Arm, Open-Label, Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Renally-Impaired Adults with Chronic Hepatitis C Virus Genotype 1–6 Infection (EXPEDITION-4)

Methods

Phase 3, single arm, open-label, multicentre study to evaluate the efficacy and safety of ABT-493/ABT-530 for 12 weeks in HCV GT1 – GT6 infected treatment-naïve or prior treatment-experienced, i.e.: had failed prior

- interferon [IFN] or pegylated interferon [pegIFN] with or without ribavirin [RBV], pegIFN/RBV plus sofosbuvir [SOF], or SOF plus RBV

- subjects with or without cirrhosis, who had severe renal impairment or end-stage renal disease, including those on dialysis.
- subjects were categorized during screening as having chronic kidney disease (CKD) Stage 4 or Stage 5. Among HCV GT3-infected subjects, only treatment-naïve subjects with or without cirrhosis were eligible for enrolment.

Treatments

ABT-493/ABT-530 300 mg/120 mg once daily (QD) for 12 weeks.

Objectives

Primary objectives

- evaluate SVR12 after 12 weeks of treatment with ABT-493/ABT-530
- evaluate safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus (HCV) genotype (GT) 1 – GT6 infection with chronic renal impairment

Secondary objectives

- calculate the percentage of subjects with on-treatment virologic failure and
- calculate the percentage of subjects with post-treatment relapse
- assess PK and emergence and persistence of viral variants with this treatment regimen.

Outcomes/endpoints

Primary efficacy endpoint

- percentage of subjects who achieved SVR12 12 weeks after the last actual dose of study drug

Secondary efficacy endpoints

- percentage of subjects with on-treatment virologic failures;
- percentage of subjects with post-treatment relapse

Sample size

approximately 100 subjects.

Blinding (masking)

Open-label

Statistical methods

No formal hypothesis was tested.

Primary efficacy analysis

Number and percentage of subjects in the ITT population achieving SVR12 were summarized.

Secondary efficacy analysis

Percentage of subjects meeting each secondary efficacy endpoint was summarized.

Numbers analysed

104 subjects were enrolled and received at least 1 dose of study drug

Phase 2 studies

An Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without Ribavirin in Subjects with Chronic Hepatitis C Virus (HCV) Genotype 1, 4, 5, and 6 Infection (SURVEYOR-I)

Methods

This was a Phase 2, open-label, multicentre, 2-part study to evaluate the efficacy, safety, and pharmacokinetics of co-administration of ABT-493 and ABT-530 in chronic HCV GT1-, GT4-, GT5-, and GT6-infected subjects with compensated cirrhosis (GT1 only) or without cirrhosis (GT1, GT4, GT5, or GT6).

Treatments

Part 1

- Arm A: ABT-493 200 mg once daily (QD) + ABT-530 120 mg QD for 12 weeks
- Arm B: ABT-493 200 mg QD + ABT-530 40 mg QD for 12 weeks

Part 2

initiated based on evaluation of efficacy and safety results from Part 1, as follows:

- Genotype 1-infected TN or PR-experienced subjects without cirrhosis were enrolled into Arm K.
- Genotype 1-infected TN or PR-experienced subjects with compensated cirrhosis were enrolled into Arm F.
- Genotype 4-, GT5-, and GT6-infected TN or PR-experienced subjects without cirrhosis were enrolled into Arm I.

The regimens corresponding to each of those arms (30 subjects planned per arm) were:

- Arm K: ABT-493 300 mg QD + ABT-530 120 mg QD for 8 weeks
- Arm F: ABT-493 200 mg QD + ABT-530 120 mg QD for 12 weeks
- Arm I: ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks

Objectives

Primary objectives

- assess the efficacy and safety of ABT-493 and ABT-530 with or without ribavirin (RBV) in adults with chronic HCV genotype (GT) 1, 4, 5 and 6 infection with compensated cirrhosis (GT1 only) or without cirrhosis (GT1, GT4, GT5, or GT6)

Secondary objectives

- to assess the pharmacokinetics of ABT-493, ABT-530, and RBV
- to assess the emergence and persistence of viral variants with this treatment regimen.

Outcomes/endpoints

Primary efficacy endpoints

- the percentage of subjects who achieved SVR12

Secondary endpoints

- The percentage of subjects with SVR4;
- The percentage of subjects with on-treatment virologic failure;
- The percentage of subjects with post-treatment relapse.

The following additional efficacy endpoints were summarized descriptively by treatment arm:

- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of subjects who achieved SVR24;
- The percentage of subjects who relapsed after achieving SVR12.

Sample size

up to 350 subjects (approximately 80 subjects in Part 1; approximately 270 subjects in Part 2)

Blinding (masking)

Open-label

Statistical methods

Primary efficacy analysis
For each treatment arm, the number and percentage of subjects achieving SVR12 were summarized.

Secondary efficacy analysis
For each treatment arm, the number and percentage of subjects meeting each secondary efficacy endpoint were summarized.

Numbers analysed

174 subjects (79 in Part 1 and 95 in Part 2) were enrolled and received at least 1 dose of study drug

A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without Ribavirin in Subjects With Chronic Hepatitis C Virus (HCV) Genotypes 2, 3, 4, 5, or 6 Infection (SURVEYOR-II)

Methods

This was an expanded Phase 2, randomized, open-label, multipart, multicentre study. The study consisted of 4 independent parts, with Parts 1 and 2 representing the supportive/exploratory parts of the study and Parts 3 and 4 representing the confirmatory/registrational parts of the study.

Treatments

Part 1

- GT2-infected treatment-naïve (TN) and treatment-experienced (TE) subjects without cirrhosis were randomized in a 1:1:1 ratio into 1 of 3 treatment arms:
  - Arm A: ABT-493 300 mg once daily (QD) + ABT-530 120 mg QD for 12 weeks
  - Arm B: ABT-493 200 mg QD + ABT-530 120 mg QD for 12 weeks
  - Arm C: ABT-493 200 mg QD + ABT-530 120 mg QD + RBV 1,000 mg or 1,200 mg (weight based) divided twice daily (BID) for 12 weeks

- GT3-infected TN and TE subjects without cirrhosis were randomized in a 1:1:1:1 ratio into 1 of 4 treatment arms:
  - Arm D: ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks
  - Arm E: ABT-493 200 mg QD + ABT-530 120 mg QD for 12 weeks
  - Arm F: ABT-493 200 mg QD + ABT-530 120 mg QD + RBV 1,000 mg or 1,200 mg (weight based) divided BID for 12 weeks
  - Arm G: ABT-493 200 mg QD + ABT-530 40 mg QD for 12 weeks

Subjects were stratified in Part 1 by prior HCV treatment history (naïve or experienced).

Part 2

Arms in Part 2 were enabled for enrolment based on pre-specified safety and efficacy criteria for data from Part 1 Arms A – G, once all subjects in Part 1 had reached Post-Treatment Week 4. AbbVie determined which of the enabled arms in Part 2 would be enrolled. Based on favourable Part 1 results, all planned treatment arms in Part 2 were enabled per protocol. AbbVie decided to enrol enabled Arms J, L, O, and P in Part 2.

- GT2-infected TN and TE subjects without cirrhosis were enrolled into:
  - Arm J: ABT-493 mg QD + ABT-590 120 mg QD for 8 weeks

- GT3-infected TN and TE subjects without cirrhosis were enrolled into:
  - Arm LTN: ABT-493 300 mg QD + ABT-530 120 mg QD for 8 weeks
  - Arm LTE: ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks

- GT3-infected TN subjects with cirrhosis were randomized in a 1:1 ratio into 1 of 2 treatment arms:
  - Arm O: ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks
  - Arm P: ABT-493 300 mg QD + ABT-530 120 mg QD + RBV 800 mg QD for 12 weeks

Part 3

Arms in Part 3 were enabled for enrolment of GT3-infected subjects based on pre-specified criteria for efficacy data from Part 2 Arms L (TE cohort) and O (TN cohort) once all applicable subjects in Arms L and O had reached Post-Treatment Week 4. AbbVie determined which of the enabled arms in Part 3 for non-cirrhotic and/or cirrhotic subjects would proceed to enrolment.

Non-cirrhotic and/or cirrhotic subjects meeting all eligibility criteria were randomized in a 1:1 ratio into 1 of 2 treatment arms in Part 3 with randomization stratified by presence or absence of cirrhosis and by prior HCV treatment history (naïve or experienced) for cirrhotic subjects.

Arms Q and R in Part 3 for all GT3 cohorts (non-cirrhotic and cirrhotic) were enabled based on the supporting data from Part 2 and the pre-specified efficacy criteria.

- GT3-infected TN subjects with cirrhosis were only enrolled into:
  - Arm Q: ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks

- GT3-infected TE subjects without cirrhosis were randomized in a 1:1 ratio into 1 of 2 treatment arms:
  - Arm Q: ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks
  - Arm R: ABT-493/ABT-530 300 mg/120 mg QD for 16 weeks

- GT3-infected TE subjects with cirrhosis were only enrolled into:
  - Arm R: ABT-493/ABT-530 300 mg/120 mg QD for 16 weeks

Part 4

Approximately 100 GT2-infected and approximately 60 GT4 – 6-infected TN and TE subjects without cirrhosis were enrolled into:

- Arm S: ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks

Objectives

Primary objectives

Parts 1 to 4 of the study:

- to assess the efficacy and safety of ABT-493 and ABT-530 coadministered with or without ribavirin (RBV) in adults with chronic HCV genotype (GT) 2, 3, 4, 5, or 6 infection with or without cirrhosis.

In addition, the primary objectives for Part 4 included:

- the assessment of the efficacy (sustained virologic response 12 weeks post-dosing [SVR12]) of treatment with the ABT-493/ABT-530 combination regimen in GT2-infected direct-acting antiviral agent (DAA)-naïve subjects without cirrhosis compared to a historical SVR12 rate of treatment with sofosbuvir (SOF) plus RBV in GT2-infected DAA-naïve subjects without cirrhosis.

Secondary objectives

- to assess the pharmacokinetics of ABT-493, ABT-530, and RBV and the emergence and persistence of viral variants with these treatment regimens.

Outcomes/endpoints

Primary efficacy endpoint

- percentage of subjects who achieved SVR12

Secondary efficacy endpoints

- percentage of subjects who achieved SVR4;
- percentage of subjects with on-treatment virologic failure;
- percentage of subjects with post-treatment relapse

Sample size

up to 685 subjects,

- approximately 175 subjects in Part 1
- approximately 150 subjects in Part 2

- approximately 200 subjects in Part 3
- approximately 160 subjects in Part 4

Randomisation

See Treatments

Blinding (masking)

Open-label

Statistical methods

Primary efficacy analysis

For each arm, or for each population within an arm, as applicable, the number and percentage of subjects achieving SVR12 were summarized along with 95% confidence intervals using Wilson score intervals

In Part 4, the percentage of GT2-infected DAA-naïve subjects without cirrhosis treated with ABT-493/ABT-530 who achieved SVR12 would be non-inferior to the historical 95% SVR12 rate of the current standard of care (SOF + RBV for 12 weeks) in GT2-infected DAA-naïve subjects without cirrhosis if the lower confidence bound (LCB) of the 2-sided 95% confidence interval using normal approximation of the percentage of these subjects with SVR12 was > 89%.

Secondary efficacy analysis

For each treatment arm, the number and percentage of subjects meeting each secondary efficacy endpoint were summarized along with 95% Wilson score intervals.

Numbers analysed

692 subjects were randomized and received at least 1 dose of study drug:

- 195 subjects in Part 1
- 162 subjects in Part 2
- 131 subjects in Part 3
- 203 subjects in Part 4

A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 (or ABT-493/ABT-530) With and Without Ribavirin in Adults With Chronic Hepatitis C Virus (HCV) Infection Who Failed a Prior Direct-Acting Antiviral Agent (DAA)-Containing Therapy (MAGELLAN-1)

Methods

Expanded Phase 2, randomized, open-label, multicentre study, consisting of 2 parts, to evaluate efficacy, safety, and pharmacokinetics of coadministration of ABT-493 and ABT-530 with or without RBV in subjects with chronic GT1 (Parts 1 and 2) or GT4 – GT6 (Part 2) HCV infection who failed a prior anti-HCV DAA-containing regimen.

Treatments

Part 1

- Arm A: ABT-493 200 mg once daily (QD) + ABT-530 80 mg QD for 12 weeks
- Arm B: ABT-493 300 mg QD + ABT-530 120 mg QD + RBV 800 mg QD for 12 weeks
- Arm C: ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks

Part 2

- Arm D: ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks
- Arm E: ABT-493/ABT-530 300 mg/120 mg QD for 16 weeks

Objectives

Primary objectives

- Part 1: assess the efficacy and safety of ABT-493 and ABT-530 with or without ribavirin (RBV) in adults with chronic HCV genotype (GT) 1 infection who previously failed treatment with a DAA-containing regimen.
- The arm(s) in Part 2 of the study, which met the pre-specified efficacy and safety criteria, were studied in Part 2 of the study, where the efficacy and safety of the regimen were confirmed by evaluating it in a broader and larger subject population.

Secondary objectives

- Part 1:
    - to assess the pharmacokinetics of ABT-493, ABT-530, and RBV, and
    - to evaluate the role of RBV.

Outcomes/endpoints

Primary efficacy endpoint

- The percentage of subjects who achieved SVR12

Secondary efficacy endpoint

- The percentage of subjects who achieved SVR4
- The percentage of subjects with on-treatment virologic failure
- The percentage of subjects with post-treatment relapse.

Sample size

up to 130 subjects:

- approximately 50 subjects in Part 1
- approximately 80 subjects in Part 2

Randomisation

Part 1

- approximately 50 subjects were to be enrolled and randomized in a 1:1:1 ratio to one of 3 treatment arms.

- Enrolment in Arm A was stopped with Amendment 3 based upon the decision not to pursue development of the doses in Arm A (ABT-493 200 mg QD + ABT-530 80 mg QD). Subjects were subsequently randomized in a 1:1 ratio to Arms B or C, with 20 subjects each in Arms B and C.

Randomization in Part 1 was stratified by HCV GT1 subtype (1b or non-1b) and by previous experience to any of the 3 following DAA regimen classes:

- Any experience with a nonstructural viral protein 5A (NS5A) inhibitor (± protease inhibitors [PI]) (e.g., daclatasvir [DCV] + sofosbuvir [SOF], DCV + asunaprevir, DCV + simeprevir [SMV], ledipasvir + SOF, ombitasvir + paritaprevir/ritonavir); or
- NS5A inhibitor-naïve/PI-experienced (e.g., SMV + SOF, SMV + pegylated interferon and RBV [PR], telaprevir + PR, boceprevir + PR); or
- All other previous DAA-containing regimens not captured above (e.g., SOF + PR, SOF + RBV).

Part 2

approximately 80 HCV GT1- or GT4 – GT6-infected, DAA treatment-experienced subjects with compensated liver disease with or without cirrhosis were to be randomized in a 1:1 ratio to one of 2 treatment arms.

Randomization in Part 2 was stratified by HCV genotype (GT1 or GT4 – GT6) and by previous experience to the following 2 DAA regimen classes:

- NS5A inhibitor (± PI)-experienced, limited to
  - DCV-,
  - ledipasvir-, or
  - ombitasvir, or
- NS5A inhibitor-naïve/non-structural viral protein 3/4A (NS3/4A) PI-experienced, limited to:
  - paritaprevir/ritonavir-,
  - SMV-, or
  - telaprevir-, or
  - boceprevir

Blinding (masking)

Open-label

Statistical methods

Primary efficacy analysis

- number and percentage of subjects achieving SVR12 were summarized per treatment arm.

Secondary efficacy analysis

- number and percentage of subjects meeting each secondary efficacy endpoint were summarized per treatment arm.

Numbers analysed

141 subjects were randomized and received at least 1 dose of study drug

- 50 in Part 1
- 91 in Part 2

Summary of main efficacy results

A total of 2,376 subjects were randomized or enrolled in the registrational studies or supportive Phase 2 studies. The percentage of subjects who prematurely discontinued study drug was low (1.6%), with 0.5% of subjects discontinuing due to an AE.

Main demographic characteristics in the phase 2 and phase 3 analysis sets are summarized below:

Table 10 - Demographic Characteristics (ITT Population, Phase 2 and 3 Analysis Set)

	Genotype						Phase 2 and 3 Analysis Set
Characteristic	GT1 N = 998	GT2 N = 466	GT3 N = 643	GT4 N = 182	GT5 N = 32	GT6 N = 48	N = 2369
Sex, n (%)							
Male	544 (54.5)	234 (50.2)	375 (58.3)	120 (65.9)	18 (56.3)	27 (56.3)	1318 (55.6)
Female	454 (45.5)	232 (49.8)	268 (41.7)	62 (34.1)	14 (43.8)	21 (43.8)	1051 (44.4)
Race, n (%)							
White	825 (82.7)	350 (75.1)	564 (87.7)	133 (73.1)	21 (72.4)	5 (10.4)	1898 (80.2)
Black or African American	74 (7.4)	24 (5.2)	9 (1.4)	38 (20.9)	4 (13.8)	0	149 (6.3)
Asian	88 (8.8)	80 (17.2)	49 (7.6)	11 (6.0)	2 (6.9)	42 (87.5)	272 (11.5)
American Indian or Alaska native	2 (0.2)	1 (0.2)	9 (1.4)	0	0	1 (2.1)	13 (0.5)
Native Hawaiian or other Pacific Islander	2 (0.2)	7 (1.5)	8 (1.2)	0	0	0	17 (0.7)
Multiple	7 (0.7)	4 (0.9)	4 (0.6)	0	2 (6.9)	0	17 (0.7)
Missing	0	0	0	0	3	0	3
Ethnicity, n (%)							
Hispanic or Latino	122 (12.2)	37 (7.9)	46 (7.2)	4 (2.2)	2 (6.3)	0	211 (8.9)
Not Hispanic or Latino	876 (87.8)	429 (92.1)	597 (92.8)	178 (97.8)	30 (93.8)	48 (100)	2158 (91.1)
Geographic region, n (%)							
North America	325 (32.6)	260 (55.8)	289 (44.9)	64 (35.2)	4 (12.5)	22 (45.8)	964 (40.7)
Europe	464 (46.5)	109 (23.4)	190 (29.5)	100 (54.9)	15 (46.9)	13 (27.1)	891 (37.6)
Rest of world	209 (20.9)	97 (20.8)	164 (25.5)	18 (9.9)	13 (40.6)	13 (27.1)	514 (21.7)
Age, years							
Median	54.0	58.0	51.0	55.0	59.5	53.0	54.0
Min – Max	19.0 – 84.0	21.0 – 88.0	20.0 – 76.0	19.0 – 83.0	20.0 – 75.0	32.0 – 75.0	19.0 – 88.0
Age category, years							
< 65	856 (85.8)	358 (76.8)	606 (94.2)	158 (86.8)	20 (62.5)	43 (89.6)	2041 (86.2)
≥ 65	142 (14.2)	108 (23.2)	37 (5.8)	24 (13.2)	12 (37.5)	5 (10.4)	328 (13.8)
< 75	974 (97.6)	451 (96.8)	642 (99.8)	178 (97.8)	30 (93.8)	47 (97.9)	2322 (98.0)
≥ 75	24 (2.4)	15 (3.2)	1 (0.2)	4 (2.2)	2 (6.3)	1 (2.1)	47 (2.0)
BMI, kg/m^2							
Median	25.8	26.4	26.1	26.2	28.3	22.7	25.9
Min – Max	18.0 – 55.4	17.4 – 65.7	17.4 – 51.0	18.2 – 49.0	19.8 – 43.5	17.3 – 31.6	17.3 – 65.7

The overall population included in the development program was roughly balanced according to sex, European patients account for almost 40% of the population. A fair amount of patients is more than 65 years old. Besides the GT1, the GT3 population is significant. GT5 and GT6 were also represented (32 (including 2 cirrhotic) and 48 (7 cirrhotic) respectively).

Main baseline disease characteristics were the following:

Table 11 - Baseline Disease Characteristics (ITT Population, Phase 2 and 3 Analysis Set)

Variable	Genotype						Phase 2 and 3 Analysis Set
	GT1 N = 998	GT2 N = 466	GT3 N = 643	GT4 N = 182	GT5 N = 32	GT6 N = 48	N = 2369
Prior HCV medication history, n (%)							
TN	561 (56.2)	369 (79.2)	521 (81.0)	122 (67.0)	26 (81.3)	41 (85.4)	1640 (69.2)
TE	437 (43.8)	97 (20.8)	122 (19.0)	60 (33.0)	6 (18.8)	7 (14.6)	729 (30.8)
P/R- or SOF/R-experienced	328 (32.9)	97 (20.8)	122 (19.0)	56 (30.8)	6 (18.8)	7 (14.6)	616 (26.0)
P/R-experienced	318 (31.9)	80 (17.2)	80 (12.4)	55 (30.2)	6 (18.8)	7 (14.6)	546 (23.0)
SOF/R-experienced	10 (1.0)	17 (3.6)	42 (6.5)	1 (0.5)	0	0	70 (3.0)
PI-experienced	72 (7.2)	0	0	3 (1.6)	0	0	75 (3.2)
NS5A inhibitor-experienced	72 (7.2)	0	0	3 (1.6)	0	0	75 (3.2)
Cirrhotic status, n (%)							
Yes	126 (12.6)	35 (7.5)	116 (18.0)	22 (12.1)	2 (6.3)	7 (14.6)	308 (13.0)
No	872 (87.4)	431 (92.5)	527 (82.0)	160 (87.9)	30 (93.8)	41 (85.4)	2061 (87.0)
BASELINE FIBROSIS STAGE							
F0-F1	714 (71.8)	341 (73.2)	409 (63.6)	131 (72.4)	23 (71.9)	33 (68.8)	1651 (69.8)
F2	68 (6.8)	40 (8.6)	40 (6.2)	11 (6.1)	5 (15.6)	1 (2.1)	165 (7.0)
F3	87 (8.8)	51 (10.9)	79 (12.3)	19 (10.5)	2 (6.3)	7 (14.6)	245 (10.4)
F4	125 (12.6)	34 (7.3)	115 (17.9)	20 (11.0)	2 (6.3)	7 (14.6)	303 (12.8)
MISSING	4	0	0	1	0	0	5
Chronic kidney disease stages 4 and 5, n (%)							
Yes	55 (5.5)	16 (3.4)	11 (1.7)	20 (11.0)	1 (3.1)	1 (2.1)	104 (4.4)
No	943 (94.5)	450 (96.6)	632 (98.3)	162 (89.0)	31 (96.9)	47 (97.9)	2265 (95.6)
BASELINE HCV RNA LEVEL (IU/ML)							
< 1,000,000	422 (42.3)	153 (32.8)	266 (41.4)	97 (53.3)	14 (43.8)	10 (20.8)	962 (40.6)
>= 1,000,000	576 (57.7)	313 (67.2)	377 (58.6)	85 (46.7)	18 (56.3)	38 (79.2)	1407 (59.4)
BASELINE HCV RNA LEVEL (IU/ML)							
< 6,000,000	854 (85.6)	303 (65.0)	478 (74.3)	168 (92.3)	27 (84.4)	22 (45.8)	1852 (78.2)
>= 6,000,000	144 (14.4)	163 (35.0)	165 (25.7)	14 (7.7)	5 (15.6)	26 (54.2)	517 (21.8)
BASELINE HCV RNA LEVEL (IU/ML)							
< 10,000,000	941 (94.3)	376 (80.7)	545 (84.8)	179 (98.4)	32 (100)	32 (66.7)	2105 (88.9)
>= 10,000,000	57 (5.7)	90 (19.3)	98 (15.2)	3 (1.6)	0	16 (33.3)	264 (11.1)

A total of 308 patients (13%), of which 116 GT3 with cirrhosis received GLE/PIB in the phase II/III studies. Most of the patients had F0-F1 fibrosis (70%) and patients with baseline fibrosis stage F3 account for 10% (n=245) of the studied population. The majority of the treatment experienced population consists in PR pretreated patients including a small proportion of patients with also experience to SOF.

A summary of SVR12 according to subgroup is presented:

- In non-GT3 patients,

SVR_{12} rate were high regardless of cirrhosis status. Rates of on treatment virologic failures or relapses were very low across treatment arms (durations) and genotypes, next table.

GLE/PIB demonstrated non-inferiority to corresponding pre-specified historical controls in the individual studies (M13-590, M15-464 and M14-868). Furthermore, in GT1-infected subjects, GLE/PIB for 8 weeks was non-inferior to 12 weeks using the protocol-specified NI-margin (5%) in study M13-590. The one and only genotype-1 infected patient with virological failure (8 week-arm, table below), had OTVF (not relapse) and a fibrosis stage of F0/F1.

Table 12 - Outcome summary for non-GT3-infected subjects by cirrhosis status (TN + TE-PRS Subjects, Phase 2 and 3 Analysis Set)

	n/N (%)									
	GT1		GT2		GT4		GT5		GT6	
Endpoint	8 Weeks	12 Weeks	8 Weeks	12 Weeks	8 Weeks	12 Weeks	8 Weeks	12 Weeks	8 Weeks	12 Weeks
Subjects Without Cirrhosis										
SVR_{12}	383/387 (99.0)	400/401 (99.8)	193/197 (98.0)	232/234 (99.1)	43/46 (93.5)	111/112 (99.1)	2/2 (100)	28/28 (100)	9/10 (90.0)	31/31 (100)
OTVF	1/387 (0.3)	0/401	0/197	0/234	0/46	0/112	0/2	0/28	0/10	0/31
$Relapse_{12}$	0/384	0/400	2/195 (1.0)	0/232	0/45	0/111	0/2	0/27	0/10	0/30
Subjects With Cirrhosis										
SVR_{12}		98/101 (97.0)		35/35 (100)		20/20 (100)		2/2 (100)		7/7 (100)
OTVF		0/101		0/35		0/20		0/2		0/7
$Relapse_{12}$		1/98 (1.0)		0/35		0/19		0/2		0/7

Numbers with GT4-6 are limited. However, failures were very rare. The two relapses occurred in genotype 2-infected patients treated for 8 weeks; both were treatment experienced, and with a fibrosis stage of F0/F1 and F3, respectively. (As mentioned, numbers of genotype 2-infected with F2/F3 fibrosis who received 8 weeks was around 30). Further, in vitro results shown in the pharmacodynamics section support bridging of efficacy to that obtained in genotype 1-infection. In addition, with regards to early viral kinetics, nearly 100 % of patients had unquantifiable HCV RNA at week 4 across genotypes in the above studies (data not shown).

Table 13 - SVR12 rates by prior treatment experience, HCV genotype and duration for non-GT3-infected subjects (ITT population, phase 2 and 3 analysis set)

	n/N (%)									
	GT1		GT2		GT4		GT5		GT6	
Treatment Group	8 Weeks	12 Weeks	8 Weeks	12 Weeks	8 Weeks	12 Weeks	8 Weeks	12 Weeks	8 Weeks	12 Weeks
TN	245/248 (98.8)	310/313 (99.0)	172/174 (98.9)	193/195 (99.0)	36/39 (92.3)	83/83 (100)	2/2 (100)	24/24 (100)	7/8 (87.5)	33/33 (100)
TE-PRS	138/139 (99.3)	188/189 (99.5)	21/23 (91.3)	74/74 (100)	7/7 (100)	48/49 (98.0)	N/A	6/6 (100)	2/2 (100)	5/5 (100)
TN + TE-PRS										
All	383/387 (99.0)	498/502 (99.2)	193/197 (98.0)	267/269 (99.3)	43/46 (93.5)	131/132 (99.2)	2/2 (100)	30/30 (100)	9/10 (90.0)	38/38 (100)
Difference % (8-week – 12-week) 95% CI	–0.7 (–2.1, 0.6)		–1.4 (–4.4, 1.7)		–5.6 (–14.1, 2.9)		0.0 (–73.3, 73.3)		–10.5 (–37.8, 16.9)	

Evidently, the presence of baseline polymorphisms in NS3 and/or NS5A did not have an impact on SVR_{12} rates for subjects infected with these genotypes (previously untreated or PRS experienced). Treatment-emergent substitutions at A156V (in NS3) plus Q30R/L31M/H58D (in NS5A) were seen in the two failures with genotype 1a-infection, and no emergent substitutions were seen in the two failures with genotype 2-infection.

While prior treatment by PR or PRS is not expected to raise issue on cross resistance, it is acknowledged that such patients are still selected for other parameters that may have a negative impact on the

likelihood of achieving SVR, regardless of the treatment chosen. The data highlight the limitation in terms of SVR rate in TE-PRS GT2 8 weeks and in terms of sample size for GT 5-6 however bridging efficacy with GT1 based on in vitro activity and lack of expected cross resistance with PR/PRS can be acknowledged.

- In GT3 patients,

A stepwise approach was adopted for GT3 patients. Thus, the pivotal phase III ENDURANCE-3 study included GT3 treatment-naïve patients only and GT3 patients were not included in the pivotal study in cirrhotic (EXPEDITION-1) or in the DAA-failure study (MAGELLAN-1). However, GT3 cirrhotic patients and GT3 treatment-experienced but DAA-naïve patients were later included in a dedicated part of the SURVEYOR-II study.

In ENDURANCE-3, GT3 **treatment-naïve subjects without cirrhosis** were randomized in a 2:1 ratio to receive GLE/PIB 12 weeks or SOF+DCV 12 weeks. After enrollment in those arms was completed, additional subjects were to be assigned to GLE/PIB 8 weeks.

Numbers with F3 fibrosis are limited, but in fact the highest in the 8-week arm (i.e. not favouring the outcome in that arm).

Table 14 - Main demographics in ENDURANCE-3

	GLE/PIB 12 weeks N = 233	**SOF + DVC 12 weeks N = 115**	**GLE/PIB 8 weeks N = 157**
Male gender, %	52	45	58
White race, %	88	90	85
Median HCV-RNA, IU/ml	6.14	6.01	6.06
Fibrosis stage, n (%) F0-F1	201 (86)	97 (84)	122 (78)
F2	12 (5)	8 (7)	8 (5)
F3	20 (9)	10 (9)	27 (17)

SVR rates within treatment arms are presented below:

Table 15 - Outcomes in ENDURANCE-3

	GLE/PIB 12 weeks N = 233	**SOF + DVC 12 weeks N = 115**	**GLE/PIB 8 weeks N = 157**
SVR_{12}, n/N (%)	222/233 (95.3)	111/115 (96.5)	149/157 (94.9)
95% CI	92.6, 98.0	93.2, 99.9	91.5, 98.3
Nonresponse, n/N (%)	11/233 (4.7)	4/115 (3.5)	8/157 (5.1)
Reasons for nonresponse, n/N (%)			
Virologic failure	4/233 (1.7)	1/115 (0.9)	6/157 (3.8)
On-treatment virologic failure	1/233 (0.4)	0/115	1/157 (0.6)
Relapse	3/222 (1.4)	1/114 (0.9)	5/150 (3.3)
Nonvirologic failure	7/233 (3.0)	3/115 (2.6)	2/157 (1.3)
Premature drug discontinuation	4/233 (1.7)	1/115 (0.9)	0/157
Missing SVR_{12} data	3/233 (1.3)	2/115 (1.7)	2/157 (1.3)

Non-inferiority of GLE/PIB 12 weeks as compared to SOF+DCV 12 weeks was achieved in the ITT and PP population (ITT: lower bound of 95% CI for the difference was –5.6%, which was above the

non-inferiority margin of –6%). However, it is noteworthy that there were numerically higher rate of virologic failure, notably relapse in GLE/PIB arms (1.4-3.3%) as compared to SOF/DCV (0.9%). Moreover, there were 2 breakthroughs in GLE/PIB arms versus none in SOF/DCV.

Non-inferiority of the 8 weeks GLE/PIB regimen to that of the 12 weeks regimen was also achieved in the ITT and PP populations (ITT: lower bound of 97.5% CI for the difference was –5.4%, which was above the non-inferiority margin of –6%). However, more relapses were observed in the 8 weeks treatment arm (3.3%) as compared to the 12 weeks treatment arms (1.4%).

Two patients with F3 fibrosis relapsed following 8 weeks of therapy (2/27 treated). Both had the A30K polymorphism present in the baseline virus, which may have played a role as well. In summary, there is a tendency (without statistical significance) for lower results in patients with moderate and severe fibrosis treated for 8 weeks. Baseline HCV-RNA levels do not seem of relevant importance for the outcome (even with the shorter treatment duration).

Table 16 - Virologic Response (SVR12) for Subgroups in ENDURANCE-3 (ITT Population)

Subgroup	12 weeks (A) N = 233	8 weeks (C) N = 157	Arm C – Arm A (95% CI)[a]
Baseline body mass index			
BMI < 30 kg/m^2	186/197 (94.4)	125/133 (94.0)	–0.4 (–6.4, 4.6)
≥ 30 kg/m^2	36/36 (100)	24/24 (100)	0.0 (–13.8, 9.6)
< 1,000,000 IU/mL	104/107 (97.2)	71/73 (97.3)	0.1 (–6.9, 5.6)
≥ 1,000,000 IU/mL	118/126 (93.7)	78/74 (92.9)	–0.8 (–9.0, 6.1)
< 6,000,000 IU/mL	162/168 (96.4)	119/123 (96.7)	0.3 (–4.9, 4.8)
≥ 6,000,000 IU/mL	60/65 (92.3)	30/34 (88.2)	–4.1 (–19.6, 7.5)
< 10,000,000 IU/mL	188/194 (96.9)	130/137 (94.9)	–2.0 (–7.3, 2.3)
≥ 10,000,000 IU/mL	34/39 (87.2)	19/20 (95.0)	7.8 (–12.1, 22.3)
F0 – F1	192/201 (95.5)	119/122 (97.5)	2.0 (–3.0, 6.2)
F2	11/12 (91.7)	6/8 (75.0)	-16.7
F3	19/20 (95.0)	24/27 (88.9)	–6.1 (–23.5, 13.9)

While some concerns could have been raised on the limited difference in SVR rates in F3, even though acknowledging that the difference might be accentuated by random baseline imbalances, useful complementary data on 8 weeks of GLE+ PIB therapy in genotype 3 was provided by Abbvie upon request (TN, non-cirrhotic patients; SURVEYOR-II, part 2, arm L), table below. Here 28/29 achieved SVR12, the 1 patient with "failure" had end of treatment response, SVR4 and SVR12 data is missing.

	Arm L	
	TN 8 weeks	TE 12 weeks
	(N = 29)	(N = 24)
F0-F1, n	21	14
F2, n	2	4
F3, n	6	6
SVR12	28/29	22/24
Relapse	0	1/24 (F0F1)
BT	0	1/24 (F0F1)
Non-virological	1/29 (F3)	0

GT3-infected TE-PRS (pegIFN- or SOF-experienced) subjects without cirrhosis

GT3-infected patients **TN or TE-PRS with cirrhosis** were included in different arms of the SURVEYOR-II study.

A summary of SVR rates observed in GT3 patients across the ENDURANCE-3 and SURVEYOR-II studies is presented below according to cirrhosis status and treatment duration:

Table 17 - Efficacy summary for GT-3 infected patients (ITT, Phase 2/3)

	n/N (%)			
	TN		TE	
Endpoint	**8 Weeks**	**12 Weeks**	**12 Weeks**	**16 Weeks**
Subjects Without Cirrhosis				
SVR_{12}	177/186 (95.2)	258/270 (95.6)	44/49 (89.8)	21/22 (95.5)
OTVF	1/186 (0.5)	1/270 (0.4)	1/49 (2.0)	0/22
$Relapse_{12}$	5/178 (2.8)	3/257 (1.2)	4/48 (8.3)	1/22 (4.5)
Subjects With Cirrhosis				
SVR_{12}		64/65 (98.5)		48/51 (94.1)
OTVF		0/65		1/51 (2.0)
$Relapse_{12}$		0/64		2/50 (4.0)

As rather unexpected the TE with PRS seems to have somewhat higher impact than cirrhosis on likelihood of SVR. The highest relapse rate in the pooled data set is seen in TE non-cirrhotic patients treated for 12 weeks (in SURVEYOR-II). The virological failure rate in those treated for 16 weeks was low; indeed 48/51 (94%) achieved SVR12 of those hardest to cure, cirrhotic patients with prior treatment failure.

Outcome by baseline polymorphisms, and resistance in those failing (GT 3)

While not predicted from in vitro data, the presence of A166S in NS3 or A30K in NS5A irrespective of other polymorphisms was associated with lowered SVR_{12} rates (next table). The overall SVR_{12} rate in the presence of A30K without A166S was 85.7% (8 weeks) and 92.9% (12 weeks), whereas the SVR_{12} rate in the presence of A166S without A30K was 92.3% (8 weeks) and 100% (12 weeks), suggesting that impact of the combination of these polymorphisms was more strongly associated with NS5A-A30K than with the NS3 polymorphism. Given the overall 6.3% prevalence of A30K among GT3-infected patients, the predicted decrease in SVR_{12} attributable to impact of A30K between 8 and 12 weeks durations in treatment-naïve subjects without cirrhosis is < 1%. The frequency of double mutation (A166S + A30K) is very low.

Table 18 - Impact of A166S in NS3 and/or A30K or Y93H in NS5A on treatment outcome in GT3-infected subjects, non-virological failures excluded.

		No Cirrhosis				Cirrhosis	
	Baseline Polymorphism	**Treatment-Naïve**		**TE-PRS**		**Treatment-Naïve**	**TE-PRS**
		8 Weeks	**12 Weeks[a]**	**12 Weeks**	**16 Weeks**	**12 Weeks**	**16 Weeks**
	SVR_{12} % (n/N)						
NS3	With A166S	82.4 (14/17)	100 (20/20)	80.0 (4/5)	100 (2/2)	100 (6/6)	60.0 (3/5)
	Without A166S	98.2 (161/164)	98.3 ((231/235)	90.9 (40/44)	94.7 (18/19)	100 (53/53)	97.7 (42/43)
NS5A	With A30K	77.8 (14/18)	92.9 (13/14)[b]	25.0 (1/4)	(0/1)	100 (1/1)	-
	Without A30K	98.8 (161/163)	98.8 (240/243)	95.6 (43/45)	100 (20/20)	100 (58/58)	93.8 (45/48)
	With Y93H	100 (10/10)	90.9 (10/11)	50.0 (2/4)	-	100 (5/5)	-

	Without Y93H	96.5 (165/171)	98.8 (243/246)	93.3 (42/45)	95.2 (20/21)	100 (54/54)	93.8 (45/48)
	A30K without Y93H	77.8 (14/18)	100 (13/13)	25.0 (1/4)	(0/1)	100 (1/1)	-
	Y93H without A30K	100 (10/10)	100 (10/10)	50.0 (2/4)	-	100 (5/5)	-
	A30K+Y93H	-	(0/1)	-	-	-	-
	Without A30K or Y93H	98.7 (151/153)	98.7 (230/233)	100 (41/41)	100 (20/20)	100 (53/53)	93.8 (45/48)
NS3+ NS5A	A166S without A30K	92.3 (12/13)	100 (20/20)	100 (4/4)	100 (2/2)	100 (6/6)	60.0 (3/5)
	A30K without A166S	85.7 (12/14)	92.9 (13/14)	33.3 (1/3)	(0/1)	100 (1/1)	-
	A166S + A30K	50.0 (2/4)	-	(0/1)	-	-	-
	Without A166S or A30K	99.3 (149/150)	98.6 (218/221)	95.1 (39/41)	100 (18/18)	100 (52/52)	97.7 (42/43)

a. One GT3a-infected subject was determined at the time of failure to be reinfected with a GT3a virus distinct from the one present at baseline after the database lock, and was included in the mITT-VF population. This subject did not have baseline polymorphisms at signature amino acid positions in NS3 or NS5A.
b. One subject who experienced virologic failure had A30K+Y93H present at baseline.

Treatment emergent substitutions in the overall GT3 population:

Overall 18 GT3 patients experienced virological failure in phase II/III. The baseline RAS and variants present at time of failure for those 18 GT3 patients are presented in the following table:

Table 19 - Individual baseline polymorphisms and treatment-emergent substitutions in subjects experiencing virologic failure at signature amino acid positions (PVF Population, genotype-3 infected)

Study	GT	Duration (Wks)	TE or TE	Cirr-hosis (Y/N)	Type of failure	Baseline	Time of VF	Baseline	Time of VF
						Variant (% Prevalence within subject´s viral population)			
						NS3		NS5A	
M13-594	3a	8	TN	N	BT	A166S (60.6) Q168R (61.4)	Q80R (59.2) A156G (99.6)	A30K (99.6)	A30K (99.9) Y93H (99.7)
	3a	8	TN	N	R	A166S (52.4)	Y56H (88.5) A166S (3.8) Q168L (95.5)	A30K (99.8)	A30K (99.8) Y93H (99.8)
	3a	8	TN	N	R	T54S (98.4)	T54S (99.4)	None	None
	3a	8	TN	N	R	A166S (99.2)	A166S (97.7) A166Y (2.3)	None	Y93H (99.6)
	3a	8	TN	N	R	None	Y56H (99.5)	A30K (99.8)	A30K (99.8) Y93H (99.6)
	3a	8	TN	N	R	None	Q168L (98.9)	A30K (99.7)	A30K (99.8) Y93H (99.7)
	3a	12	TN	N	BT	Q168R (28.5)	Y56H (98.5), Q168R (99.2)	A30K (16.3) A30V (39.2) Y93H (37.2)	A30K (99.9) Y93H (99.8)
	3a	12	TN	N	R	None	None	None	A30G (32.8) Y93H (99.9)
	3b	12	TN	N	R	None	Q80K (99.0)	V31M (99.8)	V31M (99.8) Y93H (99.8)
	3a	12	TN	N	R	None	None[b]	None	Y93H (99.8)[b]
M14-868	3a	12	TE	N	R	None	Y56H (90.8) Y56N (3.9) Q80K (2.2) Q80R (12.6) Q168R (83.6)	P29Q (2.0) A30K (99.8)	P29Q (2.5) A30K (99.9) P58T (2.2) Y93H (99.5)
	3a	12	TE	N	BT	A166S (97.0)	Y56H (95.5) Y56N (4.3) A166S (98.3) Q168L (69.0)	A30K (99.7)	P29Q (2.6) A30K (99.8) P58Q (2.2) P58T (2.1) Y93H (99.5)

	3a	12	TE	N	R	None	Q80K (2.7)	A30V (3.7) Y93H (38.7)	L31F (38.9) Y93H (99.3)
	3a	12	TE	N	R	None	None	P29Q (2.2) A30K (99.6)	A30K (99.8) Y93H (99.6)
	3a	12	TE	N	R	Q80K (2.5)	None	A30V (4.6) P58T (2.6) Y93H (99.3)	Y93H (99.6)
	3a	16	TE	Y	R	Q80K (2.0) A166S (95.1)	Q80K (2.2)	None	M28G (97.5)
	3a	16	TE	N	R	None	Y56H (99.4) Q168R (99.8)	A30K (99.8)	A30K (99.9) Y93H (99.9)
	3a	16	TE	Y	R	None	None	Y93H (4.8)	L31F (99.7) Y93H (99.8)
	3a	16	TE	Y	BT	A166S (99.0)	A156G (99.3) A166S (99.2)	Y93H (2.7)	A30K (99.8) Y93H (99.7)

TN: treatment naïve; TE: prior treatment failure with pegIFN + RBV or SOF + RBV; BT virological breakthrough on treatment; R: relapse;

a. Variants at signature amino acid positions relative to subtype-specific reference sequences in NS3 and NS5A at 2% detection threshold are listed. None indicates that polymorphisms or substitutions at signature amino acid positions were not detected at 2% detection threshold. At time of VF, treatment-emergent substitutions and pre-existing polymorphisms at signature amino acid positions are listed.
b. Subject had a GT3a virus at time of virologic failure that was distinct from the sequences present at baseline, and was determined to have been HCV re-infected.

A typical pattern of resistance in patients failing therapy is that touched upon in the pharmacodynamic section, where A30K is present at baseline, and A30K + Y93H at failure (NS5A, FC 70), accompanied by key mutation 156 or 168 in NS3 at failure.

Some patients who failed therapy certainly did end up with a virus with troublesome resistance with regards a successful immediate re-treatment. For reasons discussed in the pharmacodynamics section there are reasons to believe that NS3 resistance would revert rather rapidly post treatment, which may yield options for successful re-treatment, for example with the addition of sofosbuvir. It is expected that data will be gained in the future.

Of note, failures to the bi-therapy in the clinical development programme were rescued by the FDC intensified with sofosbuvir and ribavirin (MAGELLAN-3 study). The applicant was asked to discuss options to rescue GLE/PIB failure and to provide any available data from the ongoing MAGELLAN-3 study at the D90. The data submitted in response concern limited numbers or preliminary data (notably no SVR12 data for MAGELLAN-3). It is noted, that re-treatment studies concern agents where the resistance is either not an issue (peg-IFN + ribavirin + sofosbuvir) or where sofosbuvir +/- ribavirin is added to the NS3/4A and NS5A class and the treatment duration is increased in order to optimize therapy.

In patients with DAA-experience to NS5A and/or PI

The applicant conducted a dedicated phase II study in patients with prior DAA (NS5A and/or PI) failure with or without cirrhosis. The study only planned to enroll patients infected with GT1 or GT4-6 (MAGELLAN-1):

Part 1 included chronic HCV GT1-infected adult subjects without cirrhosis. Different doses/regimens were tested, including addition of ribavirin. In part 1, overall SVR12 rates were > 86% in all treatment arms. The virologic failure rate among those with available SVR12 data in Arms B and C was the same at 4.5% (1/22), suggesting that the presence of RBV in the regimen does not improve efficacy.

Part 2 of the study included a broader population: HCV GT1 or GT4 – GT6-infected DAA-experienced subjects with compensated liver disease with or without cirrhosis.

In part 2, HCV GT1- or GT4 – GT6-infected, DAA treatment-experienced subjects with compensated liver disease with or without cirrhosis were to be randomized in a 1:1 ratio to one of 2 treatment arms:

- Arm D: ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks

- Arm E: ABT-493/ABT-530 300 mg/120 mg QD for 16 weeks.

Randomization was stratified by HCV genotype (GT1 or GT4 – GT6) and by previous experience to the following 2 DAA regimen classes:

1. NS5A inhibitor (± PI)-experienced, limited to DCV-, LDV-, or OBV-containing combination regimens; or

2. NS5A inhibitor-naïve/NS3/4A PI-experienced, limited to: PTV/r-, SMV-, TVR-, or BOC-containing combination regimens.

The study in practice concern GT-1 infection; all but 4 patients had genotype 1, the other 4 had genotype 4-infection. Notably the study does not deliver any re-treatment data on genotype-3 infected patients. The median time since prior treatment differs between arms; this could have an impact on outcomes, in particular for those for those exposed to NS3/4A for reasons discussed in the pharmacodynamics section (reversion of resistance).

Table 20 - Main characteristics (Study M15-410 – Parts 1 [arm C only] and 2)

Variable		GLE/PIB 12w Arm C N = 22	GLE/PIB 12w Arm D N = 44	GLE/PIB 16w Arm E N = 47
Male gender, %		81.8	70.5	70.2
Median age, year		59.0	57.0	56.0
BMI, kg/m^2 < 30 %		54.5	68.2	55.3
HCV genotype/subtype, n	1a	20	35	32
	1b	2	8	11
	1c or 4a/c/d/e/r	0	1	4
PI experienced/NS5A naïve		11	14	13
NS5A experienced/PI naïve		4	16	18
NS5A experienced/PI experienced		7	14	16
NS5A experienced (all)		11	30	34
Median time since last DAA treatment, months		25	19	10
Range, months		3 - 104	2 - 94	3 - 61
Baseline fibrosis stage, n	F0 – F1	11	20	29
	F2	6	2	2
	F3	5	8	4
	F4	0	14	12
Cirrhotics, n		0	15	12

The overall prevalence of baseline polymorphisms at key amino acid positions (for the NS3/4A and NS5A classes) was around 15 % in NS3 and 60 % in NS5A. Of those with prior exposure to the NS5A class, key substitutions were detected in around 80% (using a 15% threshold of deep sequencing); for those with prior NS3/4A experience, key NS3 substitutions were detected in 20% of cases (15/75). Approximately 30 % had no baseline polymorphisms in either target.

Six GT1-infected subjects in the 12-week arms and 4 GT1-infected subjects in the 16-week arm experienced virologic failure. Main data is summarised below. Please note that the second part of the table concern the mITT-VF population (patients with non-virological failure excluded)

Table 21 - SVR_{12} rates in M15-410, by genotypes and BL RAVs

Overall – ITT population		**Arm C + D 12 Weeks**	**Arm E 16 Weeks**
Overall		58/66 (88)	43/47 (91)
GT1a		46/53 (87)	28/32 (87)
Gt1b		11/12 (92)	10/10
GT1 other		-	2/2
GT4		1/1	3/3
By BL polymorphisms using a 15% detection threshold (mITT-VF population)			
PI-experienced/ NS5A inhibitor-naïve	NS3 only	100 (2/2)	100 (3/3)
	NS5A only	100 (2/2)	100 (3/3)
	NS3 + NS5A	100 (2/2)	-
	No BP	100 (17/17)	100 (6/6)
NS5A inhibitor-experienced/ PI-naïve	NS3 only	100 (1/1)	-
	NS5A only	88.9 (16/18)	91.7 (11/12)
	NS3 + NS5A	-	-
	No BP	100 (1/1)	100 (4/4)
NS5A inhibitor-experienced/ PI-experienced	NS3 only	-	100 (1/1)
	NS5A only	83.3 (10/12)	100 (8/8)
	NS3 + NS5A	60.0 (3/5)	25.0 (1/4)
	No BP	100 (4/4)	100 (3/3)

Among PI-experienced/NS5A inhibitor-naïve subjects, the presence of baseline polymorphisms had no impact on treatment outcome, 12/12 achieved SVR_{12}.

As expected, NS5A RAVs were highly prevalent among NS5A inhibitor-experienced subjects, whether the previous treatment was with an NS5A inhibitor alone or an NS5A inhibitor plus a PI. Those naïve to PIs maintained high SVR rates overall, and in the recommended 16-week arm there was only 1 virologic failure.

In subjects experienced to both classes, the lower response was driven by subjects who had mutations in both NS3 (positions 155, 156, 168) and NS5A targets (positions 24, 28, 30, 31, 58, 92, 93); here the response rate was 4/9. Among subjects that did not have baseline polymorphisms in both targets, the overall SVR12 rate was 92.9 % (26/28), including 87.5 % (14/16) at the 12-week duration and 100% (12/12) at the 16-week duration.

There were 27 subjects with cirrhosis in the study of which 14/15 (93.3 %) subjects who received GLE/PIB for 12 weeks reached SVR12 and 9/12 (75.0 %) who received GLE/PIB for 16 weeks reached SVR12, results lower than in non-cirrhotic patients.

Below outcomes by prior actual regimens, commonly used in the EU, are shown. Of note, time since that prior failure is not taken into account.

Table 22 - Number and percentage of subjects responding with SVR_{12} by previous DAA regimen (ITT population)

	Arm C + D 12 Weeks	**Arm E 16 Weeks**	**Total**
Previous DAA regimen	**SVR12 n/N (%)**		
LDV + SOF	11/12 (91.7)	9/10 (90.0)	20/22 (90.9)
OMB/PAR/R +/- DAS +/- RBV	6/7 (85.7)	5/6 (83.3)	11/13 (84.6)
SIM + SOF	1/2 (50.0)	3/3 (100.0)	4/5 (80.0)
DCV + PR	7/8 (87.5)	7/7 (100.0)	14/15 (93.3)
TVR or BOC + PR	16/17 (94.1)	9/9 (100.0)	25/26 (96.2)
Multiple courses of DAA regimens	6/7 (85.7)	4/6 (66.7)	10/13 (76.9)
Other	11/13 (84.6)	6/6 (100.0)	17/19 (89.5)

As expected the failure rate was higher in those exposed to both the NS3/4A and the NS5A inhibitor classes. At failure, and sometime after, double class resistance can be detected in the virus in the majority of such patients, including key NS3 mutations conferring cross resistance to GLE, for GZR D168 and 156; for PTV D168 and R155. Over time the NS3 substitutions revert to WT. The proportion of patients with a virus that contain NS5A *double mutations* conferring cross resistance to GLE (at failure) is more limited, but does exist.

A total of 10 virological failures were reported in this study.

The impact of any single specific polymorphism was difficult to determine due to low prevalence in the overall subject population or its presence in combination with other variants within a single subject. Based on phenotype data for the different combinations of polymorphisms present at baseline in subjects who experienced virologic failure, there was no predictive value for treatment outcome based on drug susceptibility. In addition, the combination of polymorphisms seen from patient to patient did not show a specific pattern that was predictive of virologic failure.

Resistance outcomes (baseline and at failure) for those failing therapy in MAGELLAN-1 is shown in the next table.

Those data illustrate that patients with DAA experience are more likely to experience BT. As a matter of fact, among the 10 virologic failures reported, 6 were breakthrough and 4 were relapse. Patients with both NS5A and PI experience are overrepresented in the patients experiencing virologic failure.

The majority of patients do seem to end up with a virus that would be very hard to treat.

Table 23 - Individual baseline polymorphisms and treatment-emergent substitutions in subjects experiencing virologic failure, Study M15-410, Arms C, D, and E (PVF Population)

GT	Duration (Weeks)	Prior treatment experience	Cirrhosis (Y/N)	Out-come	Baseline	Time of VF	Baseline	Time of VF
					Variant (% Prevalence within subject´s viral population)			
					NS3		NS5A	
1a	12	PI + NS5A	N	BT	Y56H (4.6), D168A (94.1), D168T (2.9)	V36M (6.5), Y56H (99.4), D168A (99.8)	M28V (3.1), Q30R (98.0) H58C (98.9)	M28G (99.4), Q30R (98.9), H58C (99.7)
1a	12	NS5A only	Y	BT	None	A156V (99.8)	K24E (2.0), M28V (3.5), Q30E (66.0), Q30K (29.3), Q30R (3.6)	P29Q (2.1), Q30K (99.7), Y93H (97.6), Y93N (2.1)
1a	12	PI + NS5A	N	R	V36M (99.3), V55I (60.8), Q80L (99.2), R155K (41.5)	V36M (99.9), V55I (2.5), Q80L (99.5), R155K (98.3), A156T (98.2)	M28V (98.1), Q30R (96.2)	M28G (98.8), Q30R (98.8)
1a	12	NS5A only	N	R	V55A (99.8)	V55A (99.1)	Q30R (97.3), H58D (98.2)	Q30R (99.0), H58D (98.8)
1a	12	PI + NS5A	N	R	None	None	Q30E (4.9), Q30G (93.5)	P29R (99.5), Q30G (99.0)
1b	12	PI + NS5A	N	R	Y56F (98.8)	Y56F (99.8)	L28M (28.4), P32deletion (92.1)	L28M (99.8), P32deletion (99.8)
1a	16	PI + NS5A	Y	BT	Y56H (97.3), Q80K (99.3), D168E (94.8)	V36M (97.8), Y56H (99.4), Q80K (99.6), D168E (99.4)	K24Q (99.8), Y93H (98.7)	K24Q (81.1), K24R (18.7), Q30K (95.7), H58D (4.3), Y93H (99.0)
1a	16	NS5A only	Y	BT	None	I132V (5.4), A156V (99.9)	Q30R (98.9), L31M (99.7)	Q30R (99.5), L31M (99.8), H58D (99.2)
1a	16	PI + NS5A	N	EOT failure	Y56H (98.9), Q80K (99.9), D168A (98.3)	V36A (4.5), V36M (5.1), Y56H (99.4), Q80K (99.9), A156G (89.2), D168A (94.1), D168T (5.8)	M28T (41.1), M28V (35.1), Q30L (2.2), Q30R (97.6), L31M (99.5), H58D (4.7)	NA
1a	16	PI + NS5A	Y	BT	Y56H (12.6), Q80K (99.5), R155T (2.1), D168A (25.5), D168T (3.1)	Q80K (100), R155T (99.9), A156V (99.9), D168A (99.9)	Q30H (99.4), Y93H (98.7)	M28A (29.0), Q30H (99.7), H58D (70.8), Y93H (99.6)

BT = breakthrough; NA = sequence not available due to technical reasons; PVF = primary virologic failure; R = relapse; VF = virologic failure

a. Variants at signature amino acid positions relative to subtype-specific reference sequences in NS3 and NS5A at 2% detection threshold are listed. None indicates that polymorphisms or substitutions at signature amino acid positions were not detected at 2% detection threshold. At time of VF, treatment-emergent substitutions and preexisting polymorphisms at signature amino acid positions are listed.

Clinical studies in special populations

- Patients with severe renal impairment

The applicant conducted a dedicated phase III study in GT1-6-infected patients with CKD stage 4 or 5 (EXPEDITION-4). Given that sofosbuvir is not an appropriate option in these patients and that grazoprevir/elbasvir only covers CKD with GT1 or GT4, this dedicated study was welcome for this FDC the PK of which being marginally affected by renal impairment.

The CKD population mainly consisted in GT1 patients, with balanced TN and TE population (with almost exclusively IFN pretreatment, only 2 patients with SOF pretreatment. Around 82% were undergoing dialysis.

SVR12 was achieved by 98.1% (102/104) of subjects in the ITT population. No subject experienced on-treatment virologic failure or post-treatment relapse.

- Patients with HIV-HCV coinfection

In ENDURANCE-1, a total of 33 HIV-HCV GT1 co-infected patients were included, all were on stable ART regimen containing either dolutegravir, raltegravir or rilpivirin. All achieved SVR12.

A dedicated study in HCV GT1-6/HIV co-infected patients (EXPEDITION-2) is ongoing. As part of the responses to the D90, some contributory data (notably on 8 weeks regimen for GT2 and GT3) were provided as follows:

Table 24 - Preliminary SVR12 Rates (mITT) for HCV/HIV-1 Co-Infected Subjects from EXPEDITION-2

Genotype[a]	Non-Cirrhotics 8 Weeks % (n/N)	Cirrhotics 12 Weeks % (n/N)
1	100% (87/87)	100% (10/10)
2	100% (9/9)	--
3	100% (21/21)	75% (3/4)[b]
4	100% (16/16)	100% (1/1)
6	100% (3/3)	--
Total	**100% (136/136)**	**93% (14/15)**

a. Performed by phylogenetic analysis. If a phylogenetic analysis result was not available, then determined by the central laboratory.

b. One TN GT3-infected subject had on-treatment virologic failure, but had incomplete study drug adherence.

Table 25 - Baseline Characteristics for HCV/HIV-1 Co-Infected Subjects Without Cirrhosis from Study M14-730 (EXPEDITION-2)

	Non-Cirrhotics 8 Weeks (N = 137)
Baseline Fibrosis Stage	
F0-F1	120 (87.6%)
F2	2 (1.5%)
F3	15 (10.9%)

Subgroup analysis

In the Phase 2 and 3 Analysis Set, after stratification by prior treatment experience, HCV genotype, treatment duration, and study, the differences observed in SVR12 rates across demographic and baseline disease characteristics of race, age, ethnicity, HCV subtype, HCV treatment history, IL28B genotype, baseline fibrosis stage, geographic region, country, baseline measurement of BMI, HOMA-IR, platelets, albumin, creatinine clearance, estimated glomerular filtration rate, HIV-1 infection, history of diabetes, history of depression or bipolar disorder, history of bleeding disorder, baseline metabolic syndrome, cirrhosis, severe renal impairment, injection drug use, concomitant use of proton pump inhibitors, and stable opiate substitution use were not statistically significant.

The statistically significant subgroup results were:

- Sex: Females tend to have higher SVR12 rates than males: 98.7% versus 96.4%,

- Baseline HCV RNA level: There was a significantly higher SVR12 rate in subjects with baseline HCV RNA < 1 million IU/mL than in glecaprevir/pibrentasvir subjects with baseline HCV RNA ⩾ 1 million IU/mL : 98.5% versus 96.6%. The largest observed differences were 12.1% for the overall rate among TE-NS5A and/or TE-PI subjects and 11.0% among TE-PRS GT3-infected subjects),

- Baseline polymorphisms in NS3 and/or NS5A: there was a significant difference in SVR12 rates between subjects with baseline polymorphisms in NS3 only (100.0%), NS5A only (96.0%), both NS3 and NS5A (61.1%), and none (98.0%). The low overall SVR12 rate of 61.1% for subjects with both NS3 and NS5A baseline polymorphisms was largely driven by 5 failures among the 9 subjects (Study M15-410) with both prior NS5A and PI experience who had RAS in both targets (overall SVR12 rate of 44.4%).

- DAA compliance: there was a significantly higher SVR12 rate in subjects who were compliant (97.8% of subjects, based on overall compliance between 80% and 120%) compared to those who were not (94.0%).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The main studies were conducted in non-cirrhotic treatment-naive patients or patients having failed previous treatment with PegIFN+RBV (including some patients with PegIFN+RBV+ Sofosbuvir, ("PRS")).

The applicant's choice in terms of clinical development does not capitalize on the theoretical potential added value of this new NS5A for HCV GT3 patients with viral strains harbouring NS5A RAS. Indeed, the population of pretreated patients mostly consists of Peg-IFN+Ribavirin (+/- sofosbuvir) and only a small sample sized study (MAGELLAN-1) has been dedicated in DAA experienced patients and without targeting GT3 patients. Thus scrutinizing the virologic response according to NS5A baseline RAS +/- NS3/4 is the only way to substantiate this theoretical added value.

Another potential added value relies on the marginal renal elimination of both components of this FDC making this option a potential candidate for the challenging population of patients with renal impairment including patients with dialysis. This potential added value has been adequately substantiated when considering that not only a PK study has been performed in patients with renal impairment including haemodialysis but also a dedicated study in HCV infected patients with CKD 4-5 has been performed (EXPEDITION-4/M15-462). As recognized by the CHMP when granting the accelerated review, GLE/PIB could cover an unmet medical need, considering that sofosbuvir cannot be used in patients with renal impairment and that grazoprevir/elbasvir can only be used in patients with GT1 and GT4 with CKD.

The clinical development also included several so-called "registrational" studies, as well as supportive studies. Among them, one was an active controlled open label study (ENDURANCE-3/M13-594) versus sofosbuvir-daclatasvir 12 weeks in GT3 treatment naïve non cirrhotic patients.

Another study was double blind placebo controlled (ENDURANCE-2/ M15-464) in GT2 treatment naïve or treatment experienced non cirrhotic patients.

Other studies were non-comparative open label studies targeting different patient populations according to genotype and testing different treatment duration (8 weeks, 12 weeks, 16 weeks).

Overall, around 300 patients with compensated cirrhosis were included in the clinical development with notably one dedicated study in compensated cirrhotic patients with GT1, GT2, GT4, GT5 and GT6 (EXPEDITION-1/M14-172). Based on PK and safety grounds this FDC is not recommended in patients with moderate hepatic impairment and contra-indicated in patients with severe hepatic impairment. As a whole, NS3/4A inhibitors are likely not adequate candidates for treating patients with hepatic

decompensation for PK reasons (plasma levels increase up to 10-fold). Nevertheless, in clinical practice other effective options may not be available. This is especially true for the management of GT3 patients with very limited therapeutic options.

Prior treatment with PR or PRS is not an issue with regards to GLE or PIB resistance. However, such patients are still selected for other parameters that may have a negative impact on the likelihood of achieving SVR, regardless of the treatment chosen. On the basis of subgroup analyses by prior treatment experience (TN and TE-PRS) the claimed dosing regimen is the same for patients infected with HCV genotypes 1,2, 4-6, with or without such prior therapy (i.e. 8 weeks in non-cirrhotic patients and 12 weeks in cirrhotic patients). For genotype-3 infected patients, the same durations are suggested for TN patients (i.e. 8 weeks in non-cirrhotic patients and 12 weeks in cirrhotic patients) while a prolonged duration of 16 weeks is suggested for those with prior failure on a PRS regimen, regardless of cirrhosis.

Efficacy data and additional analyses

GLE/PIB dosed 300/120 mg QD has been evaluated in a large number of patients (2369 in the phase 2/3 safety population).

Treatment durations of 8 and 12 weeks were studied in non-cirrhotic patients infected with genotypes 1,2,4,5 and 6, with or without a prior treatment failure with peg-IFN + ribavirin. For these patients both durations were equally effective, virological failure rates being very low. Although this study population mainly concerned patients with very limited fibrosis (F0/F1), the numbers with F2/F3 treated for 8 weeks were deemed sufficient by CHMP to support the 8 week treatment duration in non-cirrhotic patients (throughout the range to F3 fibrosis), having the close to 100% SVR rate in mind. As expected, numbers treated with genotyped 4-6 is limited. However, not a single failure was seen in those treated, and the same treatment recommendation is supported by the in vitro data presented, as well as previous experiences of treating these genotypes. Of note, early viral kinetics was similar across genotypes, with close to 100 % of patients having unquantifiable HCV RNA at week 4.

Cirrhotic patients (prior treatment failure with peg-IFN + ribavirin included) with the mentioned genotypes were treated for 12 weeks. Observed SVR rates were 99%, a single relapse occurred in a patient with genotype 1-infection, supporting 12 weeks of treatment for such patients.

With such success rates, baseline polymorphisms in NS3 and NS5A targets did not have an impact on treatment outcomes in these patients.

P*reviously untreated*, patients with genotype-3 infection, without cirrhosis, were studied in a dedicated trial (ENDURANCE-3). GLE/PIB was compared to active control, sofosbuvir + daclatasvir, both given for 12 weeks. Following an amendment, GLE/PIB for 8 weeks was also studied, restricted to non-cirrhotic patients. All three treatments yielded high SVR rates (95-96%). GLE/PIB for 12 weeks was non-inferior to control, and GLE/PIB for 8 weeks was non-inferior to GLE/PIB for 12 weeks. The 8 weeks treatment resulted in a numerically higher relapse rate (5/150, 3.3%) than did 12 weeks (3/222, 1.4%). However, the difference was limited and was non-significant, and CHMP agreed that the results can be considered supportive of 8 weeks treatment for non-cirrhotic, previously untreated patients with genotype 3-infection. The simplicity of an 8 week regimen, regardless of the HCV genotype, is considered important as part of an programmatic approach for HCV eradication. Treatment-naïve cirrhotics were treated for 12 weeks in SURVEYOR-II and EXPEDITION-4, resulting in an SVR rate of 64/65 (no virological failures), supporting that option for this population.

Two more studies (SURVEYOR-II, EXPEDITION-4) included (in part) genotype-3 infected patients with or without cirrhosis and *with or without prior treatment failure* (IFN or peg-IFN +/- ribavirin or sofosbuvir + ribavirin +/- peg-IFN). Twelve and 16 weeks of treatment were explored. For patients with prior

treatment failure, the 12 week treatment (only studied in non-cirrhotics) resulted in a numerically higher relapse rate (4/48, 8.3%) than did 16 weeks, which notably gave SVR in 48/51 treatment experienced patients with cirrhosis (those hardest to cure). The results support the conservative approach proposed by the applicant: a 16 week treatment duration of patients with prior failure to the mentioned treatments.

For genotype-3 infected patients, an impact by a naturally occurring polymorphism in NS5A was seen. It concerns the presence of A30K, detected in 6% of baseline samples. When comparing the relapse rates in previously untreated, the relapse rate was numerically higher in those treated for 8 weeks than in those treated for 12 weeks (4/18 vs 1/14). However, taking into account the prevalence of the A30K mutation, the overall SVR rate with 8 weeks of treatment would be predicted to increase some single percent if the substitutions were screened for and such patients were excluded/treated longer. In summary, CHMP agreed that a general recommendation for the screening of baseline resistance in genotype-3 infected is not considered warranted.

In addition to the above, a study was performed in patients who had failed prior treatment that included agents from one or both DAA classes of interest (NS3/4A and NS5A), around 30% had cirrhosis (MAGELLAN-1). The study overwhelmingly concerned genotype 1 infection (in addition 4 patients infected with genotype-4 infection), and genotype 3-infected patients were not included. Patients were treated for 12 or 16 weeks. In those previously exposed to NS3/4A only (n=38) there were no virological failures; in those exposed to NS5A only (n=38) there were 3 failures, and in those exposed to both classes (n=37) there were 7 failures, without any interpretable difference between treatment arms (12 or 16 weeks). Of note, in those with dual class resistance, where key polymorphisms to NS3 and NS5A were detected at baseline samples, 5 out of 9 failed therapy. When looking at resistance at failure, advanced resistance to both classes was seen in the majority of patients. On the basis of these outcomes the company proposes that prior exposure to the NS3/4A class does not have to be accounted for, and that patients with prior exposure to NS5A, regardless genotype (genotype-3 infection included), may be recommended GLE/PIB therapy for 16 weeks.

Patients with prior PI-experience, but naïve to the NS5A class did not have relevant NS3 mutations at baseline, as the time since prior therapy was considerable and resistance had generally reverted, and also since the linear PIs used in prior regimens primarily selects for key mutations not conferring cross resistance to glecaprevir. Thus, these patients may not be representative for the bulk of “PI experienced patients” eligible for re-treatment today and in the future.

At present the main protease inhibitors of relevance would be paritaprevir and grazoprevir, which both may confer cross resistance to glecaprevir, which would be relevant if reversion has not yet taken place. Indeed, in patients with prior failure on a regimen including both NS3 and NS5A inhibitors, time since prior failure (i.e. the duration where NS3 resistance have time to revert to wild type) was shown to be an important factor, as anticipated. Thus, although PI-experienced, NS5A naïve, patients were successfully treated in MAGELLAN-1, prior NS3 failure cannot be disregarded if GLE/PIB would be used for retreatment in patients failing on the presently used first line regimens. It is a matter of what agents that were used (key mutations selected) and timing, and the likelihood of success would be based on guesswork without the use of resistance screening, unless a considerable time has passed since the prior treatment failure.

The sample size of NS5A experienced, PI naïve patients is limited to 38 patients who mostly had genotype 1a infection. The sample size is too small to generate a general resistance algorithm that can be adequately used to predict treatment failure. Those failing this re-treatment end up with advanced dual class resistance, including high level resistance to pibrentasvir, which is likely the present NS5A inhibitor for which the least impact of common viral variability or resistance mutations on potency is seen.

Notably, 32% (6/19) of the GT1-infected subjects previously treated with ombitasvir and paritaprevir ± dasabuvir [i.e. Viekirax/Exviera, one of the standard regimens use in the EU) had resistance-associated substitutions in both virological targets at the time of enrolment in MAGELLAN-1. As double class resistance was associated with a suboptimal outcome, this indicates that GLE/PIB is not a suitable regimen for the re-treatment of such patients, in particular as a resistance testing algorithm that can be used to guide therapy is not available.

In the subset of double class experienced patients, GLE/PIB therapy seemed to cure all patients with a baseline virus that lacked NS3 resistance. However, some NS5A experienced, but PI naïve patients (without NS3 key mutations) also failed therapy. Hence, screening for NS3 class resistance is not a sufficient tool to decide which of these vulnerable patients would be better of receiving an optimised retreatment regimen including sofosbuvir.

In summary, the sample size of MAGELLAN-1 is not large enough to derive a resistance algorithm that can adequately predict what genotype-1 infected patients may use GLE/PIB as a retreatment regimen. Further, the limited data available only concern genotype 1-infection; data is lacking for other genotypes and an extrapolation is not considered possible. Given the accumulation of resistance seen in case of failure with GLE/PIB retreatment, GLE/PIB is currently not considered an adequate re-treatment option for patients with prior failure on a regimen that included the NS3 or NS5A class.

2.5.4. Conclusions on clinical efficacy

Of particular interest this FDC comprises two pangenotypic components with high potency and high genetic barrier. In the HCV GT1-infected population (the most widely represented in the EU) the observed results -with 99% SVR12 achieved with a convenient 8 weeks treatment duration in non-cirrhotic TN or TE-PRS patients and 97% in cirrhotic patients with a 12 weeks treatment duration- support the fact that this FDC will represent an optimization in the therapeutic armamentarium.

As part of the response to CHMP questions throughout the assessment, some clarifications and some additional data from ongoing studies (EXPEDITION-2 notably) were provided by the applicant in support of the efficacy of the product. CHMP thus acknowledged that the applicant's proposal for a treatment recommendation could overall be followed in DAA treatment naïve patients, having in mind the possibility of bridging efficacy from GT1 based on comparable *in vitro* activity leading to favour a simplified regimen for a programmatic approach to HCV eradication (targeted by 2030 by WHO).

Nevertheless, CHMP noted that since the clinical development has been built mainly to promote the use of this dual therapy in first line treatment rather than in retreatment, the limited sample sized MAGELLAN-1 study (without GT3 patients) in DAA TE leaves many uncertainties for the use of this dual therapy in patients failing DAA.

2.6. Clinical safety

Patient exposure

For the evaluation of the safety data, the applicant used three analysis sets:

- **Placebo-controlled analysis set** using safety data from study M15-464 (ENDURANCE-2), a double blind, placebo-controlled study in HCV GT2-infected subjects without cirrhosis comparing GLE/PIB 300mg/120mg versus placebo for 12 weeks (GLE/PIB n= 202, PLA n= 100).

- **Active-controlled analysis set** using safety data from study M13-594 (ENDURANCE-3), an open-label, active-controlled study in HCV GT3-infected subjects without cirrhosis comparing GLE/PIB 300mg/120mg with SOF+ DCV for 8 or 12 weeks (GLE/PIB n= 390, SOF+DCV n=115).

- **Phase 2 and 3 analysis set** using safety data from all subjects (n= 2, 369) in the 21 arms of the Phase 2 and 3 studies who received at least 1 dose of a co-administered or co-formulated GLE 300 mg QD and PIB 120 mg QD, without RBV (N = 2,369). This analysis set includes subjects with compensated liver disease and/or with or without CKD Stages 4 – 5 (Study M15-462).

In the summary of the clinical safety, the Phase 2 and 3 analysis set was primarily presented excluding study in patients with renal impairment (M15-462) corresponding to a total 2265 patients. Safety data derived from the 104 patients in study M15-462 were presented and discussed separately, which is acceptable. A summary of the main safety data derived from other Phase 2 studies not included in the Phase 2 and 3 analysis set was also provided.

Overall, a total of 2, 369 HCV-infected adult subjects received the fixed dose combination GLE/PIB or co-administered GLE and PIB at the dose of 300mg/120mg once daily. Excluding the 104 subjects with CKD in study M15-462 that are discussed separately in the summary of clinical safety, the Phase 2 and 3 analysis set comprise a total of 2,265 patients, which is consistent with the ICH recommendations to assess the safety profile of the drug and to detect the most commonly reported adverse drug reactions. Among those, 850 subjects were assigned for 8- week treatment duration (37.5%), 1295 subjects assigned for 12 weeks treatment duration (57.2%) and 120 subjects were assigned for 16 weeks (5.3%).

A total of 288 patients with compensated cirrhosis (Child Pugh A) were included in the Phase 2-3 program. The safety of GLE/PIB in subjects with moderate or severe hepatic impairment was not assessed in the clinical development program. At this stage only a few patients are co-infected with HIV-1 (n=33).

Adverse events

The safety profile of GLE/PIB is overall good with few severe AEs or serious AEs reported respectively in 2.9% and 2.1% of subjects in the Phase 2 and 3 analysis set. There was no obvious difference in the percentages of subjects with any AE and any drug-related AEs with placebo and active comparator arm (SOF/DCV) in the placebo or active controlled studies. Few subjects (0.4%) discontinued study drugs due to AEs.

Table 26 - Overview of adverse events

Any AE	**Placebo-controlled study**		**Active-controlled study**		**Phase 2 and 3 analysis set**
	GLE /PIB 12 weeks N=202	**Placebo 12 weeks N=100**	**GLE /PIB 12 weeks N=233**	**SOF/DCV 12 weeks N=115**	**GLE /PIB N=2265**
Any AE	64,4%	58%	76%	69,6%	67,5%
Any DAA-related AE	31,7%	33%	48,1%	43,5%	41%
Any SAE	1,5%	1%	2,1%	1,7%	2,1%
Any DAA-related SAEs	0	0	0	0	<0,1%
Discontinuation due to AE	0	0	1,3% (3)	0,9%(1)	0,4% (8)
Death	0	0	0	0,9%	0,3% (6)

The commonly reported adverse events in the Phase 2 and 3 analysis set for which a differential risk was evidenced compared with subjects receiving placebo were fatigue, headache and gastrointestinal disorders such nausea, diarrhea and abdominal distension or pain, and insomnia. Pruritus was also

frequently reported (4,5%) but with a similar frequency in both treatment group whatever the relatedness with the drug.

AEs (regardless of causality)	Placebo-controlled study		Phase 2 and 3 analysis set
	GLE /PIB N=202	Placebo N=100	GLE /PIB N=2265
Fatigue	11,4%	10,0%	14, 6%
Headache	11,9%	12%	18, 1%
Nausea	7,4%	3%	9,2%
Diarrhoea	9,9%	3%	6,4%
Abdominal distension	4%	1%	1,5%
Abdominal pain	3%	0	2,6%
Pruritus	5,9%	6%	4,5%
Insomnia	3,5%	4%	3,8%

Drug-related AEs	Placebo-controlled study Treatment Group, n (%)		Phase 2 and 3 analysis set
	GLE /PIB N=202	Placebo N=100	GLE / PIB N=2265
Fatigue	8,4%	8%	11,4%
Headache	8,9%	6%	13,2%
Nausea	6,4%	3%	7,6%
Diarrhoea	5%	2%	3,8%
Abdominal distension	3,5%	1%	1,0%
Abdominal pain	0,5%	0	1,3%
Pruritus	2,5%	2%	3,3%
Insomnia	3%	1%	2,4%

Adverse events reported with GLE/PIB were generally of mild intensity, and did not lead to study drug discontinuation. Of note, one subject with history of angiotectasia in the jejunum and episodes of gastro-intestinal bleeding experienced an event of diarrhoea with positive re-challenge of GLE/PIB in study M15-642. Furthermore, two subjects discontinued GLE/PIB due to gastrointestinal disorders (dyspepsia for one, nausea, diarrhoea, abdominal pain for the second), with positive de-challenge and with a drug causality suspected by the investigator.

Serious adverse events and deaths

A total of seven deaths were reported in the Phase 2 and 3 analysis set, including one death in study M15-462. Two other deaths were reported in the Phase 2 clinical studies not included in the Phase 2 and 3 analysis set since subjects received other dosing regimens of GLE and PIB than the final recommended. All occurred in the post-treatment period and were considered as not related to study drug:

Subject Age/Sex/Race	Duration of Exposure[a] (Days)	Day of Onset[b]	Preferred Term[c]	Investigator Relationship/ AbbVie Relationship to DAA Study Drug	Significant Medical History/ Alternative Etiology(ies)
Study M15-410					

Subject Age/Sex/Race	Duration of Exposure[a] (Days)	Day of Onset[b]	Preferred Term[c]	Investigator Relationship/ AbbVie Relationship to DAA Study Drug	Significant Medical History/ Alternative Etiology(ies)
65/male/white	85	156 (71)	Hepatic cancer metastatic	No reasonable possibility/ No reasonable possibility	No significant medical history/ metastatic hepatocellular carcinoma with metastases to bone and lung
Study M14-868					
63/male/white	86	227 (141)	Pneumonia	No reasonable possibility/ No reasonable possibility	History of chronic obstructive pulmonary disease, asthma, and congestive heart failure/ chronic obstructive pulmonary disease
Study M13-590					
43/female/black or African American	85	99 (14)	Death	No reasonable possibility/ No reasonable possibility	History of gastric bypass for obesity, heartburn, hypothyroidism, osteomyelitis, former injection drug abuse (on methadone for opiate substitution), and smoker /unknown cause pending autopsy report
Study M13-594					
23/male/white	56	133 (77)	Accidental overdose	No reasonable possibility/ No reasonable possibility	History of suicidal ideation, anxiolytic and opioid dependence, intravenous drug use, opioid overdose/pre-existing condition
Study M14-172					
40/male/white	84	143 (59)	Cerebral haemorrhage	No reasonable possibility/ No reasonable possibility	History of von Willebrand disease Type III and previous bleeding episodes, including cerebral hemorrhages/cerebral hemorrhage related to hemophilia
Study M15-462					
41/male/Asian	85	99 (14)	Cerebral haemorrhage	No reasonable possibility/ No reasonable possibility	History of hypertension, end-stage renal failure, type 2 diabetes/ uncontrolled hypertension
Study M14-867					

Subject Age/Sex/Race	Duration of Exposure[a] (Days)	Day of Onset[b]	Preferred Term[c]	Investigator Relationship/ AbbVie Relationship to DAA Study Drug	Significant Medical History/ Alternative Etiology(ies)
67/female/white	29	29	Adenocarcinoma	No reasonable possibility/ No reasonable possibility	History of renal insufficiency and hypoechoic lymph nodes/ enlarged peripancreatic nodes

DAA = direct-acting antiviral agent; GLE = glecaprevir; PIB = pibrentasvir; QD = once daily

a. All subjects received coformulated GLE/PIB 300 mg/120 mg QD or coadministered GLE 300 mg QD and PIB 120 mg QD.

b. Numbers in parentheses indicate the number of days after the last dose of study drug.

c. Preferred terms reported as having an outcome of death.

Of note, autopsy report available in the DSUR confirmed acute ethanol and combined methadone toxicity for the cause of death.

In the Phase 2 and 3 analysis set (excluding safety data from study M15-462), a total of 48 patients (2.1%) experienced at least one SAE.

The reported SAEs concerned mostly the system organ class (SOCs), neoplasms, infections and infestations and the SOC injury poisoning and procedural complications. No specific pattern in the type of SAEs was evidenced. Only one SAE was considered as related to study drug: a SAE of transient ischemic attacks occurring on treatment Day 11 and later post-treatment 24. The patient's medical history comprises obesity, smoking, and cardiac conduction abnormality that are known risk factors for TIA. No similar cases were reported in the dossier.

Six subjects (0.3%) experienced an event of de novo HCC. All cases were evidenced during treatment or within 4 months post-treatment and did not seem concurrent to GLE/PIB virological failure. The case of aggressive metastatic hepatic cancer with fatal outcome reported in a non-cirrhotic subject is worth being noted. As part of the D90 RSI, it was stated to the applicant that the PRAC conclusions on article 20 referral procedure regarding the risk of recurrent and de novo HCC for all DAA containing products also applies to the RMP for GLE/PIB.

One non-serious case met the criteria for potential cases of hepatotoxicity. This subject had elevations of ALT > 5N and concomitant Grade 2 total bilirubin increased that were all evidenced at Day 87, one day after ending 12 weeks of treatment. The review of the laboratory findings for this patient, and the presence of gallstones seen by ultrasound several days later are rather in favor of the result of a transient obstructive pattern than a drug-induced liver toxicity.

Laboratory findings

The rate of Grade 3-4 laboratory abnormalities including liver function tests was low in the Phase 2-3 analysis sets and no major signal was identified.

ALT elevations

Asymptomatic Grade 3 ALT elevations were reported in Phase 1 studies among healthy subjects who received higher doses of GLE. ALT elevations were also reported in DDI studies with atazanavir/ritonavir and with ethinyl-estradiol containing oral contraceptives.

In the Phase 2 and 3 analysis set, as expected with the clearance of viral HCV infection, an improvement from baseline in ALT values was observed with GLE/PIB compared with placebo. Only, four subjects had potentially clinically relevant ALT elevations defined as follows:

Criteria	**Phase 2 and 3 analysis set N= 2265[a]**
ALT > 5 x ULN and ≥ 2 x baseline	1/2263 (<0.1%)
ALT > 3 x ULN (Grade 2+ and increase from nadir grade) and total bilirubin ≥ 2 x ULN	2[b]/2263 (<0.1%)
Increase from nadir by Grade in ALT **ALT > 5-20 x ULN (Grade 3)** **ALT > 20 X ULN (Grade 4)**	 3/2263 (0.1%) 0/2263

[a] excluding subjects from study M15-462

One subject was previously presented. The remaining three Grade 3 ALT elevations were transient and occurred in a context of an overall improving ALT trend with antiviral treatment and are not indicative of a direct drug-induced liver toxicity. No Grade 4 ALT elevations were reported in the Phase 2 and 3 analysis set.

Overall, ALT elevations are low in patients receiving GLE/PIB 300mg/120mg in the Phase 2 and 3 clinical studies and did not seem clinically relevant. However, safety data from Phase 1 studies with higher GLE exposures in healthy subjects or in combination with atazanavir or ethinyl-estradiol containing products in the DDI studies lead to consider that GLE/PIB would not be devoid of any hepatic risk in some situations that could be met in the real-life setting.

Bilirubin elevations

The proportion of Grade 1, Grade 2 and Grade 3 bilirubin elevations in the Phase 2 and 3 analysis set was 6.8%, 2.3% and 0.4% respectively. No Grade 4 value was reported.

In the placebo and active controlled studies, more patients experienced Grade 1-3 hyperbilirubinemia in GLE/PIB 12weeks arm than in the comparator arm (i.e 7.2% versus 2.6% in the active –controlled study and 11.8% versus 4% in the placebo controlled study). The majority of bilirubin elevations were linked to elevation in indirect fraction of bilirubin in relation to the GLE-induced inhibition of bilirubin metabolism. These elevations are generally transient and asymptomatic. Few subjects (n=7, 0,3%) had direct hyperbilirubinemia. Two of them had also concomitant ALT elevations, and those cases were not indicative of the role of the study drugs. None of patients with hyperbilirubinemia experienced AEs such as jaundice, ocular icterus or laboratory or clinical events suggestive of liver failure. Despite no major safety was highlighted from these data, a statement on the risk of hyperbilirubinemia in patients receiving GLE/PIB is added in section 4.8 of the SmPC.

Comparison with other previously authorized NS3/4A protease inhibitors

As shown in the table below, the hepatic risk of GLE/PIB seems overall lower than that previously described with previously authorized NS3/4A protease inhibitors. This is somewhat mitigated by the fact EE-based regimens were prohibited during Phase 2 and 3 clinical trials, placing thus GLE/PIB in the best case scenario as compared with Viekirax.

	Viekirax All-treated subjects	**GZR/EBR 12week safety pool**	**GLE/PIB Phase 2-3 analysis**

	N=2632	N=1033	set N=2265
At least Grade 3 ALT elevations	1%	1,4%	0,4%
Grade 4 ALT elevations	0,2%	0,6%	0
% Grade 3 ALT elevations in females with EE	6/23 (26,1%)	0	EE-based regimens prohibited during Phase 2 and 3 CT (only two subjects exposed)
Discontinuation due to ALT elevations	0,07% (n=2)	At least 2 subjects discontinued GZR/EBR due to Late ALT elevations (ISP)	0
Grade 3-4 ALT elevations in patients with cirrhosis	2,8% (6/212)	No clear difference according to cirrhosis status	0
Grade 3 Bilirubin increased*	3DAA only 1,8% (all patients) higher rate in cirrhotics	0,4%	0,4% (all) 0,7% (cirrhotic)
Other aspects	Impact of RBV Expert hepatic panel	Late ALT elevations	
Safety in compensated cirrhosis	N=212	N=124	N=288
Safety in decompensated cirrhosis	Not studied during CT SmPC: CI in CP-C, not recommended in CP-B Monitoring for patients with cirrhosis	Not studied during CT CI in CP-C and CP-B	Not studied during CT SmPC: CI in CP-C, not recommended in CP-B

Grade 3 ALT elevation were defined as > 5-20ULN for Viekirax and GLE/PIB, they were defined as >5-10 XULN for Zepatier
Grade 4 ALT elevation > 20ULN for Viekirax and GLE/PIB, > 10ULN for Zepatier
*Grade 3-4 bilirubin increased were defined as >2XULN for Viekirax, > 3xULN for GLE/PIB, >2.6 for Zepatier

Safety in special populations

Safety in patients with chronic kidney disease (n=104)

In the study, 26.9% of subjects were > 65 years and BMI was > 30kg/m2 in 24% of subjects. A history of cardiovascular disease was reported in 89.4% of patients (coronary artery disease in 12.5% and/or a history of hypertension in 85.6%). A history of diabetes was reported in 41.3% of subjects.

Except pruritus that is known to be more commonly reported in CKD subjects on haemodialysis, the distribution of AEs in GLE/PIB treated subjects with CKD is similar to that observed in non CKD subjects. No subjects met criteria for potential hepatotoxicity based on results for a single laboratory parameter (ALT or total bilirubin) or based on results for both ALT and total bilirubin. In relation with the underlying comorbidities in this population of patients, notably hypertension and cardiomyopathy, a higher rate of cardiovascular AEs is reported, some of them with suggestive chronology with study drug, without a causal association can be confirmed. Specific attention should be paid on these issues in the post marketing setting.

Safety in patient with cirrhosis (n=288)

In the Phase 2 and 3 Analysis Set (excluding Study M15-462), 288 (12.7%) subjects with cirrhosis were included. The percentage of patients with any SAE or Grade 3 AEs is higher in patients with cirrhosis (5.9% and 6.9%) compared to non-cirrhotic patients (1.6% and 2.3%). However, none of SAE and severe AE reported in patients with cirrhosis were judged as potentially related to study drugs by the investigator. Fatigue, diarrhoea and pruritus were reported in greater frequency in patients with compensated cirrhosis (Child Pugh A). For laboratory abnormalities, more cirrhotic subjects had Grade 3-4 decreased platelets, total bilirubin increased and hyperglycemia. However, the differences observed do not seem clinically meaningful. Otherwise there was no reliable difference in the incidence and the pattern of AEs reported in cirrhotic patients compared with non-cirrhotic patients.

Table 27 - Laboratory adverse events by cirrhosis status (Phase 2 and 3 analysis set)

	Phase 2 and 3 analysis set n (%)	
	With cirrhosis n=288	**Without cirrhosis n= 1977**
ALT increase		
Grade 1	0,3% (n=1)	1,0% (n=20)
Grade 2	0,7% (n=2)	0,2% (n=3)
Grade 3 (>5xULN)	0	0,1% (=2)
Bilirubin increase		
Grade 1	13,5%	5,8%
Grade 2	3,5%	2,1%
Grade 3 (>3XULN)	0,7%	0,3%

HIV coinfection

In Study M13-590, HCV/ HIV co-infected subjects were eligible and 33 were enrolled. No formal conclusion can be reached on the safety profile of GLE/PIB in patients with HIV/HCV co-infection due to the small number of patients enrolled. However, it is agreed that the limited data do not raise particular concern.

A dedicated study M14-730 in HCV-infected subjects who are co-infected with HIV-1 is ongoing (approximately 160 subjects were planned). This study will provide further safety information in this specific population of patients.

Influence of intrinsic factors (age, gender, race, BMI)

No major of influence of age, gender, race/ethnicity and BMI was observed when regarding the type and the incidence of adverse events and the description of laboratory abnormalities reported in the Phase 2 and 3 analysis set. A greater percentage of subjects ≥ 65 years of age experienced any SAE (7.3% versus 2.4%) and any AE of Grade ≥ 3 (7.3% versus 3.2%) compared with younger subjects. This was apparently driven by the data of study M15-462 where a higher percentage of subjects > 65 years of age and a higher rate of comorbidities were reported compared with in other studies. Similarly, a higher proportion if black subjects experienced any SAE (7.1% vs 2.8%) and any severe AE (7.1% versus 3.6%) compared with non-black subjects, this seems again driven by a greater rate of black subjects in the study with CKD with higher rate of comorbidities. Otherwise, no trend was observed for the pattern of reported AEs and the Grade 3 or 4 laboratory abnormalities.

Immunological events

Immunological events were not specifically discussed by the applicant. There was no evidence towards a significant risk of hypersensitivity reactions with GLE/PIB.

Discontinuation due to adverse events

In the Phase 2 and 3 Analysis Set, 0.4% of subjects (n=8) discontinued study drug due to any AE. In the Phase 2 and 3 analysis set, 8 patients (0,4%) stopped study drug due to adverse events. Among these, three were considered as related to GLE/PIB by the investigator. In other Phase 2 studies not included in the analysis set, two additional subjects reported AEs leading to permanent discontinuation of study drugs including one case in which relatedness with GLE/PIB was suspected by the investigator. Among the ten subjects who stopped study drugs, three stopped due to neoplasm, none of them were considered linked to the DAA. Among the four cases where a causal relationship with study drugs was suspected by the investigator, three described gastro-abdominal disorders (abdominal pain, dyspepsia, diarrhoea) that resolved after treatment was stopped.

2.6.1. Discussion on clinical safety

The safety database for this application includes a total of 2369 HCV-infected adult subjects who received the intended recommended dose of GLE/PIB 300mg/120mg once daily, including 1295 subjects who received 12 weeks of treatment duration. This is in line with ICH recommendations in terms of required patient exposure.

Among 2369 subjects who received GLE/PIB 300mg/120mg QD in the clinical development program, 104 patients had severe renal impairment, the majority under haemodialysis (study M15-462), and a total of 308 were cirrhotic patients. Safety of GLE/PIB in subjects with CKD was assessed separately. Subjects with decompensated Child Pugh B or C cirrhosis were not included in the program, and no further studies are planned for such patients.

The safety profile of GLE/PIB is overall favourable with few severe AEs or serious AEs, reported in 2.9% and 2.1%, respectively (phase 2 and 3 analysis set, excluding subjects with CKD). Only four Grade 3 and 1 SAE were considered related to study drugs by the investigator, with no specific pattern identified. Few patients discontinued the study drug due to AEs (0.4%). The most commonly adverse drug reactions reported in the Phase 2 and 3 analysis set were fatigue, headache and gastrointestinal disorders such as diarrhoea and nausea. These adverse reactions are included in section 4.8 of the Maviret SmPC and reflected in the package leaflet.

The safety profile of GLE/PIB was similar in patients with compensated cirrhosis and in non-cirrhotic subjects~~,~~ in patients with severe renal impairment and/or haemodialysis, except a higher rate of pruritus (which is not unexpected in patients under haemodialysis). The overall safety profile did not strictly differ from the rest of the population with normal renal function. However, in line with underlying comorbidities in this population of patients, notably hypertension and cardiomyopathy, a higher rate of cardiovascular AEs was reported in this population, some of them with suggestive chronology with study drug. A causal association cannot be confirmed, but specific attention should be paid on this issue in the post-marketing setting.

A total of seven deaths were reported during the phase 2 and 3 clinical studies with GLE/PIB 300mg/120mg once daily. All deaths occurred during the post-treatment period and none was considered related to study drug. The diagnosis of a rapidly aggressive hepatic cancer with metastasis leading to death 2.5 months after the end of antiviral therapy in one patient without cirrhosis is worth being noted. It was concluded that the impact of DAAs treatment on the incidence and type of de novo HCC warrants further investigations, through a prospective cohort study in HCV-infected patients. A joint study involving all MAHs was encouraged.

The rate of de novo HCC was 0.3% (6/2369) in the clinical development program and 1.7% (5/288) in patients with cirrhosis, which is in the range of the expected incidence of HCC in this population of patients. Since patients with a history of HCC were not included in the studies, no recurrence rates of HCC could be reported. Similarly, no cases of HBV reactivation were observed, since HBV/HCV co-infected cases were not allowed to be enrolled in the studies. The class labelling agreed by the PRAC on the latter issue is included in section 4.4 of the Maviret SmPC. Furthermore, the PRAC conclusions regarding the HCV DAA article 20 referral procedure on HCC recurrence and de novo and on HBV reactivation are adequately reflected in the RMP of GLE/PIB.

With regard to laboratory abnormalities, no signal is identified, with low percentages of Grade 3-4 abnormalities for all laboratory values identified. The rate of Grade 3 ALT elevations (>5 XULN) in the phase 2-3 analysis set was 0.1% (n=3). There were no Grade 4 ALT values. One patient met the criteria of potential cases of hepatotoxicity with elevations of ALT > 5N and concomitant Grade 2 total bilirubin increased that were evidenced at Day 87, one day after 12 weeks of treatment. The review of the laboratory findings for this patient, and the presence of gallstones seen by ultrasound several days later are in favour of a transient obstructive pattern rather than a drug-induced liver toxicity as etiology of the ALT and total bilirubin elevations. Other Grade 3 ALT elevations are not indicative of drug causality. No monitoring is mandated on the basis of these findings.

Bilirubin elevations with potential clinical interest were reported in 1.2% of patients in the phase 2 -3 analysis set, the majority of them of indirect predominance in relation to the known inhibition of bilirubin metabolism induced by GLE. Seven subjects (0.3%) reported bilirubin elevations with direct or mixed predominance, none of them describing a serious pattern. Nevertheless, physicians are informed about the potential for bilirubin elevations through a statement added in section 4.8 of the Maviret SmPC.

Overall, data available from the phase 2 and 3 clinical studies are quite reassuring as regards the risk of ALT elevations that seems overall lower than that seen with previous NS3/4A protease inhibitor and without clinical significance. However, safety data from phase 1 studies with higher GLE exposures in healthy subjects or in some DDI studies with atazanavir and ethinyl-estradiol containing products lead to the consideration that GLE/PIB would not be totally devoid of any hepatic risk in some situations that could be met in the real life setting. Due to substantially higher GLE exposures yielded by co-treatment with atazanavir/r, and ALT elevations reported in healthy subjects with this combination, CHMP agreed that such co-administration is rightly contraindicated in the Maviret SmPC. Further, due to ALT elevations reported in patients treated with ethinyl estradiol (EE) in a DDI study on oral contraceptives, EE-containing regimens were prohibited medications in the Phase 2-3 clinical trials and no further clinical data were gained with this combination. A potential increased risk of clinically significant ALT elevations or even hepatotoxicity in female patients receiving EE-based oral contraception cannot therefore be ruled out in real life setting. Consequently, CHMP agreed that EE-containing medications are contra-indicated in the SmPC of Maviret.

2.6.2. Conclusions on the clinical safety

The safety profile of Maviret (glecaprevir/pibrentasvir) is favourable with no major concern identified. While the risk of ALT elevations seems lower as compared to previously authorized NS3/4A, it remains that some situations (namely in case of combination with EE-based regimens) have been identified at increased hepatic risk. This has been appropriately covered in the Maviret SmPC by the addition of a contra-indication with EE-containing medicines.

2.7. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important identified risks	HBV reactivation
	Resistance development
Important potential risks	Recurrence of hepatocellular carcinoma
	Emergence of hepatocellular carcinoma
	Drug-drug interactions: – Concomitant use with other drugs that are strong inhibitors of OATP1B1 or OATP1B3 (e.g., ciclosporin 400 mg, darunavir with or without ritonavir, and lopinavir/ritonavir) – Concomitant use with drugs that are inducers of P-gp/CYP3A (e.g., efavirenz) – Concomitant use with drugs that are sensitive substrates of P-gp (e.g., digoxin) – Concomitant use with drugs that are sensitive substrates of OATP1B1 or OATP1B3 (e.g., lovastatin, pravastatin, rosuvastatin)
Missing information	Safety in patients with moderate hepatic impairment (Child-Pugh B)
	Safety in liver transplant patients
	Safety in pregnant and breastfeeding patients
	Safety in patients with previous hepatocellular carcinoma

Pharmacovigilance plan

Study / Activity Type, Title and Category (1 – 3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
The MAH shall conduct and submit the results of a prospective safety study using data derived from a cohort of a well-defined group of patients, based on an agreed protocol setting out criteria for entry	To evaluate the recurrence of hepatocellular carcinoma associated with GLE/PIB.	Potential risk of recurrence of hepatocellular carcinoma associated	Planned	Interim results Q4 2019 Final study report Q2

Study / Activity Type, Title and Category (1 – 3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
and follow-up. Category 1		with DAA treatment.		2021
The MAH shall conduct a prospective cohort study in HCV infected patients with cirrhosis to assess the impact of DAA treatment on the incidence and type of de novo hepatocellular carcinoma. Category 3	To assess the impact of DAA treatment on the incidence and type of de novo hepatocellular carcinoma.	Potential risk of de novo hepatocellular carcinoma	Planned	Feasibility assessment was submitted in June 2017.
Study M13-576 A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy (ABT-493 and/or ABT-530) in Subjects Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection. Category 3	To assess the persistence of specific HCV amino acid substitutions associated with drug resistance in subjects who experienced virologic failure.	Risk of resistance development	Started	Interim: Dec 2016 Final CSR: January 2021
Study M13-596 A Single-Arm, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of ABT-493/ABT-530 in Adult Post-Liver or Post-Renal Transplant Recipients with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (MAGELLAN-2) Category 3	To assess the safety and efficacy of GLE/PIB in approximately 90 non-cirrhotic TE and TN adult post-liver or post-renal transplant recipients with chronic HCV GT1 – 6 infection	Missing information: Safety in liver transplant recipients	Started	Final Primary analysis CSR (SVR12): Dec 2017

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Identified risk – HBV reactivation	Warning in Section 4.4 (Special warnings and precautions for use) of SmPC and section 2 (What you need to know before you take Maviret) of the PL. Restricted medical prescription.	None proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Identified risk – Resistance development	Restricted medical prescription. Advice on appropriate dosing and administration to achieve maximal efficacy will be provided in the proposed product information: Section 4.2 (Posology and method of administration) of the SmPC Section 3 (How to take Maviret) of the PL. Commercial packaging and product labeling have been designed to reduce dosing errors (Module SVI.4.2).	None proposed.
Potential risk –Recurrence of hepatocellular carcinoma	Restricted medical prescription.	None proposed.
Potential risk – Emergence of hepatocellular carcinoma	Restricted medical prescription.	None proposed.
Potential risk – Drug-drug interactions	Contraindications and dose adjustments or monitoring will be listed in the proposed product information: Section 4.3 (Contraindications), section 4.4 (Special warnings and precautions for use), and section 4.5 (Interaction with other medicinal products and other forms of interaction) of the SmPC Section 2 (What you need to know before you take Maviret) of the PL. Restricted medical prescription.	None proposed.
Missing information – Safety in patients with moderate hepatic impairment (Child-Pugh B)	Recommendations and contraindications will be listed in the proposed product information. Section 4.2 (Posology and method of administration) and section 4.4 (Special warnings and precautions for use) of the SmPC Section 2 (What you need to know before you take Maviret) of the PL Restricted medical prescription.	None proposed.
Missing information – Safety in liver transplant patients	Currently available data in this population will be provided in the proposed product information: Section 4.2 (Posology and method of administration). Warnings in section 4.4 (Special warnings and precautions for use) of the SmPC and section 2 (What you need to know before you take	None proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	Maviret) of the PL. Restricted medical prescription.	
Missing information – Safety in pregnant and breastfeeding patients	Information with respect to reproductive studies performed in animals will be provided in the proposed product information: Section 4.6 (Fertility, pregnancy and lactation), section 5.3 (Preclinical safety data) of the SmPC, and section 2 (What you need to know before you take Maviret) of the PL will provide information on pregnancy. Restricted medical prescription.	None proposed.
Missing information – Safety in patients with previous hepatocellular carcinoma	Restricted medical prescription	None proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The new EURD list entry will use the EBD (which is also the international birth date (IBD)) to determine the forthcoming Data Lock Points.

2.9. New Active Substances

The applicant compared the structures of glecaprevir and that of pibrentasvir with active substances contained in authorised medicinal products in the European Union and declared that they are not salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of any of them.

The CHMP, based on the available data, considers glecaprevir and pibrentasvir to be new active substances as they are not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Maviret (glecaprevir / pibrentasvir) is included in the additional monitoring list as it includes two new active substances.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Glecaprevir-pibrentasvir is new fixed dose combination for the treatment of adult patients with chronic hepatitis C. Natural history of HCV infection is a continuum that goes worsening over approximatively 20 years and evolves from minimal liver fibrosis (F0-F1) to compensated and then to decompensated cirrhosis (F4, Child Pugh C) and/or hepatocarcinoma. HCV is the main cause of liver transplant. There are 6 major different HCV viral genotypes, GT1 to GT6 with different subtypes and with a different geographical repartition. Genotype 1 is the most prevalent in Europe, accounting for 70% of chronically infected Europeans, with GT1b subtype predominating over GT1a in most European countries including those with the highest prevalence. Genotype 3 is the next most common genotype in Europe.

3.1.2. Available therapies and unmet medical need

After almost 20 years with the bi-therapy with (Peg-)IFN+ Ribavirin (PR) and then with the first generation of Direct Antiviral Agents (DAA), boceprevir and telaprevir (two NS3/4A protease inhibitors that were still to be used with PR and had concerning tolerance profile) major advances have been made in the management of chronic HCV infection.

Several other DAA are now approved in the EU, within the three existing pharmacological classes: NS5B inhibitors (sofosbuvir, dasabuvir), NS5A inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir), NS3/4A inhibitors (simeprevir, grazoprevir, paritaprevir). These DAAs are now part of various IFN free regimens. Given its antiviral activity and its high genetic barrier, a sofosbuvir-containing DAA regimen is the most widely currently used IFN free regimen. Thanks to these new agents/regimens, SVR rates >90% can be achieved in most patients.

Difficult-to-treat patients are cirrhotic patients who may require intensified regimens, with a longer treatment duration or addition of ribavirin. Moreover, in patients experiencing virologic failure the likelihood of a successful rescue is dependent on the accumulated resistance (RAS) that may persist long term. To this purpose, while NS3/4A RAS can reverse to wild type after sufficient time and while signature mutation to the NS5B inhibitor sofosbuvir (S282T) is rare, NS5A RAS are much more challenging, as it

would appear that they tend to persist. In particular, the likelihood of the virologic response of HCV GT3 to treatment is compromised by the presence of the Y93H mutation with current NS5A inhibitors. GT3 as a whole and especially NS5A experienced HCV GT3-infected patients has become the most difficult-to-treat population.

This new FDC comprises two pan-genotypic components. In December 2016 the CHMP has considered that this FDC has the potential to respond to an unmet medical need and to represent a significant advance for the therapeutic management of patients in case its benefit-risk balance would be concluded positive, and thus agreed with the applicant's request for an accelerated review.

From a public health perspective there is a need for regimens that can be administered with the same simple posology regardless of the HCV genotype and of the cirrhosis status (which is currently not the case with available DAA), in order to enable hepatitis C treatment to be handled quickly and easily in order to have a meaningful impact on the HCV epidemiology. Indeed, the 2014 World Health Assembly requested the World Health Organization (WHO) to examine the feasibility of eliminating hepatitis B and C, and the 2015 Agenda for Sustainable Development commits to combating viral hepatitis with a goal of eradicating hepatitis B and C by 2030. Effective and simple treatment of HCV (and HBV) infection is an important part of achieving that goal.

3.1.3. Main clinical studies

As illustrated in the following table, the Maviret clinical development program covers all the 6 major HCV genotypes GT1-6 and includes efficacy and safety data from 8 registrational studies and 3 supportive Phase 2 studies that were conducted in various populations and tested different treatment durations (8 weeks (short term treatment in non-cirrhotic patients), 12 weeks, 16 weeks). The non-inferiority hypothesis was tested to compare 8 vs 12 weeks of treatment in non-cirrhotic patients (-5% in ENDURANCE-1/M13-590, -6% in ENDURANCE-3 study/M13-594), while the comparison of 12 versus 16 weeks of treatment was made with only descriptive statistics.

Overall around 2300 patients were enrolled in the clinical development.

Genotype (GT)	Clinical study	Summary of study design
TN and TE subjects without cirrhosis		
GT1	ENDURANCE-1	GLE/PIB for 8 (n=351) or 12 weeks (n=352)
	SURVEYOR-I	GLE/PIB for 8 weeks (n=34)
GT2	ENDURANCE-2	GLE/PIB (n=202) or Placebo (n=100) for 12 weeks
	SURVEYOR-II	GLE/PIB for 8 weeks (n=199) or 12 weeks (n=25)
GT3	ENDURANCE-3	GLE/PIB for 8 (n=157) or 12 weeks (n=233) Sofosbuvir + daclatasvir for 12 weeks (n=115)
	SURVEYOR-II	GLE/PIB for 8 (TN only) (n=29) or 12 weeks (n=76) or 16 (TE only) weeks (n=22)
GT4, 5, 6	ENDURANCE-4	GLE/PIB for 12 weeks (n=121)
	SURVEYOR-I	GLE/PIB for 12 weeks (n=32)
	SURVEYOR-II	GLE/PIB for 8 weeks (n=58)
TN and TE subjects with cirrhosis		
GT1, 2, 4, 5, 6	EXPEDITION-1	GLE/PIB for 12 weeks (n=146)
GT3	SURVEYOR-II	GLE/PIB for 12 weeks (TN only n=64) or 16 weeks (TE only n=51)
Subjects with CKD stage 4 and 5 with or without cirrhosis		
GT1-6	EXPEDITION-4	GLE/PIB for 12 weeks (n=104)
NS5A inhibitor and/or PI-experienced subjects with or without cirrhosis		
GT1, 4	MAGELLAN-1	GLE/PIB for 12 (n=66) or 16 weeks (n=47)

TN=treatment naïve, TE=treatment experienced (includes previous treatment that included pegIFN (or IFN), and/or RBV and/or sofosbuvir), PI=Protease Inhibitor, CKD=chronic kidney disease

The main studies were conducted in *non-cirrhotic* treatment-naive patients or patients having failed previous treatment with PegIFN+ribavirin (PR), including some patients with previous treatment with PR+ sofosbuvir (PRS). Those are mainly the ENDURANCE studies (ENDURANCE-1 in GT1, ENDURANCE-2 in GT2, ENDURANCE-3 in GT3, ENDURANCE-4 in GTs 4-6) together with the SURVEYOR studies (SURVEYOR I and II) that complete the ENDURANCE studies to some extent.

One study was an active controlled open label non-inferiority (margin -6%) study (ENDURANCE-3/ M13-594) versus sofosbuvir-daclatasvir 12 weeks in GT3 treatment naïve non cirrhotic patients.

Another study was double blind placebo controlled (ENDURANCE-2/ M15-464) and was conducted in HCV GT2 treatment naïve or TE-PRS non cirrhotic patients.

A study of limited size (identified by the applicant as supportive) was performed in DAA treatment experienced patients (almost exclusively GT1, in addition four GT4 subjects), the MAGELLAN-1 (M15-410) study. Some HIV co-infected patients were also included in the Maviret development programme and a dedicated study is ongoing in this population (EXPEDITION-2).

Overall, around 300 compensated cirrhotic patients were included in the Maviret clinical development with notably one dedicated study in compensated cirrhotic patients with GT1, GT2, GT4, GT5 and GT6 (EXPEDITION-1/M14-172). Based on PK and safety grounds this FDC is not recommended in patients with moderate hepatic impairment and contra-indicated in patients with severe hepatic impairment. Moreover, it is acknowledged that as a whole NS3/4A are not adequate candidates for treating patients with hepatic decompensation due to the risk of worsening the liver disease.

Finally a dedicated study was performed in patients with CKD 4-5 (EXPEDITION-4/M15-462).

Apart from the double blind placebo controlled study (ENDURANCE-2), all studies are open label studies.

The standard Sustained Virologic Response 12 weeks after end of treatment (SVR12) was the primary endpoint.

3.2. Favourable effects

Of particular interest, Maviret comprises two components of pan-genotypic activity.

Notably, in contrast to previous protease inhibitors, glecaprevir has important potency against GT 2 and GT3.

Pibrentasvir appears similarly highly potent (picomolar activity) in all HCV genotypes. As a significant improvement as compared to other NS5A available, PIB is the first NS5A inhibitor with a conserved activity against viral strains containing the Y93H mutation (no impact in GT3 and GT1b and 7-fold reduced activity in GT1a). Having in mind the fact that the presence of Y93H at baseline is the main reason for lower response rates seen in GT3 patients treated with current NS5A inhibitors, and that this mutation is selected in case of NS5A failure in GT3 population, the antiviral activity of PIB against Y93H HCV strains makes Maviret of potential interest for this difficult to treat population.

In the HCV GT1 population, the genotype most widely represented in the EU, the results observed in TN or TE-PRS patients, with 99% SVR12 achieved with a convenient 8 weeks treatment duration in non-cirrhotic patients and 97% in cirrhotic patients with a 12 weeks treatment duration without need for ribavirin, are supportive of the fact that this FDC will likely represent an optimization in the therapeutic armamentarium. Similar results, regardless of the prior PRS failure, were obtained in patients infected with HCV genotypes 2 and 4-6.

In TN HCV GT3-infected patients, the 8 weeks treatment resulted in a numerically higher relapse rate (5/150, 3.3%) than did the 12 weeks treatment arm (3/222, 1.4%). However, CHMP agreed that the difference can be seen as non-significant, and that the results are considered supportive of 8 weeks treatment for non-cirrhotic, previously untreated patients with HCV genotype 3-infection. CHMP also noted that the simplicity of an 8 week regimen, and the same treatment duration in previously untreated patients, regardless of the HCV genotype, is also considered an important part of a programmatic approach for HCV eradication (targeted by 2030 by WHO).

Moreover, in line with the marginal renal elimination and the PK study in patients with renal impairment, the dedicated phase III study in GT1-6-infected patients with CKD stage 4 or 5 (EXPEDITION-4) has shown that GLE/PIB could adequately cover an unmet medical need for these patients. Indeed, in this study with around 82% of patients undergoing dialysis, a high SVR12 rate was achieved [98.1% (102/104)].

In MAGELLAN-1 (in practice concerning genotype 1-infection), 12 or 16 weeks of Maviret was given to patients who had failed prior treatment that included agents from one or both DAA classes of interest (NS3/4A and NS5A), of which around 30% had cirrhosis. In those exposed to NS3/4A only (n=38) there were no virological failures, likely because resistant virus selected by prior therapy had reverted to wild type virus prior to study entry. In those exposed to NS5A only (n=38) 3 failures were seen, and in those exposed to both classes (n=37) 7 failures, without an interpretable difference between arms (12 or 16 weeks). Of note, for the latter group where key polymorphisms to NS3 and NS5A were detected at baseline samples, 5 out of 9 patients failed therapy.

3.3. Uncertainties and limitations about favourable effects

The evaluation of 8 versus 12 weeks of therapy (for the non-cirrhotic population) to a very large extent concerned patients with very limited fibrosis (F0/F1), with limited numbers having more severe fibrosis (F2/F3), i.e. those patients who may have a higher risk for relapse with shorter treatment duration. However, the numbers with F2/F3 treated for 8 weeks are still deemed sufficient by CHMP to support the 8 week treatment duration in non-cirrhotic patients (throughout the range to F3 fibrosis), having the close to 100% cure rate in mind.

As expected, numbers treated with infections with HCV genotypes 4-6 are also limited. However, not a single failure was seen in those treated, and the same treatment recommendation is also supported by the in vitro data presented. Of note, early viral kinetics was similar across genotypes, with close to 100 % of patients having unquantifiable HCV RNA at week 4.

For patients with prior exposure to the NS3/4A and or NS5A class, an overall limited population, CHMP agreed that the results obtained in the small MAGELLAN-1 study should be interpreted cautiously. Since cross-resistance between classes are seen, it was shown that the outcome with GLE/PIB re-treatment depends on what prior regimen the patients failed on, and for the NS3/4A class, on how much time has passed since the administration of that failing treatment. Due to the limited sample size, it is not possible to generate a relevant resistance testing algorithm to select patients for whom retreatment with GLE/PIB is appropriate. Furthermore, there is uncertainty about the impact of the additional resistance generally incurred in case of retreatment failure. Importantly, the study did not include genotype 3-infected patients with prior failure to sofosbuvir + an NS5A inhibitor. Although pibrentasvir seems fully active to genotype-3 virus with the key mutation typically seen at failure with other NS5A inhibitors (Y93H), it is still not certain that the in vivo response would be as expected (taking other potential amino acid substitutions into account).

3.4. Unfavourable effects

The safety profile of GLE/PIB has been assessed in a large population of HCV-infected subjects including patients with severe renal impairment or under haemodialysis and patients with cirrhosis. The total number of exposed HCV-infected subjects to the dosing regimen of GLE/PIB 300mg/120mg once daily is considered acceptable by CHMP.

No major safety concern was identified in the Maviret clinical development program. Besides fatigue, which is a very common AE reported in the core population, the safety profile of GLE/PIB is mainly marked by non-serious gastrointestinal adverse drug reactions, notably diarrhoea, nausea and abdominal distension or pain. Despite they were of mild intensity and that they generally did not lead to drug discontinuation, these ADRs were overall reported more commonly in patients receiving GLE/PIB than placebo in the placebo-controlled study ENDURANCE-2 (M15-464).

Severe bilirubin elevations (Grade 3-4), the majority of them with indirect predominance (in relation to the impact of GLE on bilirubin metabolism) have been reported in 1.2% of subjects in the phase 2- 3 analysis set. While the rate of hyperbilirubinemia of mixed or direct origin was low and was not describing a serious pattern, CHMP deemed important that this was underlined in the Maviret SmPC.

While ALT elevations have been seen in healthy subjects that received higher doses of GLE, but also in drug-drug interactions studies with atazanavir on the one hand and with ethinyl-oestradiol containing medications on the other hand, CHMP agreed that the clinical data derived from the phase 2-3 analysis set were not indicative of a risk of clinically significant ALT elevations with Maviret.

As an increase of GLE exposure was expected to be > 10-fold in subjects with severe liver impairment (Child-Pugh C), thus exceeding the safety margin, the use of GLE/PIB has been contra-indicated in this population of patients. The use of GLE/PIB in subjects with moderate hepatic impairment is not recommended, as GLE exposures are expected to double in these subjects.

Finally, the main unfavourable effect is the risk for development of double class resistance, which is seen in a high proportion of the few patients failing therapy. For patients already carrying viruses with resistance to the NS3 and NS5A class (MAGELLAN-1), further resistance developed, resulting in viruses that would seem hard to cure with available DAA options.

3.5. Uncertainties and limitations about unfavourable effects

A potential risk of higher incidence of de novo and recurrent hepatocellular carcinoma in DAA-treated subjects has emerged in the literature and has extensively been discussed at the PRAC level as part of an Article 20 referral. Further studies have been requested by PRAC to investigate this potential risk and changes in the RMP for all concerned DAA-containing medicinal products have consequently been requested. This request also applies for Maviret since it is not expected that the impact of GLE/PIB-based therapy would diverge from the other DAA for this issue.

In the clinical development program of Maviret, six cases of HCC were collected (0.3%).

Hepatic decompensation and hepatic failure have been reported in the post-marketing setting in patients with advanced liver disease receiving already authorized NS3/4A protease inhibitors containing products. The GLE/PIB program did not contain patients with decompensated cirrhosis (Child Pugh B/C). In such patients the exposure of GLE is increased (around a factor 5 in Child Pugh B, yet much higher in Child Pugh C), whereas PIB exposure is not affected. CHMP noted that GLE/PIB is “not recommended” for the treatment of Child Pugh B patients, but such patients may still be treated (for example in case of also having renal impairment). It is unknown whether the safety profile is impacted in such patients.

Initially, the applicant proposed to not recommend the combination of GLE/PIB with EE-containing products in the Maviret SmPC. However, given the risk of ALT elevations identified in the drug-drug interaction study, strongly indicating a drug-induced pattern, and the fact that no clinical data have been gained with such a combination in the clinical program (EE-containing medications were disallowed), a more conservative approach has been taken and CHMP asked that a contra-indication is added in section 4.3.

Overall, the occurrence of serious hepatic events in the real life setting notably in patients cumulating several risk factors or DDI cannot be excluded and should be closely monitored within PSURs.

3.6. Effects Table

Effect	Population	Regimen	Response rate	Uncertainties/ Strength of evidence
Favourable effects				
ENDURANCE-1 ENDURANCE-2 ENDURANCE-4 SURVEYOR-II	GT1,2,4,5,6 Non cirrhotic	GLE/PIB 8W	SVR12=98-99% GT1, GT2 or GT4-6	No virological failure apart 1 BK in 1 GT1a and 2 relapses in 2 GT2a. All were TE-PRS => 91.3% SVR12 in TE-PRS GT2 Only 2 GT5 and 10 GT6 (all but 2 TN) received 8 weeks of treatment
EXPEDITION-1	GT1,2,4,5,6 Cirrhotic	GLE/PIB 12W	SVR12=97-100%	Only 1 virological failure in 1 GT1a few GT5 or 6
ENDURANCE-3 SURVEYOR-II	GT3 TN Non cirrhotic	GLE/PIB 8W or 12w	SVR12~95%	Non inferiority 12w versus SOF+DCV 12w (lower bound 95% CI=-5.6%) but numerically more relapses in GLE/PIB arms Non inferiority 8w versus 12w but numerically more relapses in 8w (3.3% vs 1.4%)
SURVEYOR-II	GT3 TN cirrhotic	GLE/PIB 12W	SVR12=97.5%	No virological failure
SURVEYOR-II	GT3 TE With or without cirrhosis	GLE/PIB 16W	SVR12=95.7%	Relapse rate=2.9% but few number of patients with pejorative mutations at baseline (1 with A30K and none with Y93H)
	Effect of RAVs			A30K is associated with lower response rate Double mutants (notably A30K+Y93H) emerging at failure
MAGELLAN-1	NS5Aand/or PI failure	GLE/PIB 16W	SVR12=81.3-100%	- PI-experienced/NS5A-naïve subjects had an SVR12 rate of 100% (14/14) - NS5A-experienced/PI-naïve subjects had a higher SVR12 rate with 16 weeks (94.4%:17/18) - SVR12 rates in subjects who were both NS5A- and PI-experienced were 78.6% for 12 weeks of treatment and 81.3% for 16 weeks of treatment (13/16)

Effect	Population	Regimen	Response rate	Uncertainties / Strength of evidence
	Effect of RAVs			Across both arms, subjects who were both NS5A- and PI-experienced had a higher rate of virologic failure (20.0% [6/30]) compared with NS5Aexperienced/PI-naïve (8.8% [3/34]) and PI-experienced/NS5-naïve (0% [0/27]) subjects. Presence of RAS at both targets at baseline is particularly pejorative Complex profile of mutations at failure with uncertain retreatment option
EXPEDITION-4	GT1-6 CKD stage 4/5	GLE/PIB 12W	SVR12= 98.1% (102/104)	No virological failure 20% cirrhotic patients
Unfavourable effects				
Phase 2-3 studies	Phase 2-3 analysis set	GLE/PIB 300mg/120mg	Gastrointestinal ADRs	Higher rate of diarrhoea, nausea, abdominal pain/distension in GLE/PIB treated patients than placebo – frequency common
Phase 2-3 studies	Phase 2-3 analysis set	GLE/PIB 300mg/120mg	Hyperbilirubinemia	Predominantly indirect Dose exposure relation ship Higher rate in cirrhotic subjects
Phase 1 studies	Healthy subjects	GLE + PIB	ALT elevations	-With higher GLE exposure in healthy subjects -In combination with ATZ In DDI study - In combination with EE-containing oral contraceptives in DDI study.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

GLE/PIB provides a simple, highly effective and well tolerated pan-genotypic regimen. *For the main bulk of patients to be treated in the future, namely non-cirrhotics without prior therapy,* particular advantages are seen, since genotyping is not necessary, and a treatment of 8 weeks is sufficient. Therapy for 12 weeks yielded excellent results, without the use of ribavirin, in the cirrhotic previously untreated patients.

Patients with severe renal impairment and infected with HCV genotypes other than 1 and 4, are currently lacking treatment alternatives, as an appropriate dosing regimen for sofosbuvir has not been determined, and, furthermore, those infected with genotype 1a may need ribavirin as part of available regimens. Ribavirin is problematic to give to such patients, both due to a considerable impact on pharmacokinetics, as well as due to its haematological side effect, to which patients with renal insufficiency are more susceptible. For these patients GLE/PIB is an important new regimen, which can be given without dose adjustments, without ribavirin, and with the same efficacy and safety as in other patients.

Patients still to be treated, and with prior failure to peg-IFN + ribavirin, is a population of diminishing size. In practice this mainly concern patients with genotype 1-infection (poor response rates to such therapy), and many of them have already been successfully treated with other new DAA regimens. For genotype-1 infected patients, GLE/PIB given for 8 weeks or 12 weeks (when cirrhosis is present) also yielded the same excellent results in these selected patients. CHMP noted that fairly limited numbers of HCV

genotype-3 infected patients who failed therapy with peg-IFN + ribavirin (or possibly sofosbuvir + ribavirin) are yet to be treated (response rates relatively high with prior therapies). Of note, many such patients may already have been successfully treated with sofosbuvir + daclatasvir or sofobuvir/velpatasvir in the EU. Although GLE/PIB yielded high cure rates also for these patients (selected for negative predictors for cure), if given for 16 weeks, such patients have other 12 week options that are highly effective, and the role of GLE/PIB for such patients may be more limited.

Patients who failed prior therapy that included the NS3- or NS5A class, or both, have been studied in limited numbers. Of note, this population is quite limited, since the new regimens have been shown to yield very high efficacy outcomes also in real life (not only in clinical trials), and these patients should be managed by experts. High overall efficacy was seen in such patients treated with GLE/PIB for 12 or 16 weeks. However, the regimen is not optimal for many patients, and the limited sample size does not allow for the identification of a resistance testing algorithm to identify patients suitable for retreatment with GLE/PIB (rather than with a triple-class regimen including sofosbuvir). Failure on GLE/PIB retreatment is anticipated to aggravate NS3/4A and NS5A-class resistance. Therefore, the use of GLE/PIB in such patients may incur a loss of chance, and CHMP agreed that the use of GLE/PIB as a retreatment regimen cannot be recommended on the basis of the available, limited dataset.

No particular concern is raised on the safety profile of this FDC on the basis of >2000 patients exposed so far. However, CHMP agreed that the Maviret SmPC should more adequately reflect that the use of this FDC could be associated with gastrointestinal symptoms and notably diarrhoea. ALT elevations have been observed throughout the clinical development without raising major issue. However, the clinical development with a selected population (limited co-administrations) might not fully predict the situation in real life. This will have to be kept under scrutiny.

For the sake of consistency with other DAA the RMP has been adjusted taking into account the outcome of the recent PRAC referral on signal of HCC recurrence.

The risk for double class resistance following a treatment failure is considered the one identified important unfavourable effect of this regimen. Such resistance may result in a low chance for SVR with a subsequent regimen, in particular if re-treatment needs to be undertaken without too much delay (cirrhotic patients), prior to a potential reversion of NS3 resistance.

3.7.2. Balance of benefits and risks

The benefit of Maviret (glecaprevir/pibrentasvir) (efficacy) outweighs the risks (resistance development) with the proposed recommendation (8-16 weeks of therapy) for patients without prior exposure to the NS3 and NS5A DAA class.

For the quite limited population with prior exposure to these DAA classes there is a risk for treatment failure since cross resistance within the classes does occur and where a (second) treatment failure with GLE/PIB may lower the chance considerably for a successful subsequent treatment. Re-treatment with GLE/PIB in such patients could be guided by resistance screening, but at present the company has not been able to provide data on what specific baseline resistance that would carry a risk for treatment failure.

3.8. Conclusions

The overall benefit-risk balance of Maviret (glecaprevir/pibrentasvir) in the treatment of adult patients with chronic hepatitis C is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Maviret is favourable in the following indication:

Treatment of chronic hepatitis C virus (HCV) infection in adults.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): In order to evaluate the recurrence of hepatocellular carcinoma associated with	Q2 2021

Description	Due date
Maviret, the MAH shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol. The final study report shall be submitted by:	

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that glecaprevir and pibrentasvir are new active substances, as they are not constituents of a medicinal product previously authorised within the European Union.