EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2019
EMA/154469/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Maviret

International non-proprietary name: glecaprevir / pibrentasvir

Procedure No. EMEA/H/C/004430/II/0012

Marketing authorisation holder (MAH): AbbVie Deutschland GmbH & Co. KG

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AUC	area under the curve
CHC	chronic hepatitis C
CI	confidence interval
CKD	chronic kidney disease
C_{max}	maximum observed plasma concentration
CSR	clinical study report
DAA	direct-acting antiviral
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GLE	glecaprevir
GT	genotype
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IFN	interferon
IPK	intensive pharmacokinetic
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
PDCO	Paediatric Committee
pegIFN	pegylated interferon
PIB	pibrentasvir
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)

PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QD	once daily
RBV	ribavirin
RMP	risk management plan
RNA	ribonucleic acid
SmPC	summary of product characteristics
SOF	sofosbuvir
SVR	sustained virologic response
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 6 June 2018 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to extend the Maviret indication to adolescents (from 12 to <18 years of age) with chronic hepatitis C infection, based on new clinical data from study M16-123, an open-label, multi-centre study to evaluate the pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in paediatric subjects with genotypes 1 - 6 chronic hepatitis C virus infection (DORA), using the adult co-formulated tablets in adolescents. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
In addition, the marketing authorisation holder (MAH) submitted a revised RMP version 4, updated in accordance with the second revision of the RMP template.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 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 Decision 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.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Joseph Emmerich

Timetable	Dates
Submission date	6 June 2018
Start of procedure	23 June 2018
CHMP Rapporteur Assessment Report	22 August 2018
CHMP Co-Rapporteur Assessment Report	22 August 2018
PRAC Rapporteur Assessment Report	22 August 2018
PRAC members comments	29 August 2018
Updated PRAC Rapporteur Assessment Report	30 August 2018
PRAC Outcome	6 September 2018
CHMP members comments	10 September 2018
Updated CHMP Rapporteur Assessment Report	14 September 2018
Request for supplementary information (RSI)	20 September 2018
CHMP Rapporteur Assessment Report	28 December 2018
PRAC Rapporteur Assessment Report	2 January 2019
PRAC members comments	9 January 2019
Updated PRAC Rapporteur Assessment Report	10 January 2019
PRAC Outcome	17 January 2019
CHMP members comments	21 January 2019
Updated CHMP Rapporteur Assessment Report	24 January 2019
Opinion	31 January 2019

2. Scientific discussion

2.1. Introduction

Hepatitis C viral infection is a global health problem, with 184 million individuals chronically infected worldwide. An estimated 13.2 million children between the ages of 1 and 15 years old are infected with HCV globally.

Within Europe's paediatric population, prevalence of HCV ranges from 0.05% to 0.36%. New HCV infections among the 5–14 year old age group represented 0.4% of all new infections, while the infections in the age group of 15–19 year represented 1.2% of all new infections in the EU/European Economic Area (EEA) during 2015.

Although the majority of children have a mild disease and do not need urgent treatment, guidance published by the Hepatology Committee of the European Society for Paediatric Gastroenterology,

Hepatology and Nutrition (ESPGHAN) in 2018 recommend that all children with chronic HCV infection should be considered for treatment, in view of the fact that the rationale underlying the indication for the treatment of adults with chronic HCV infection is also valid for children.

Current approved treatment options for children less than 12 years old remains limited, as IFN-free DAA regimens are not yet approved for use in this paediatric subset. For adolescents, ledipasvir/sofosbuvir (LDV/SOF) and SOF + RBV have been recently approved for use, but they are not pan genotypic IFN-free and the recommended regimen for HCV GT2 and GT3 infection require co-administration with RBV.

Maviret, the fixed dose combination of NS3/4A protease inhibitor glecaprevir and NS5A inhibitor pibrentasvir (GLE/PIB), was first authorized in EU in 2017 for the treatment of chronic hepatitis C infection in adults. It has been approved for treatment-naïve and treatment-experienced (i.e. who failed prior therapy with peg-IFN+RBV+/-SOF or SOF+RBV) GT1 to GT6-infected patients with compensated liver disease (with or without cirrhosis).

This application for an extension of the indication to adolescents is supported by new clinical data from part 1 of Study M16-123 [An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Subjects with Genotypes 1 - 6 Chronic Hepatitis C Virus (HCV) Infection (DORA)] which evaluated the use of the adult co-formulated tablets in adolescents (12 to < 18 years of age).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

The environmental risk assessment has been updated in accordance with the EMA Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (2006) and EMA's Questions and Answers on the Guideline (2011) (Q&A) for the extended indication.

2.2.1. Ecotoxicity / environmental risk assessment

During the initial marketing authorisation application in adults, the applicant had already performed Phase I studies for glecaprevir and pibrentasvir that revealed $PEC_{SURFACEWATER}$ values in excess of 0.01 µg/L, and Phase II studies (Tier A and Tier B) were in progress. In addition, the log D value for pibrentasvir was greater than three, which required an evaluation for the bio-concentration potential for this compound. Updated environmental risk assessments for glecaprevir and pibrentasvir were submitted for assessment and agreed upon by CHMP during subsequent regulatory procedures.

In this extension of indication application, the applicant provided a justification in lieu of a full ERA for glecaprevir and pibrentasvir.

Firstly, it was explained that the calculated $PEC_{SURFACEWATER}$ values for these compounds will be the same as the value calculated for the initially approved indication as: 1) the recommended doses for glecaprevir and pibrentasvir for adolescents will be the same as the adult doses, and 2) the F_{pen} will not change as the default (conservative) F_{pen} was used in the original calculation.

Secondly, it was highlighted that the $PEC_{SURFACEWATER}$ values originally calculated for glecaprevir and pibrentasvir exceeded the 0.01 µg/L, therefore the required Tier B studies were completed; additionally, the log D value of pibrentasvir necessitated completion of a study to evaluate its potential for bioaccumulation. To date, no effects of these compounds on the environment have been detected. Nevertheless, the marketing authorisation holder mentioned that the ERA for pibrentasvir will be updated upon completion of all required studies.

Finally, it was also explained by the marketing authorisation holder that all studies that would be required for the new indication for glecaprevir and pibrentasvir have already been completed and that no additional studies would be required and no additional revisions to the ERAs for glecaprevir and pibrentasvir to reflect this additional indication would be needed or justified. CHMP agreed with the marketing authorisation holder position.

2.2.2. Conclusion on the non-clinical aspects

The CHMP considered the non-clinical data presented by the marketing authorisation holder as sufficient for the purpose of this extension of indication application.

2.3. Clinical aspects

2.3.1. 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

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy and safety	M16-123	5.3.5.2	PK, Efficacy and safety	Open-label	Part 1: Adult Formulation GLE/PIB tablet; 300 mg/120 mg QD; PO. Part 2: Pediatric Formulation GLE/PIB	14	≥ 3 to < 18 years of age, HCV GT1—GT6, treatment naïve or treatment experienced (previous IFN ± RBV, or SOF + RBV ± IFN), with or without compensated cirrhosis, with or without HIV-1 coinfection	8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, prior treatment experience, and geographical location in accordance with the use of GLE/PIB in adults

CSR = clinical study report; GLE = glecaprevir; GT = genotype; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus-1; IFN = interferon; IPK = intensive pharmacokinetic; PIB = pibrentasvir; PK = pharmacokinetic; PO = per oral; QD = once daily; RBV = ribavirin; SOF = sofosbuvir

Note: Subjects undergoing IPK analysis had to be HCV treatment naïve (eligible for 8 or 12 weeks of treatment), HIV-1 negative, and the HCV genotype must have been identified (i.e., Screening laboratory result indicating HCV genotype 1, 2, 3, 4, 5, or 6-infection).

2.3.2. Pharmacokinetics

The approved commercial formulation for adults was used in the HCV-infected adolescent subjects (12 to < 18 years of age) in Study M16-123. This formulation was used on the basis that adolescents are likely to have a similar weight distribution as observed in the adult program, are willing to swallow tablets, and therefore are suited to take the existing GLE/PIB 100 mg/40 mg co-formulated tablet.

There are no new biopharmaceutical data applicable to this submission.

Pharmacokinetics in Adolescents

In Part 1 of Study M16-123, PK analyses were conducted for 10 subjects who took at least 1 dose of GLE/PIB and had at least 1 PK sample taken.

Intensive plasma samples for quantitation of GLE and PIB concentrations following daily administration of GLE/PIB 300 mg/120 mg were collected at Study Week 2 Visit.

It was noted that 3 subjects were excluded from the PK analyses due to unusually low GLE and PIB concentrations at the Week 2 visit. The 3 subjects were 12–13 years old and weighed 58–65 kg. Their intensive GLE and PIB concentrations collected at the Week 2 visit were exceptionally low compared to those from the other 10 subjects. Such low exposures cannot be explained by the allometry. All 3 subjects were from the same study site and were the only subjects enrolled at that site. According to the MAH, one possible explanation of the discrepancy could be due to an improper sample collection procedure at the site, since the Week 2 samples from these subjects were collected using venous catheter, instead of venipuncture, as used in other study visits. Despite unusually low GLE and PIB concentrations, all 3 subjects achieved SVR_{12} without clinically significant AEs, and tolerated the full course of GLE/PIB.

A summary of PK parameters of GLE and PIB at the Week 2 visit, including the primary PK endpoint (steady-state area under the plasma concentration-time curve [AUC]) and secondary PK endpoints (maximum observed plasma concentration [C_{max}] and clearance [CL/F]) is presented below:

Table 1 Geometric Mean (Mean, CV%) PK Parameters of GLE and PIB (Week 2 IPK)

		GLE/PIB 300 mg/120 mg QD Adult Formulation Week 2 (N = 10)	
PK Parameters	**(Units)**	**GLE**	**PIB**
		Adolescent Subjects 12 to < 18 Years of Age	
C_{max}	(ng/mL)	994 (1260, 73)	174 (178, 22)
T_{max}[a]	(h)	4.0 (4.0 – 6.0)	4.0 (4.0 – 6.0)
AUC_{24}	(ng•h/mL)	4790 (5840, 73)	1380 (1420, 24)
C_{trough}	(ng/mL)	3.41 (4.26, 71)	14.0 (15.9, 44)
CL/F	(L/h)	62.6 (75.0, 65)	87.3 (90.7, 33)

AUC_{24} = area under the plasma concentration-time curve from time 0 to 24 hours; CL/F = clearance; C_{max} = maximum observed plasma concentration; C_{trough} = pre-dose trough plasma concentration; CV = coefficient of variation; IPK = intensive pharmacokinetic; PK = pharmacokinetic; QD = once daily; T_{max} = time to maximum observed plasma concentration.

a. Median (minimum through maximum).

Population pharmacokinetic analyses used data from four Phase 2 studies (Studies M13-595, M14-867, M14-868, and M15-410) and six Phase 3 studies (Studies M13-590, M15-464, M13-594, M13-583, M14-172, and M15-462) were conducted for GLE and PIB in HCV-infected adults.

The observed GLE and PIB geometric mean steady-state exposures (AUC) in the HCV-infected adolescent subjects (12 to < 18 years of age) were 4790 ng*h/mL and 1380 ng*h/mL, respectively, and were comparable to the reported geometric mean GLE and PIB AUC values (4800 ng*h/mL and 1430 ng*h/mL, respectively) in HCV-infected non-cirrhotic adults:

Table 2 Steady-State Pharmacokinetic Parameters of GLE and PIB in HCV-Infected Adolescent and Adult Subjects

Population	GLE/PIB 300 mg/120 mg QD Adult Formulation Week 2[a]	
	GLE AUC_{24} (ng•h/mL)	PIB AUC_{24} (ng•h/mL)
HCV-infected adolescents (12 to < 18 years of age)	4790 (73) [1580 – 16300]	1380 (24) [698 – 2090]
HCV-infected noncirrhotic adults	4800 (122) [123 – 297000]	1430 (57) [148 – 14200]

AUC_{24} = Area under the plasma concentration-time curve from time 0 to 24 hours at steady-state; CV = Coefficient of variation; HCV = hepatitis C virus; QD = once daily

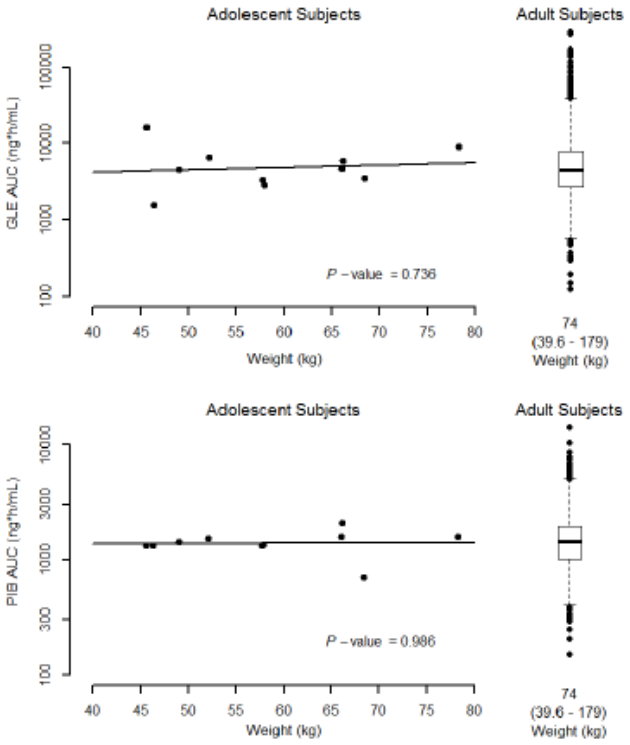
a. Geometric mean (CV%) [minimum through maximum].

The observed GLE and PIB exposure ranges in adolescents were within the exposure ranges of GLE and PIB that were shown to be well tolerated and efficacious in HCV-infected non-cirrhotic adults.

The medians of GLE and PIB C_{trough} values, defined as binned concentrations 22 to 26 hours post dosing in HCV-infected adolescent subjects from 12 to < 18 years of age were 5.06 ng/mL and 18.2 ng/mL, respectively, which were comparable to the reported median C_{trough} ranges observed in HCV-infected non-cirrhotic adult subjects in Phase 3 studies (6.11 - 7.53 ng/mL for GLE, 14.6 – 22.0 ng/mL for PIB).

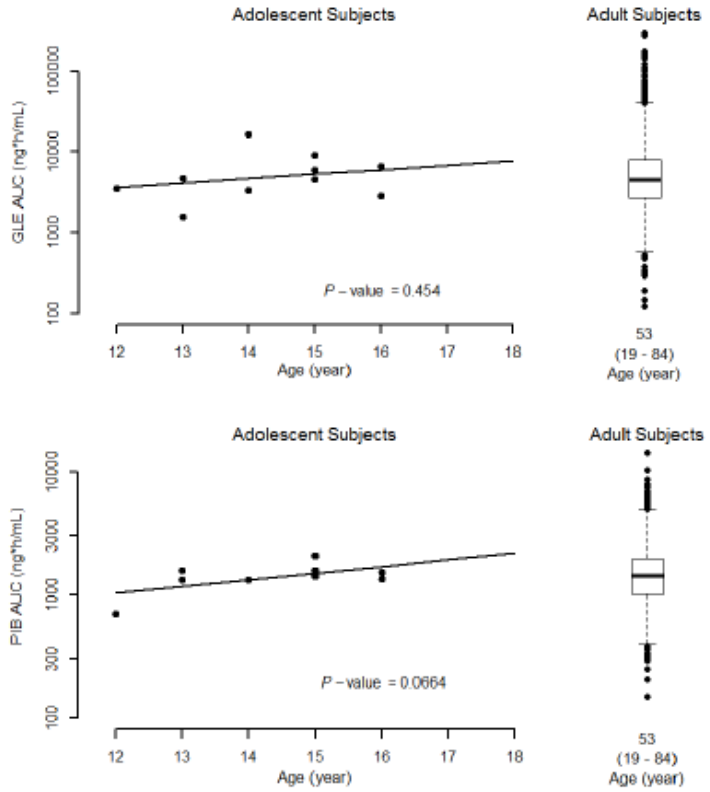
The relationships between steady-state GLE and PIB exposures (AUC_{24}) and subjects' age and weight were evaluated (graphically and by simple linear regression analysis) and no significant relationship between weight and exposures or between age and exposures was observed:

Figure 1 Relationships Between Steady-State AUC of GLE and PIB and Weight



Note: Median (range) weight was presented for adults (non-cirrhotics).

Figure 2 Relationships Between Steady State AUC of GLE and PIB and Age



Note: Median (range) age was presented for adults (non-cirrhotics).

The PK results support the use of the approved adult regimen of GLE/PIB 300 mg/120 mg QD in HCV-infected adolescent subjects (12 to < 18 years of age). No significant relationship between weight and exposures or between age and exposures was observed. The population included in this analysis covers the respective ages within the adolescent range (12 to 16 years of age and a median age of 14.5 years), with weights ranging from a minimum of 45.6 kg up to 78.3 kg and a mean of 58.7 kg, and demonstrated exposures comparable to those demonstrated in the adult HCV-infected subjects.

2.3.3. Pharmacodynamics

No new data were submitted in support of this application. This was considered acceptable by CHMP, since both glecaprevir and pibrentasvir have non-host targets and therefore no differences in antiviral activity are expected between adults and children.

2.3.4. PK/PD modelling

No new PK/PD data were submitted in support of this application. This was considered acceptable by CHMP.

2.3.5. Discussion on clinical pharmacology

CHMP noted that an expert meeting on paediatric development of CHC medicines was held at the EMA in December 2014. The main objective of the expert meeting was to improve and fasten the development of DAAs in children. Following recommendation from this EMA expert meeting, the MAH planned a paediatric study whose primary endpoint is PK exposure.

CHMP considered this approach reasonable, having in mind the high efficacy and favourable safety profile of DAA, including Maviret, in adults. It was noted that there was no obvious reason for expecting a

different efficacy/safety in children and that, provided that a comparable PK exposure was documented, extrapolation from data obtained in adults would be acceptable.

AUC_{24} at W2 has been estimated from 10 adolescent 12-18 y (all weighing $\geq$45kg) that received the adult dose and formulation. Exposure has been shown to be comparable to adults.

The adult tablet was used in adolescents (from 12 to less than 18 years of age) who are able to swallow the tablet. This has been judged agreeable by CHMP and had already been agreed upon with PDCO in the Paediatric Investigation Plan. Despite the fact that, based on simulation, the adolescent dose would be 250mg GLE/100mg PIB, it was considered agreeable to initiate the adolescent cohort with the adult dose (300/120mg) to enable earlier initiation since it was not expected the resulting 20% higher exposure would increase significantly the safety risk for this population.

CHMP noted that no weight criterion seemed to have been included in the study protocol, but that all the children included in the intensive PK cohort finally weighted more than 45kg. During the assessment, at CHMP request the marketing authorisation holder discussed the extent to which adolescents weighing less than 45 kg could safely receive Maviret, in particular since the expected weight range in 12 year old children would be 30-62 kg (5th–95th percentile). It was clarified that while no subjects in the IPK cohort weighed less than 45 kg, in the full Part 1 adolescent cohort a broader range of weights were included. The population PK analysis (of Part 1 All Adolescents in Study M16-123) included subjects with body weight ranging from 32.0 to 108.9 kg and age ranging from 12 to 17 years, which adequately covered the expected weight range. The evaluation of weight and age on the PK of GLE and PIB showed that neither body weight nor age was a significant covariate for the exposures of GLE and PIB and that all 47 adolescent subjects in the full cohort in Part 1 achieved sustained virologic response 12 weeks post treatment (SVR_{12}) and tolerated Maviret well with no reports of serious adverse events (SAEs) or adverse events (AEs) leading to interruption of or discontinuation from treatment. Estimated GLE and PIB exposures in the subjects with lower body weights were comparable to those in the subjects with higher body weight. Results from the population PK analysis also indicated that the steady-state GLE and PIB exposures of all of these subjects fell within the predicted margins of safety established by the larger adult programme. The relationships between model-predicted steady-state GLE and PIB exposures (area under the plasma concentration-time curve from time zero to 24 hours post-dose [AUC_{24}]) in the full cohort of Part 1 and subjects' age and weight were evaluated using linear regression, and no statistically significant (P-value > 0.05) or clinically meaningful relationships were observed between weight and GLE/PIB exposures or between age and GLE/PIB exposures. Since there was no relationship between body weight and exposures and the weights of the adolescent subjects dosed in M16-123 cover the lowest percentiles on growth charts, no weight restriction was proposed to be included in the Summary of Product Characteristics (SmPC), as subjects weighing less than 45 kg were successfully treated with Maviret (GLE/PIB, 300 mg/120 mg). CHMP agreed to the MAH proposal.

CHMP considered the exclusion of 3 patients from the PK analysis that was now based on 13 patients only as unfortunate, but acknowledged that the unusual concentrations reported for the 3 outliers (all included in the same site centre) was likely due to a collection issue rather than a true PK concern. Indeed, the values of the PK parameter spoke in favour of an issue linked to data collection and all 3 patients achieved SVR. Nevertheless, at CHMP request, the MAH explained that full investigations for the reason behind unusual concentrations reported in the 3 outliers from the same site centre had been explored. Use of IV line was the likely cause for the lower exposures observed and that it might have occurred due to an inadequate procedure around the IV collection. Reassuringly, the sparse PK samples for the 3 patients (identified as outliers in intensive PK study) were comparable to those of other study patients. As a measure to ensure quality of the study process, the study centre had been excluded from enrolling patients in the IPK portion of part 2 of study M16-123. CHMP agreed to the presented approach and considered it was satisfactory.

At CHMP request, during the assessment, the MAH also provided demographic data for the 3 patients with low GLE/PIB concentrations in the intensive PK analysis. It was noted that they were of different races and sexes (1 Black/African American [male], 2 White [1 male, 1 female]) and that all 3 subjects were either 12 or 13 years old. Moreover, no significant relationship between weight and exposure or age and exposure was identified in PPK analysis. Since only the IPK sampling and not the sparse PK sampling for the 3 patients showed low GLE/PIB concentration, CHMP agreed that demographic data did not account for the unusual concentrations observed and that the inadequate removal of solution in the IV line before collecting blood for the IPK sampling was the likely explanation for the 3 outliers.

CHMP also noted that PK exposure in adolescents was estimated based on intensive PK analysis on 10 adolescents aged 12-16 years of age (median: 14.5 years) weighting 45-78 kg (mean 58.7 kg). A comparable exposure between adolescents and adults is documented based on this analysis. It was considered reasonably reassuring on the similarity between the PK in adults and adolescents by the fact that no major difference has been detected on the PK data issued from such limited sample size.

During the assessment, the MAH has also submitted data from 34 additional subjects from the non-IPK analysis (see clinical section of the AR).

CHMP agreed that efficacy can be extrapolated from adults based on similar exposure.

CHMP also noted that drug-drug interactions have not been discussed by the MAH in this application, but that this was not expected to be a major concern in children. As for adults, Maviret is not the medicine of choice for HIV/HCV co-infected patients receiving boosted PI, and alternative DAA regimen are authorized in children for use in this situation.

2.3.6. Conclusions on clinical pharmacology

The CHMP considered the data presented by the marketing authorisation holder as sufficient for the purpose of this extension of indication application.

2.4. Clinical efficacy

2.4.1. Main study

Title of Study: M16-123 (DORA)

Methods

This is a Phase 2/3, open-label, multicentre study to evaluate the PK, efficacy, and safety of GLE/PIB in chronic HCV GT1 –GT6 infected paediatric subjects. The study has been designed to satisfy the different EU Paediatric Investigation Plan and US FDA iPSP requirements, the main difference of which was the inclusion of an expanded population of subjects to fulfil the iPSP requirements. Indeed, the paediatric study was recommended to include an expanded number of subjects for safety (a total of approximately 100).

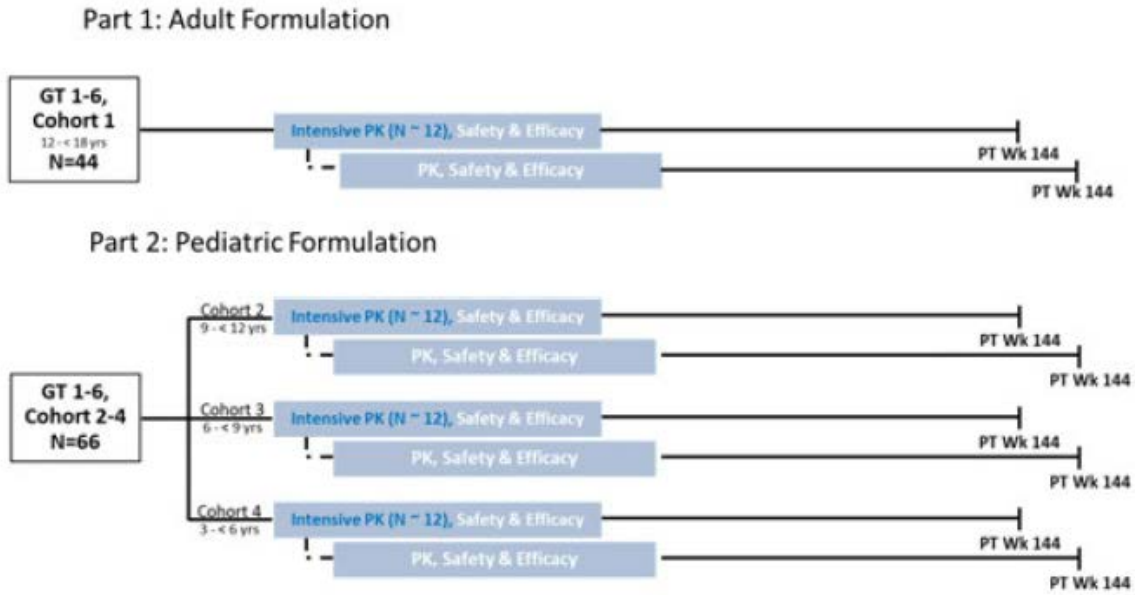
The study is divided into 2 parts:

Part 1 of the study allowed for enrolment of approximately 44 HCV GT1 - GT6 infected adolescent subjects into the 12 to < 18 years old age group who were willing to swallow the adult formulation of GLE/PIB (Cohort 1).

Part 2 of the study allows for enrolment of approximately 66 HCV GT1 - GT6 infected paediatric subjects divided into the 9 to < 12 (Cohort 2), 6 to < 9 (Cohort 3), and 3 to < 6 (Cohort 4) years old age groups who will receive the paediatric formulation of GLE/PIB.

In each cohort, subjects will be enrolled first into the IPK portion, followed by the non-IPK safety/efficacy portion.

Figure 3 Study M16-123 Schematic



Each cohort was expected to enrol approximately 12 HCV-infected paediatric subjects in the IPK portions to adequately characterize the PK of a particular age group for dose confirmation (had to be HCV TN and HIV-negative, and the HCV genotype must have been identified for these subjects), and the remainder of subjects will be enrolled for the evaluation of safety and efficacy of each age group until the total paediatric study population reaches approximately 110 subjects (TN or TE [prior IFN, RBV, or SOF exposure], with or without HIV-1 coinfection, and could include subjects with mixed or indeterminate HCV genotype).

An interim analysis for this cohort (12 to < 18 years old) occurred once all subjects undergoing IPK analysis in Part 1 of the study completed the Post-Treatment (PT) Week 12 or prematurely discontinued from the study.

The data from these analyses were initially provided in to support the addition of the adolescent population (12 to < 18 years old) to the adult tablet indication.

Of note, in the EU PIP it was agreed that a minimum number of subjects are to be enrolled in each IPK age cohort, in order to expedite paediatric development and accelerate access to patients, also in accordance with the EMA Report of the paediatric hepatitis C therapy expert meeting (EMA/87232/2015).

Data from 34 additional adolescent subjects, which became available in Q3 2018, were also submitted during the procedure.

Study participants

Main Inclusion Criteria:

- Male or female (pre-menarche and not sexually active, permanently surgical sterile OR practicing at least 1 protocol specified method of birth control), subjects ≥ 3 to < 18 years of age at time of enrolment.

- Positive anti-HCV antibody and plasma HCV RNA viral load ≥1000 IU/mL at Screening Visit.

- Chronic HCV infection defined as being positive for anti-HCV antibody or HCV RNA at least 6 months before Screening.

- Subject co-infected with HIV-1 must have been on a stable antiretroviral therapy (ART) for at least 8 weeks prior to screening, consisting of the qualifying ART regimens.

- Subject must have a weight consistent with the recommended weight band for their age at the time of Screening. Subjects that fall out of the weight band for their age at the time of Screening, could be screened into the safety and efficacy parts of the study upon therapeutic area medical director (TA MD) approval.

- For subjects in Part 1: Willingness to swallow tablets.

Main Exclusion Criteria:

- Female subject who was pregnant, breastfeeding, or considering becoming pregnant during the study, or for approximately 30 days after the last dose of study drug.

- Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could have precluded adherence to the protocol in the opinion of the investigator.

- Any cause of liver disease other than chronic HCV infection.

- Current hepatitis B virus (HBV) infection on Screening tests; defined as:

  - A positive test result for hepatitis B surface antigen (HBsAg), or
  - HBV DNA > lower limit of quantitation (LLOQ) in subjects with isolated positive Anti-HBc (i.e., negative HBsAg and Anti-HBs).

- Any current or past clinical evidence of Child-Pugh B or C classification (Child-Pugh Score ≥ 7) or clinical history of liver decompensation such as ascites (noted on physical examination), variceal bleeding, or hepatic encephalopathy.

- Confirmed presence of hepatocellular carcinoma (HCC).

- Consideration by the investigator, for any reason, that the subject was an unsuitable candidate to receive GLE/PIB.

- History of severe, life-threatening, or other significant sensitivity to any excipients of the study drug.

Treatments

Part 1 Adult Formulation:

The study drug (GLE/PIB) was dispensed as film coated co-formulated 100 mg/40 mg tablets. Subjects were instructed to take study drug orally as 3 tablets QD (corresponding to GLE/PIB 300 mg/120 mg) to be swallowed whole.

All subjects were assigned to receive 8 weeks of treatment in the IPK part.

Objectives

The primary objectives of this study are:

- to assess the steady state area under the concentration-time curve (AUC), and to assess the pharmacokinetics (PK) of GLE/PIB in paediatric subjects following multiple dosing by age group;

- to evaluate the safety and tolerability of GLE/PIB by age group, cirrhosis status and across all subjects.

The secondary objectives of this study are to further assess the efficacy of GLE/PIB by assessing:

- Maximum observed plasma concentration (C_{max}) and clearance of GLE and PIB;
- The percentage of subjects with sustained virologic response for 12 weeks post-treatment (SVR_{12}) in HCV genotype (GT)1 - GT6 infected paediatric subjects summarized for each age group and overall (primary objective for the US regulatory agency only);
- The percentage of subjects with on-treatment HCV virologic failure (i.e., breakthrough or failure to suppress at the end of treatment) summarized for each age group and overall;
- The percentage of subjects with post-treatment HCV relapse summarized for each age group and overall;
- The percentage of subjects with new HCV infection (or reinfection) summarized for each age group and overall;
- Assess PK and emergence/persistence of viral variants in subjects with available samples;
- Assessment of palatability/acceptability of paediatric formulation.

Outcomes/endpoints

The primary PK endpoints were:

- Steady state AUC values for GLE and PIB estimated by non-compartmental analysis or population PK analysis including AUC at Week 2 in subjects with IPK samples and AUC in all subjects with or without IPK samples.

The secondary endpoints in Part 1 and Part 2 were:

- C_{max} and clearance of GLE and PIB at Week 2;
- The percentage of subjects with SVR_{12} by age group and overall (*primary efficacy variable for US regulatory agency*);
- The percentage of subjects with on-treatment virologic failure (i.e., breakthrough or failure to suppress at end of treatment) by age group and overall;
- The percentage of subjects with post-treatment relapse by age group and overall;
- The percentage of subjects with new HCV infection (i.e., reinfection) at any time up to the last study visit by age group and overall;
- Assessment of palatability/acceptability of the paediatric formulation.

Sample size

Planned: Approximately 110 subjects overall including approximately 48 subjects in the IPK portion of the study (12 subjects for each age group).

Analysed: A total of 14 subjects were enrolled in the Part 1 IPK portion of the study (12 to < 18 years old age group) and 13 subjects received at least 1 dose of the study drug.

Results

Recruitment

A total of 8 sites in the United States (US; and its territory, Puerto Rico) enrolled subjects in the intensive pharmacokinetic (IPK) portion of Part 1 of the study.

A total of 14 subjects were enrolled and 13 subjects received at least 1 dose of study drug. No subject prematurely discontinued study drug.

Table 3 Disposition of Subjects (All Enrolled Subjects)

	Number of Subjects GLE/PIB
Enrolled	14
Treated	13
Study drug disposition	
Completed study drug	13
Discontinued study drug	0
Study disposition	
Completed study	0
Discontinued study	1[a]
Ongoing[b]	13

IPK = intensive pharmacokinetics

a. Subject [redacted] was enrolled but was never dosed.

b. Ongoing refers to subjects who had not completed or prematurely discontinued the study at the time of the Part 1 IPK primary analysis.

Note: Subjects who were randomized but did not receive study drug are included in the analysis of discontinued study. The analysis of completed or discontinued study drug only includes subjects who received study drug.

Conduct of the study

Protocol amendments

The original protocol (dated 15 December 2016) was amended 4 times (2 global and 2 country-specific). Thirteen subjects were enrolled under the original protocol and 1 subject was enrolled under Global Protocol Amendment 1.

The protocol changes described in the amendments did not affect the interpretation of the results in this study.

Amendment Number/Date	Description of Key Changes
Amendment 1 (global)/ 10 July 2017	• Included specific changes for subjects in Japan to account for the participation of subjects in Japan. • Updated language regarding the SVR_{12} efficacy analysis to clarify the criteria that will establish when the Wilson's score method will be used as opposed to the normal approximation to the binomial distribution in determination of the CI as per FDA Biometric comment.
Amendment 1.01 (US only)/25 July 2017	• Updated primary efficacy endpoint per FDA request to move the SVR_{12} endpoint as another primary endpoint.
Amendment 2 (global)/ 09 March 2018	• Provided dosing details about the GLE/PIB pediatric formulation to be used in Part 2 for subjects 3 to 11 years old. • Updated the proposed doses for 3 to 11 year old (proposed dosing for each age group and weight range were added based on the current knowledge of the GLE and PIB exposures). • Included retreatment study information clarifying subjects in Part 1 who met the virologic failure criteria in the PT period have the option to enroll into Study M15-942 for retreatment of their virologic failure. • Included information on Study M17-142 results for pediatric formulation to support the proposed pediatric formulation dosing. • Updated the recommendations for use of pravastatin or rosuvastatin dose to clarify the timing of statin management. • Updated the statistical analysis section to clarify the number of planned analyses and to align the description of endpoints with the approved PIP.
Amendment 2.01 (US and PR only)/16 March 2018	• All changes made under the Global Amendment 2.

Protocol deviations

There were no ICH defined protocol deviations reported. In addition, deviations from the protocol were assessed for impact on analyses and data integrity or subject's safety. None of the deviations was considered to have affected the study outcome or interpretation of the study results or conclusions.

No significant PK sampling time deviations occurred during the conduct of this study.

Baseline data

The MAH initially submitted data from the 13 patients included in the IPK analysis. Additional data from 34 additional subjects from the non-IPK analysis were submitted during the procedure.

Demographic Characteristics

Table 4 Demographic Characteristics (ITT Population)

Variable		GLE/PIB Cohort 1 (N = 13) n	(%)
Sex	Female	7	(53.8)
	Male	6	(46.2)
Race	White	10	(76.9)
	Black or African American	3	(23.1)
	Asian	0	
	American Indian or Alaska Native	0	
	Native Hawaiian or other Pacific Islander	0	
	Multiple	0	
Black race	Black	3	(23.1)
	Non-black	10	(76.9)
Ethnicity	Hispanic or Latino	2	(15.4)
	None of the above	11	(84.6)
Age (years)	≥ 12 to < 18	13	(100.0)
	≥ 9 to < 12	0	
	≥ 6 to < 9	0	
	≥ 3 to < 6	0	
Weight (kg)	≥ 12 to < 20	0	
	≥ 20 to < 30	0	
	≥ 30 to < 45	0	
	≥ 45	13	(100.0)
Height z score	< –1	1	(7.7)
	–1 to 1	7	(53.8)
	> 1	5	(38.5)
BMI z score	< –1	1	(7.7)
	–1 to 1	6	(46.2)
	> 1	6	(46.2)
Country	United States	13	(100.0)
Geographic region	North America	13	(100.0)

Baseline Disease Characteristics

Table 5 Baseline Disease Characteristics (ITT Population)

Variable		GLE/PIB Cohort 1 (N = 13) n	(%)
HCV genotype[a]	1	11	(84.6)
	2	1	(7.7)
	3	1	(7.7)
	4	0	
	5	0	
	6	0	
HCV subtype[a]	1a	7	(53.8)
	1b	4	(30.8)
	2a/2c	1[b]	(7.7)
	3a	1	(7.7)
Cirrhosis status	Cirrhotic	0	
	Non-cirrhotic	13	(100.0)
Prior HCV treatment history	Naïve	13	(100.0)
	Experienced	0	
	Other	0	
Baseline HCV RNA level (IU/mL)	< 1,000,000	8	(61.5)
	≥ 1,000,000 to < 2,000,000	2	(15.4)
	≥ 2,000,000	3	(23.1)
Baseline fibrosis stage	F0 - F1	13	(100.0)
	F2	0	
	F3	0	
	F4	0	
Baseline platelet count ($\times 10^9$/L)	< 90	0	
	≥ 90	13	(100.0)
Baseline albumin (g/L)	< 35	0	
	≥ 35	13	(100.0)
Baseline eGFR (mL/min/1.73 m^2)	< 30	0	
	≥ 30 to < 60	0	
	≥ 60 to < 90	0	
	≥ 90	13	(100.0)
History of bleeding disorders	Yes	0	
	No	13	(100.0)
History of depression or bipolar disorder	Yes	1	(7.7)
	No	12	(92.3)
Concomitant use of PPIs	Yes	0	
	No	13	(100.0)
HCV/HIV coinfected subjects	Yes	0	
	No	13	(100.0)

eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ITT = intention-to-treat; PPI = proton pump inhibitor; RNA = ribonucleic acid

a. HCV genotype and subtype as determined by the central laboratory.

b. The HCV genotype 2a/2c subject was determined to be HCV genotype 2q by phylogenetic analysis.

CHMP noted that all patients were from US. The study included 7 female and 6 male, most of whom were white (n=10), with the 3 remaining patients being black. All 13 had weight >45kg.

In accordance with the inclusion criterion for IPK part, all 13 patients were TN, non HIV-co-infected without cirrhosis. As a matter of fact, all 13 had F0-F1 fibrosis stage. With the exception of 1 GT3 and 1 GT2 patients, all were infected by HCV GT1 (There were 7 GT1a and 4 GT1b).

Even though CHMP acknowledged that efficacy data in other than GT1 TN non cirrhotic adolescent could likely be extrapolated from adult efficacy studies, the MAH was requested to clarify whether efficacy data was available from the full adolescent cohort to document efficacy in non GT1 and cirrhotic patients.

In response to CHMP request, apart from the already submitted data of the 13 patients included in the IPK analysis, the MAH submitted data of 34 additional patients. The final study population was now of 47 adolescents of whom 4 (8.5%) were infected with HCV GT3, 11 (23.4%) were treatment-experienced (all 11 received previous IFN-based regimen) and 2 (4.3%) were HIV/HCV co-infected. No patients had cirrhosis. As a matter of fact, almost all (n=45) were F0-F1, 1 had baseline fibrosis stage F2 and 1 had baseline fibrosis stage F3.

Table 6 Summary of Demographic Characteristics and Intrinsic Factors (M16-123 Part 1 All Adolescents)

Characteristic		All Subjects (N = 47)
Sex	Female, n (%)	26 (55.3)
	Male, n (%)	21 (44.7)
Race	White, n (%)	35 (74.5)
	Black or African American, n (%)	4 (8.5)
	Asian, n (%)	6 (12.8)
	Multiple, n (%)	2 (4.3)
Age (years)	Median (Min-Max)	14 (12 – 17)
Birth Year	2000, n (%)	5 (10.6)
	2001, n (%)	8 (17.0)
	2002, n (%)	9 (19.1)
	2003, n (%)	9 (19.1)
	2004, n (%)	10 (21.3)
	2005, n (%)	6 (12.8)
Body Weight (kg)	Mean (SD)	59.22 (14.08)
	Median (Min – Max)	57.70 (32.00 – 108.90)
	≥30 to <45 kg, n (%)	3 (6.4)
	≥ 45 kg, n (%)	44 (93.6)
Body Mass Index (kg/m^2)	Mean (SD)	22.48 (4.94)
	Median (Min – Max)	21.65 (16.29 – 42.24)
Body Surface Area (m^2)	Mean (SD)	1.6 (0.20)
	Median (Min – Max)	1.62 (1.1 – 2.3)
Country	Belgium, n (%)	3 (6.4)
	Canada, n (%)	4 (8.5)
	Germany, n (%)	4 (8.5)
	Japan, n (%)	4 (8.5)
	Russian Federation, n (%)	2 (4.3)
	Spain, n (%)	7 (14.9)
	United Kingdom, n (%)	5 (10.6)
	United States, n (%)	18 (38.3)

Table 7 Summary of Demographic Characteristics and Intrinsic Factors (M16-123 Part 1 All Adolescents) (continued)

Characteristic		All Subjects (N = 47)
Genotype	1, n (%) 2, n (%) 3, n (%) 4, n (%) 5, n (%) 6, n (%)	37 (78.7) 3 (6.4) 4 (8.5) 3 (6.4) 0 (0.0) 0 (0.0)
Treatment Experience	Naive, n (%) Experienced, n (%)	36 (76.6) 11 (23.4)
HIV Co-infection	No HIV-infection, n (%) HIV co-infection, n (%)	45 (95.7) 2 (4.3)
Cirrhosis	Without cirrhosis, n (%)	47 (100)

HIV = human immunodeficiency virus; SD = standard deviation; Min = minimum; Max = maximum.

Three GT3-infected, treatment-experienced and non-cirrhotic subjects were assigned to the 16 week treatment duration; the remaining 44 non-cirrhotic subjects were assigned to the 8 week treatment duration per protocol (and in accordance with SmPC recommendation).

Outcomes and estimation

Based on the initially submitted data, it was noted that sustained virologic response 12 weeks post-treatment was achieved by 100% (13/13) of subjects in the ITT population. No subjects experienced on-treatment virologic failure (breakthrough or end-of-treatment failure), relapse, or had a new HCV infection (reinfection) at any time up to the last study visit.

Table 8 Primary Efficacy endpoint: Virological Response at Post-Treatment Week 12 (SVR_{12}) (ITT Population)

Assessment	GLE/PIB (N = 13)
SVR_{12}, n/N (%)	13/13 (100)
95% CI[a]	(77.2, 100.0)

CI = confidence interval; HCV = hepatitis C virus; ITT = intention-to-treat; RNA = ribonucleic acid; SVR = sustained virologic response; SVR_{12} = sustained virologic response 12 weeks post-treatment

a. Confidence interval calculated using the Wilson's score method.

Note: Backward imputation, where applicable, was used to impute missing data. After applying backward imputation, if there was still no value in the window but there was an HCV RNA from a local laboratory present, then it was to be imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.

Additional efficacy endpoints included the percentage of subjects with HCV RNA < lower limit of quantitation (LLOQ) at each post-baseline visit in the Treatment Period. By Week 4, 92.3% (12/13) of subjects achieved HCV RNA < LLOQ.

After submission of the additional data by the MAH, CHMP noted that all 47 adolescents had achieved SVR_{12}.

Table 9 Virologic Response at Post Treatment Week 12 (SVR_{12}) (ITT Population)

Assessment	GLE/PIB (N = 47)
SVR_{12}, n/N (%)	47/47 (100)
95% CI[a]	(92.4, 100.0)

CI = confidence interval; GLE = glecaprevir; HCV = hepatitis C virus; ITT = intention-to-treat; PIB = pibrentasvir; RNA = ribonucleic acid; SVR = sustained virologic response; SVR_{12} = sustained virologic response 12 weeks post-treatment.

a. Confidence interval calculated using the Wilson's score method.

Note: Backward imputation, where applicable, was used to impute missing data. After applying backward imputation, if there was still no value in the window but there was an HCV RNA from a local laboratory present, then it was to be imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.

Even though no data are available in patients with advanced fibrosis (as one can expect from a paediatric population), those additional data provide further evidence of the efficacy of Maviret in more difficult to treat patients such as TE and GT3 patients.

Efficacy analysis by demographic or baseline characteristic, including baseline HCV RNA level, HCV genotype, or baseline polymorphisms in NS3 and/or NS5A was not possible given the lack of virological failure in this part.

Ancillary analyses

Virology

Table 10 Number and Percentage of Subjects with Baseline Polymorphisms in NS3 and/or NS5A at Signature Amino Acid Positions at 15% Detection Threshold (ITT Population)

HCV Subtype[a]	Target	Baseline Polymorphisms[b]	% (n/N)[c]
GT1a	NS3	Any[d]	85.7 (6/7)
		Q80K	71.4 (5/7)
		S122G/T	28.6 (2/7)
	NS5A	Any[d]	16.7 (1/6)
		L31M	16.7 (1/6)
GT1b	NS3	Any[d]	25.0 (1/4)
		V170I	25.0 (1/4)
	NS5A	Any[d]	100 (4/4)
		R30Q	25.0 (1/4)
		Q54H	75.0 (3/4)
		P58T/S	25.0 (1/4)
GT2q	NS3	Any[d]	-
	NS5A	Any[d]	(0/1)
GT3a	NS3	Any[d]	(0/1)
	NS5A	Any[d]	100 (1/1)
		Y93H	100 (1/1)

GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat; NS3 = nonstructural viral protein 3; NS3/4A = nonstructural viral protein 3/4A; NS5A = nonstructural viral protein 5A

a. Subtype determined by phylogenetic analysis of NS3/4A and/or NS5A.

b. The following are considered signature amino acid positions in GT1a/1b: 36, 43 (GT1a only), 54, 55, 56, 80, 107, 122, 132 (GT1a only), 155, 156, 158, 168, 170, and 175 (GT1b only) in NS3 and 24, 28, 29, 30, 31, 32, 54 (GT1b only), 58, 62, 92, and 93 in NS5A; the following are considered signature amino acid positions in GT2 – 6: 36, 43, 54, 55, 56, 80, 155, 156, 166 (GT3 only), and 168 in NS3 and 24, 28, 29, 30, 31, 32, 58, 92, and 93 in NS5A.

c. n = number of subjects with polymorphisms, N = total number of subjects sequenced.

d. 'Any' indicates total number of subjects with any polymorphism at signature amino acid positions within the indicated target. Total number of available sequences may vary by target.

Baseline polymorphisms in NS3 were not detected at amino acid positions 155, 156, or 168 in any of the GT1 – GT3-infected subjects. The prevalence of NS3 Q80K in GT1a-infected subjects was high (71.4%, 5/7). Baseline polymorphisms at amino acid positions 24, 28, 30, 31, 58, 92, or 93 in NS5A were detected in 33.3% (4/12) of the GT1 – GT3-infected subjects; Y93H in NS5A was detected in the single GT3a-infected subject. CHMP noted that baseline polymorphisms had no impact on treatment outcome in this interim analysis. Of note, the GT3 patients included in the IPK had Y93H at baseline and achieved SVR.

2.4.2. Discussion on clinical efficacy

Study M16-123 is a single arm open label study conducted in children from 3 to <18 years of age. CHMP considered that the overall design was acceptable. As for adults, a comparator arm would have entailed feasibility issues and was not mandatory, given the high expected SVR rate obtained with new DAA regimens.

Initially, the interim data including the PK, efficacy and safety from the 13 adolescents dosed with the adult GLE/PIB tablet in the intensive PK cohort were presented. During the procedure, data from 34 additional subjects from the non-IPK analysis were also submitted and assessed. Among these 47 subjects, there were 4 subjects (8.5%) with HCV genotype 3, 11 treatment experienced subjects (23.4%), 2 HIV/HCV co-infected subjects (4.3%), and no cirrhotic subjects.

All 47 adolescent subjects (100% [CI: 92.4, 100.0]) achieved SVR_{12}.

Along with the PK data showing comparable exposure between adolescents and adults dosed with the GLE/PIB 300/120mg regimen, the MAH requests the extension of the approved adult regimen in adolescent from 12 to <18 years of age, whatever the genotypes, TN or TE (DAA-naïve) status, presence or not of cirrhosis or HIV co-infection.

CHMP agreed that efficacy can be extrapolated from adults based on comparable exposure, but noted during the procedure that the presented data in adolescents were available from only 13 patients at this stage, all being TN non cirrhotic patients. There is no obvious reason that efficacy/safety would differ between children and adults as long as exposure is similar. Therefore the MAH was requested to provide the additional efficacy data from the full adolescent cohort. This was done and the additional data presented, despite no data were available in patients with advanced fibrosis (as could be expected from this paediatric patients), were supportive of the initial conclusion and provided further evidence on the efficacy of Maviret in more difficult to treat patients such as TE and GT3 patients.

2.4.3. Conclusions on the clinical efficacy

The CHMP agreed that this extension of indication application for Maviret is approvable from an efficacy perspective.

2.5. Clinical safety

Patient exposure

The safety population initially comprised thirteen subjects (n=13) whom all were being treated for 8 weeks.

As above underlined, there were 7 female and 6 male, and all were originated from North America (10 Non-Black, 3 Black). All patients weighed 45kg or more.

All subjects were non cirrhotic, F0-F1 fibrosis stage, treatment-naïve, with no HCV/HIV coinfection and the majority of subjects were GT1-infected.

One adolescent had a history of depression or bipolar disorder.

During the procedure, the marketing authorisation holder provided the data from the full adolescent cohort, which comprised the 13 patients from the intensive PK analysis and 34 additional patients.

The final study population consisted of 47 adolescents of whom 4 (8.5%) were infected with HCV GT3, 11 (23.4%) were treatment-experienced (all 11 received previous IFN-based regimen) and 2 (4.3%) were HIV/HCV co-infected. No patients had cirrhosis. As a matter of fact, almost all (n=45) were F0-F1, 1 had baseline fibrosis stage F2 and 1 had baseline fibrosis stage F3.

Three GT3-infected, treatment-experienced and non-cirrhotic subjects were assigned to the 16 week treatment duration; the remaining 44 non-cirrhotic subjects were assigned to the 8 week treatment duration per protocol (and in accordance with SmPC recommendation).

Summary of Resistance Analyses

Of the 47 subjects dosed in Cohort 1, the number of subjects infected with each of the following HCV subtypes by phylogenetic analysis of NS3/4A and/or NS5A sequences was: 24 GT1a (51.1%), 13 GT1b (27.7%), 1 GT2a (2.1%), 1 GT2b (2.1%), 1 GT2q (2.1%), 4 GT3a (8.5%), 2 GT4d (4.3%), and 1 GT4f (2.1%). Baseline polymorphisms in NS3 were not detected at amino acid positions 155, 156, or 168 in any of the GT1 – GT4- infected subjects. The prevalence of NS3 Q80K in GT1a-infected subjects was high

(54.2%, 13/24). Baseline polymorphisms at amino acid positions 24, 28, 30, 31, 58, 92, or 93 in NS5A were detected in 23.9% (11/46) of the GT1 – GT4-infected subjects; A30K and Y93H in NS5A were each detected in 25.0% (1/4) of the GT3a-infected subjects. All subjects in the mITT-VF population achieved SVR_{12}, indicating no evidence that baseline polymorphisms had an impact on treatment outcome.

Adverse events

Table 11 Overview of adverse events in the IPK population

	GLE/PIB Cohort 1 (N = 13)	
	n	(%)
Subjects with:		
Any AE	10	(76.9)
Any AE with a reasonable possibility of being related to DAAs (GLE/PIB)[a]	2	(15.4)
Any serious AE	0	
Any AE with a Grade 3 or higher	1	(7.7)
Any AE leading to discontinuation of study drug	0	
Any DAA related AE with a Grade 3 or higher	0	
Any AE leading to interruption of study drug	0	
Any fatal AE	0	
Deaths[b]	0	

AE = adverse event; DAA = direct-acting antiviral agent

a. As assessed by investigator.

b. Includes nontreatment-emergent deaths.

Table 12 Most frequently reported (≥ 3 subjects) AEs in the IPK population

	GLE/PIB Cohort 1 (N = 13)		GLE/PIB Cohort 1 (N = 13)	
	All Adverse Events		Study Drug-Related Adverse Events[a]	
MedDRA v20.1 Preferred Term	n	(%)	n	(%)
Any adverse event	10	(76.9)	2	(15.4)
Oropharyngeal pain	3	(23.1)	--	--
Upper respiratory tract infection	3	(23.1)	--	--
Nausea	2	(15.4)	--	--
Vomiting	2	(15.4)	--	--

MedDRA = Medical Dictionary for Regulatory Activities

a. According to investigator assessment

The majority of subjects who experienced AEs had AEs with a maximum severity of Grade 1 (mild; 60%, 6/10).

One subject with a history of depression experienced a Grade 3 AE of depression and suicidal ideation during the study (at Day 14, reported as intermittent); the event was assessed as not study drug-related.

Two subjects experienced study drug-related AEs that were Grade 1 in severity; one subject (the same patient who reported increased depression) experienced chills and decreased appetite at Day 1 and 4 respectively that were considered as related to study drug by the investigator; the other subject experienced somnolence and decreased activity at day 1 and lasted for 4 days, these events were considered related to study drug by the investigator. The drug was continued unchanged.

Based on the additional data submitted, the analysis of the full dataset showed that adverse events were mostly mild in severity and unrelated to study drug, with the most common AEs (occurring in ≥ 10% subjects) being nasopharyngitis, upper respiratory tract infection, headache, fatigue, oropharyngeal pain, and pyrexia. Most of these events were assessed as not treatment related and likely due to expected seasonal variations of AEs/medical conditions common in the paediatric population. The most frequently reported adverse drug reaction (ADR) (reported in ≥ 5% overall) was fatigue (6.4% of subjects). Overall,

the fixed-dose combination of GLE/PIB 300 mg/120 mg QD was well tolerated and demonstrated a favourable safety profile in adolescent subjects similar to the safety profile in adults. No new safety signals were identified.

Table 13 Summary of Adverse Events (Safety Population)

	GLE/PIB Cohort 1 (N = 47)			
	All Adverse Events		Study Drug-Related Adverse Events[a]	
	n	(%)	n	(%)
Subjects with:				
Any AE	41	(87.2)	9	(19.1)
Any AE with a Grade 3 or higher	1	(2.1)	0	--
Any SAE	0	--	0	--
Any AE leading to discontinuation of study drug	0	--	0	--
Any AE leading to interruption of study drug	0	--	0	--
Any fatal AE	0	--	0	--
Deaths[b]	0	--	0	--
Common AEs (MedDRA v20.1 preferred term, ≥ 5% subjects)				
Nasopharyngitis	12	(25.5)	0	--
Upper respiratory tract infection	9	(19.1)	0	--
Headache	8	(17.0)	0	--
Fatigue	5	(10.6)	3	(6.4)
Oropharyngeal pain	5	(10.6)	0	--
Pyrexia	5	(10.6)	0	--
Nasal congestion	4	(8.5)	0	--
Nausea	4	(8.5)	0	--
Vomiting	4	(8.5)	0	--
Diarrhoea	3	(6.4)	0	--

AE = adverse event; GLE = glecaprevir; MedDRA = Medical Dictionary for Regulatory Activities; PIB = pibrentasvir; SAE = serious adverse event

[a] As assessed by investigator.

[b] Includes non-treatment-emergent deaths.

Serious adverse event/deaths/other significant events

No SAE, no death and no AEs leading to study drug discontinuation were reported during the study.

No hepatic decompensation or hepatic failure were reported.

No post baseline HCC events were reported.

Patients with current HBV co-infection (subjects with positive hepatitis B surface antigen) were excluded from the clinical trial. There were no cases of HBV reactivation reported.

Laboratory findings

With the exception of a mean reduction from baseline in alanine aminotransferase (ALT) associated with clearance of HCV infection, no clinically meaningful mean changes in haematology, chemistry, or urinalysis parameters from baseline to each study visit were observed.

No subject had Grade 3/4 haematology or chemistry values that worsened in grade compared with baseline grade during the Treatment Period.

No subjects had hepatic laboratory values of specific interest.

No clinically important trends in growth and development outcomes results were observed.

Safety in special populations

No pregnancies were reported during the study.

Safety related to drug-drug interactions and other interactions

No new data applicable to this submission.

Discontinuation due to adverse events

No subjects discontinued study drug due to AEs during the study.

Post marketing experience

There are no post-marketing data available for GLE/PIB in adolescents, as it is not currently indicated for use in this patient population.

2.5.1. Discussion on clinical safety

As mentioned above, during the assessment the MAH provided the data from the full adolescent cohort consisting of the 13 patients included in the IPK analysis (already submitted in the first round) and of 34 additional patients. The final study population was of 47 adolescents, of whom 4 (8.5%) were infected with HCV GT3, 11 (23.4%) were treatment-experienced (all 11 received previous IFN-based regimen) and 2 (4.3%) were HIV/HCV co-infected. No patients had cirrhosis and almost all (n=45) were F0-F1, 1 had baseline fibrosis stage F2 and 1 had baseline fibrosis stage F3.

Three GT3-infected, treatment-experienced and non-cirrhotic subjects were assigned to the 16 week treatment duration; the remaining 44 non-cirrhotic subjects were assigned to the 8 week treatment duration per protocol.

CHMP agreed that no safety signals emerged from the expanded safety analysis pertaining to 47 subjects. The most frequently reported ADRs (>10%) were nasopharyngitis, upper respiratory tract infection, headache, fatigue, oropharyngeal pain and pyrexia. None of the events of nasopharyngitis and upper respiratory tract infections were considered as drug-related. All AEs were of mild or moderate in severity (Grade 1 or 2), the majority were of Grade 1 (61%) and only one AE was qualified of severe (AE of depression in a patient with history of depression). This patient experienced a worsening of pre-existing depression associated with suicidal ideation 14 days after the beginning of Maviret therapy. The investigator did not consider a causal relationship with the antiviral therapy and it seemed that the event was more likely related to events of school bullying. The psychiatric disorders were reported to be resolved with psychotherapy, GLE/PIB was not stopped due to the events and the SVR was achieved.

CHMP agreed that the role of GLE/PIB was difficult to ascertain in this case. No other cases of psychiatric disorders were reported during the study. However, due to the signal towards depression and suicidal ideation with other antivirals, it was agreed that the issue of psychiatric disorders, a fortiori in the vulnerable population of adolescents, should be scrutinized in forthcoming PSURs of GLE/PIB.

Nine subjects experienced study drug related AEs (19.1%). The most commonly reported ADRs were fatigue (n=3, 6.4%), abdominal pain (n=2, 4.3%) and decreased appetite (n=2, 4.3%). The remaining study-drug related AEs were reported in only one patient each (abdominal distension, chills, crystal urine present, decreased activity, hyperbilirubinaemia, proteinuria, somnolence and vasculitic rash). In the

expanded safety analysis, there were no deaths, no SAEs, no AEs leading to treatment discontinuation and no safety signals emerged.

In terms of laboratory findings, one subject had Grade 3/4 haematology or chemistry value that worsened compared with baseline during the Treatment Period. This subject had a single Grade 3 low neutrophil count on Day 1 (after dosing) that improved to Grade 2 on Day 15 and returned to within the reference range on Day 29. At PT Week 12 visit, the subject's neutrophil count decreased to Grade 2 again; no further follow-up is available. This Grade 3 low neutrophil count was not considered clinically significant by the investigator and was not reported as an AE. No other subjects had a Grade 3/4 haematology or chemistry value that worsened compared with baseline during the Treatment Period.

Overall, Maviret was well tolerated in adolescents included in this study and the safety profile remains comparable to what has been observed in adults with fatigue being one of the most commonly reported ADRs.

CHMP agreed that the provided data from the full adolescent cohort (n=47) further reinforce the positive benefit-risk balance that was estimated made on the basis of data from the 13 patients from the intensive PK cohort.

2.5.2. Conclusions on clinical safety

The CHMP agreed that this extension of indication application for Maviret is approvable from a safety perspective.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

List of Important Risks and Missing Information was not changed.

Pharmacovigilance plan

Only the summary of Objectives has been updated for the study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C/Planned.
The hepatic Questionnaire was also removed from the pharmacovigilance activities.

Risk minimisation measures

Routine risk minimization activities are still sufficient to manage the safety concerns of the product.

2.7. Update of the Product information

The agreed PI changes are included in the attached approved Product Information.

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Maviret. The bridging report submitted by the MAH has been found acceptable.

2.7.2. 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

Hepatitis C viral infection is a global health problem, with 184 million individuals chronically infected worldwide. An estimated 13.2 million children between the ages of 1 and 15 years old are infected with HCV globally.

Within Europe's paediatric population, prevalence of HCV ranges from 0.05% to 0.36%. New HCV infections among the 5 – 14 year old age group constituted 0.4% of all new infections, while the age group of 15 – 19 year olds constituted 1.2% of all new infections in the EU/European Economic Area (EEA) during 2015.

3.1.1. Disease or condition

Although the majority of children have a mild disease and do not need urgent treatment, guidance published by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2018 recommend that all children with chronic HCV infection should be considered for treatment, considering that the rational underlying the indications for treatment of adults with chronic infection is also valid for children.

3.1.2. Available therapies and unmet medical need

Current approved treatment options for children < 12 years old remains limited, as IFN-free DAA regimens are not yet approved for use in this population. For adolescents, ledipasvir/sofosbuvir (LDV/SOF) and SOF + RBV have been recently approved for use, but they are not pan genotypic IFN-free and the recommended regimen for HCV GT2 and GT3 infection require co-administration with RBV.

3.1.3. Main clinical studies

This application for an extension of the indication to adolescents is supported by new clinical data from part 1 of Study M16-123 [An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Subjects with Genotypes 1 - 6 Chronic Hepatitis C Virus (HCV) Infection (DORA)] which evaluated the use of the adult co-formulated tablets in adolescents (12 to < 18 years of age).

The application for an extension of the indication to adolescents was primarily supported by the interim analysis of study M16-123 including the PK, efficacy and safety data from the 13 adolescent from the intensive PK cohort. In response to the RSI, the MAH provided the data from the full adolescent cohort, which consists in the 13 patients included in the IPK analysis and 34 additional patients from the non-IPK analysis.

The study population now consist in 47 adolescents of whom 4 (8.5%) were infected with HCV GT3, 11 (23.4%) were treatment-experienced (all 11 received previous IFN-based regimen) and 2 (4.3%) were HIV/HCV co-infected. No patients had cirrhosis.

3.2. Favourable effects

Maviret has been shown to be highly effective in adults.

Exposure to GLE/PIB in adolescent 12-18 years receiving the adult dose has been estimated by intensive PK in 10 patients and has been shown to be comparable to adults. All 47 adolescents, including the 13 from the intensive PK analysis and 34 additional adolescent included in the non-intensive PK analysis, achieved SVR_{12}.

3.3. Uncertainties and limitations about favourable effects

Sample size is limited to 47 adolescents, including some adolescents more difficult to treat as treatment-experienced (n=11), GT3 (n=4), (GT3 TE n=3). With the exception of 1 patient with baseline fibrosis stage F2 and 1 with fibrosis F3, all were non cirrhotic patients.

3.4. Unfavourable effects

Overall, no safety concerns emerged from the expanded safety analysis pertaining to 47 subjects. The most commonly reported drug-related AE is fatigue (n=3, 6.4%) which is already listed in the Maviret SmPC.

One case of depression and suicidal ideation in a subject with a history of depression was reported during this study. On the basis of the information provided by the MAH, it seems that the event was most likely related to school bullying. Due to the signal towards depression and suicidal ideation with Viekirax, it is expected that the issue of psychiatric disorders, a fortiori in the vulnerable population of adolescents, is scrutinized in forthcoming PSURs.

3.5. Uncertainties and limitations about unfavourable effects

The number of patients is limited.

3.6. Benefit-risk assessment and discussion

The availability of potent and convenient DAA for the paediatric population is important. The clinical development issues of these medicines in this population and the willingness to accelerate the access of

children to new DAA regimens have been highlighted numerous times, including in an expert meeting held at the EMA. In this context, Maviret, a FDC including two new generation pan genotypic DAA, with its 8 weeks simplified regimen for easy to treat patients (expected to be the majority of adolescents) and no ribavirin requirement, represents a valuable therapeutic tool for the adolescent population.

Following recommendation from this EMA expert meeting and other discussions with regulators, the MAH planned a paediatric study whose primary endpoint is systemic exposure. The interim analysis of M16-123 study included PK, efficacy and safety data from the 13 adolescent included in the intensive PK portion of Part 1 study; i.e the adolescent IPK cohort. In the IPK cohort, all patients were to be TN, without cirrhosis, without coinfection and received 8 weeks regimen. PK data showed similar exposure as in adults, enabling to predict similar efficacy and safety. Additional safety/efficacy data from the full adolescent cohort (n=47) reinforced the level of reassurance as regards the efficacy of Maviret at the adult dose in adolescents and on the safe use of the drug in this population.

3.7. Conclusions

Based on the data presented in this application, the CHMP agreed that the overall benefit-risk of Maviret is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to extend the Maviret indication to adolescents (from 12 to <18 years of age) with chronic hepatitis C infection, based on new clinical data from study M16-123, an open-label, multi-centre study to evaluate the pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in paediatric subjects with genotypes 1 - 6 chronic hepatitis C virus infection (DORA), using the adult co-formulated tablets in adolescents. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance.
In addition, the marketing authorisation holder (MAH) submitted a revised RMP version 4.1, updated in accordance with the second revision of the RMP template.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for

under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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.

In addition, 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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan Decision P/0152/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to extend the Maviret indication to adolescents (from 12 to <18 years of age) with chronic hepatitis C infection, based on new clinical data from study M16-123, an open-label, multi-centre study to evaluate the pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in paediatric subjects with genotypes 1 - 6 chronic hepatitis C virus infection (DORA), using the adult co-formulated tablets in adolescents. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance.

Summary

Please refer to the Scientific Discussion – Maviret-12.