22 April 2021
EMA/372473/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Maviret

International non-proprietary name: glecaprevir / pibrentasvir

Procedure No. EMEA/H/C/004430/X/0033/G

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

AASLD	American Association for the Study of Liver Diseases
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
$AUC2_{4ss}$	area under the plasma concentration-time curve from time 0 to 24 hours at steady-state
CFR	Code of Federal Regulations
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD	chronic kidney disease
CP	Child-Pugh
CSE	Clinical Summary of Efficacy
CSR	clinical study report
CSS	Clinical Summary of Safety
DAA	direct-acting antiviral agent
DCV	daclatasvir
DDI	drug-drug interaction
DILI	drug-induced liver injury
DSV	dasabuvir
EASL	European Association for the Study of the Liver
EBR	elbasvir
EEA	European Economic Area
EMA	European Medicines Agency
EQ-5D-3L	EuroQoL-5 Dimensions-3 Level
EQ-5D-3L-HUI	EQ-5D-3L Health Utility Index
EQ-5D-3L-VAS	EQ-5D-3L Visual Analogue Scale
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
EU	European Union

FDA	United States Food and Drug Administration
FSS	Fatigue Severity Scale
GLE	glecaprevir, ABT-493
GMP	Good Manufacturing Practice
GT	genotype
GZR	grazoprevir
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus-1
HPLC	High performance liquid chromatography
IBD	international birth date
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDSA	Infectious Diseases Society of America
IFN	interferon
IND	Investigational New Drug
INR	International Normalised Ratio
IPC	In-process control
IPK	intensive pharmacokinetic
iPSP	initial Pediatric Study Plan
IRT	interactive response technology
ITT	intention-to-treat
KF	Karl Fischer titration
LDV	ledipasvir
MAA	marketing authorization application
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
mITT-VF	modified intention-to-treat virologic failure
MTCT	mother-to-child transmission
NDA	New Drug Application
NGS	next-generation sequencing
NS3	nonstructural viral protein 3

NS3/4A	nonstructural viral protein 3/4A
NS5A	nonstructural viral protein 5A
OBV	ombitasvir
PASS	post-authorization safety study
PDCO	The Paediatric Committee of the EMA
pegIFN	pegylated interferon
Ph. Eur.	European Pharmacopoeia
PI	protease inhibitor
PIB	pibrentasvir, ABT-530
PIP	Pediatric Investigational Plan
PK	pharmacokinetic(s)
PMOS	Post-Marketing Observational Study
PRAC	Pharmacovigilance Risk Assessment Committee
PT	post-treatment
PTV	paritaprevir
QD	once daily
QoL	quality of life
QTPP	Quality target product profile
R	ritonavir
RBV	ribavirin
RNA	ribonucleic acid
SAE	serious adverse event
SF-36v2-MCS	36-Item Short Form Health Survey SF-36 Mental Component Score
SF-36v2-PCS	36-Item Short Form Health Survey SF-36 Physical Component Score
SmPC	Summary of Product Characteristics
SOF	sofosbuvir
SVR12	sustained virologic response 12 weeks post-treatment
TAMC	Total Aerobic Microbial Count
TE	treatment-experienced
TN	treatment-naïve
ULN	upper limit of normal
US	United States
USP	United States Pharmacopoeia

USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
VEL	velpatasvir
VOX	voxilaprevir
WPAI	Work Productivity and Activity Impairment

1. Background information on the procedure

1.1. Submission of the dossier

AbbVie Deutschland GmbH & Co. KG submitted on 6 March 2020 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
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	II

Extension application to introduce a new pharmaceutical form (50/20 mg coated granules in sachet), grouped with a type II extension of indication variation (C.I.6.a) to include the treatment of children from 3 to 12 years of age for the approved Maviret 100 mg/40 mg film-coated tablets; as a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated accordingly. Version 5.0 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0128/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0128/2019 was completed.

The PDCO issued an opinion on compliance for the PIP: EMEA-C-001832-PIP01-15-M02.

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 MAH 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 MAH did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Jean-Michel Race

The application was received by the EMA on	6 March 2020
The procedure started on	21 May 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	27 July 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	17 August 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	04 September 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	17 September 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	15 December 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	29 January 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 August 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	25 February 2021
The MAH submitted the responses to the CHMP List of Outstanding Issues on	19 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	07 April 2021
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 April 2021

During the assessment of this application, a revised timetable has been adopted by the CHMP accounting for a delay from the initially planned timetable due to unforeseeable reasons related to the COVID-19 pandemic. This was done in line with the European Medicines Regulatory Network COVID-19 Business Continuity Plan (EMRN COVID-19 BCP) which describes mitigation measures in case of COVID-19 related delays.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Hepatitis C viral infection is a global health problem, with over 71 million individuals chronically infected worldwide. In a recent systematic review, an estimated 13.2 million children aged 1 – 15 years are infected with chronic HCV, globally.

2.1.2. Epidemiology

Within the US and Europe's paediatric population, the prevalence of HCV in children and adolescents ranges from 0.05% to 0.36%. New HCV infections among the 0 to 4-year-old age group constituted 0.4% of all new infections in EU/EEA during 2016, 5 – 14 year-olds 0.3%, and 15 – 19 year-olds 1.3%, equating to a rate of infection of 0.55, 0.21, and 1.92 per 100,000, respectively.

Within the paediatric population (< 18 years of age), mother-to-child transmission (MTCT) during the perinatal period is the most common reason for paediatric HCV infection, accounting for 60% of cases. The remaining paediatric/adolescent cases, acquired after the perinatal period, are attributable to intra-familial transmission and high-risk behaviours such as intravenous drug abuse.

There are 6 major HCV GTs, with prevalence varying by geographic region. Among the European paediatric population (≤ 14 years old) who tested positive for HCV between 2011 and 2015, genotype distribution was as follows: 15% GT1 (where not subtyped), 26.3% GT1a, 21.3% GT1b, 3.8% GT2, 18.8% GT3, 13.8% GT4, 1.3% GT5, and 0% GT6. The HCV genotype distribution in the paediatric population is similar to the HCV genotype pattern in adults.

2.1.3. Clinical presentation, diagnosis and prognosis

Although the majority of children have a mild disease and do not need urgent treatment, advanced liver disease and decompensated cirrhosis have been reported in children as young as 3 years of age. Disease progression also may occur many years after the initial infection. Guidance published by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2018 recommends 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. Guidance published by ESPGHAN also recommends that all children aged 3 to 17 years with chronic HCV infection may be considered candidates for treatment and should be considered for treatment if they develop consistently elevated serum aminotransferase levels or liver fibrosis.

2.1.4. Management

Current approved treatment options for children aged 3 years and older remains limited although expanding. Recently, ledipasvir (LDV)/sofosbuvir (SOF) and SOF + ribavirin (RBV) have been approved for use (CHMP positive opinion on 30 April 2020), but they are not pangenotypic IFN-free and the recommended regimen for HCV GT2 and GT3 infection requires co-administration with RBV. Moreover,

during the assessment of this procedure, Epclusa received EU approval for an extension of the indication in children from 6 years of age.

About the product

Maviret, the fixed dose combination of NS3/4A protease inhibitor GLECAPREVIR and NS5A inhibitor PIBRENTASVIR (GLE/PIB), was first authorized in EU on 26 July 2017 for the treatment of chronic hepatitis C infection in adults. Approval for extension of the GLE/PIB treatment regimen to adolescents was granted in the EU on 12 March 2019. 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).

A paediatric formulation, comprised of coated granules of glecaprevir and pibrentasvir in a sachet for oral administration, has been developed for use in children from 3 to <12 years of age. While the children in the intensive pharmacokinetic (IPK) part of Study M16-123 received GLE and PIB coated granules packaged separately, the same GLE and PIB coated granules were co-filled into one sachet for greater patient/care giver convenience and is the to-be marketed formulation.

Type of Application and aspects on development

The applicant is submitting the following grouping according to article 7.2 (b) of the variation regulation (cases for grouping variations listed in Annex III to Commission Regulation (EC) No 1234/2008):

- Addition of a new strength and a new pharmaceutical form (50/20 mg coated granules in sachet) developed as paediatric formulation: extension of a marketing authorisation under Annex I to Commission Regulation (EC) No 1234/2008.
- Broadening of the currently approved indication for the approved Maviret 100 mg/40 mg film-coated tablets to include the treatment of children from 3 to 12 years of age: type II variation.

This current application for an extension of the indication to children aged 3 years and older is supported by new clinical data from part 2 of Study M16-123 [An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvirin for 8, 12, or 16 weeks in HCV GT1 – GT6-infected paediatric subjects ≥ 3 to < 18 years of age (DORA)].

Part 1 of the study evaluated the use of the adult bilayer tablets in adolescents (Cohort 1) and has been previously submitted and assessed to support the extension of the indication in paediatric patients from 12 years of age. Part 2 of the study is evaluating the use of the paediatric coated granules formulation of GLE + PIB in children ≥ 3 to < 12 years of age (Cohorts 2 – 4). In each cohort, subjects are enrolled first into the IPK portion, followed by the non-IPK safety/efficacy portion. Additional IPK samples are obtained from subjects in Japan, who enrolled in the non-IPK/efficacy portion.

Development has been conducted in line with the Paediatric Investigational Plan (PIP) (EMA reference EMEA-001832-PIP01-15) and the agreed initial Paediatric Study Plan (iPSP) (US Investigational New Drug [IND] Number 127416, Reference ID: 3959249).

2.2. Quality aspects

2.2.1. Introduction

This Line Extension seeks to introduce an age-appropriate formulation needed for the extension of the indication to children from 3 years and older in addition to the already approved film-coated tablets containing 100 mg glecaprevir and 40 mg pibrentasvir.

The finished product is presented as coated granules in sachet containing 50 mg glecaprevir and 20 mg pibrentasvir.

Other ingredients are: copovidone, tocofersolan, propylene glycol monocaprylate, colloidal silicon dioxide, croscarmellose sodium (in the glecaprevir granules only), sodium stearyl fumarate, hypromellose (E464), lactose monohydrate, titanium dioxide, macrogol, iron oxide red (E172), iron oxide yellow (E172)

The product is available in polyethylene terephthalate (PET) /aluminium/polyethylene film sachets as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substances (glecaprevir and pibrentasvir) are the same as for the authorised Maviret 100 mg glecaprevir /40 mg pibrentasvir film-coated tablets. No new information on the active substances has been provided within this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is immediate release film coated, pink and yellow, granules in a sachet for oral administration. The granules are round and 2 mm in diameter. This is a fixed-dose combination product containing 50 mg glecaprevir and 20 mg pibrentasvir co-filled in each sachet.

Table 1: Description of glecaprevir/pibrentasvir 50 mg/20 mg coated granules in sachet

Parameter	Description
Appearance	Film-coated granule
Marking	Unmarked
Shape	Round, biconvex
Color	Pink film-coated granules and yellow film-coated granules
Approximate Dimension	2 mm diameter

The aim of the formulation development was to manufacture an additional age-appropriate formulation needed for the extension of the indication to children from 3 years and older.

The development of the paediatric formula was driven by the QTPP of the product and included the following key design requirements: dose flexibility, formulation acceptability and palatability for

paediatric patients, bioavailability, stability, and manufacturability. To develop the paediatric formulation, the tablet formulation was adapted to the strength of granules in sachet (half that of the tablet).

The granules contain the glecaprevir and pibrentasvir extrudate as the internal phase, an outer phase containing a glidant and a lubricant, and the film coating. The composition of the extrudates is the same as for the tablets. The qualitative composition of both outer layers is the same as for each layer of the Maviret bilayer tablet. The same excipients as in tablet formulation are used.

All the tablet core excipients comply with Ph. Eur. or NF monographs. The coating agent powder is non-compendial, but its components are of Ph. Eur. or NF (iron oxides) quality. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Lactose and propylene glycol monocaprylate are excipients with recognized action and are mentioned in the SmPC. Overall, the excipients do not pose a safety risk for the paediatric population.

The development of the manufacturing process is described. The compression and film coating to a target of 20% weight gain are critical steps. The challenge of the filling step is the accurate filling to obtain the desired strengths. Suitable process parameters and in-process controls have been defined for these manufacturing steps.

The dissolution method for the granules is based on the dissolution method used for the tablets, as the composition and manufacturing process (up to compression step) are the same. The same dissolution mechanism (via erosion) is described. The method is discriminatory for the extrusion step and is acceptable for quality control.

The primary packaging is polyethylene terephthalate (PET)/aluminium/polyethylene film sachets. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process can be divided into the pre- and post-extrusion process. The pre-extrusion process comprises preparation of the glecaprevir and pibrentasvir extrudate intermediates and is the same as for the approved tablet formulation. The same approved manufacturing site is used.

The post-extrusion manufacturing process comprises milling of extrudate intermediates, blending with outer phase excipients, compression to granules, coating of granules, and filling of granules into sachets. The site AbbVie Chicago USA is responsible for manufacturing of glecaprevir and pibrentasvir granule bulk intermediate and AbbVie Italy is responsible for manufacturing of finished medicinal product. A major objection was raised in the D120 List of Questions in relation to the GMP compliance status of the site AbbVie Chicago USA, but this was resolved by the applicant by submitting the required proof of GMP compliance.

The process is considered to be a standard process.

The overall control strategy, process parameters and in-process controls seem adequate in view of the available development data and in view of the standard nature of the manufacturing process.

An acceptable process validation scheme has been submitted explaining how major steps of the manufacturing process will be validated prior to commercialisation. From batches manufactured to date, it has been demonstrated that the manufacturing process is capable of producing the finished

product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification analytical procedures, batch analysis

The finished product release specifications include appropriate tests for this kind of dosage form: description of granules (visual), identity of the active substances (HPLC, UV), assay of active substances (HPLC), degradation products (HPLC), water content (KF), microbiological quality (Ph. Eur.), dissolution (HPLC), and uniformity of dosage units (Ph. Eur.).

The analytical methods for assay and degradation products are the same as for the approved Maviret tablets.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

In addition, a suitable justification was provided for other tests not included in specifications, namely crystallinity, residual solvents, and mutagenic impurities.

In the context of the on-going review under Article 5(3) of Regulation (EC) No 726/2004 related to the potential presence of nitrosamine impurities in human medicinal products, the applicant has presented a detailed risk assessment regarding potential nitrosamine impurities in both active substances and in the finished product. A major objection was raised in relation to this risk assessment during the procedure and this was addressed by the applicant in a satisfactory way. It has been appropriately demonstrated that the risk of presence of nitrosamines is negligible.

Batch analysis results are provided for three production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three primary stability batches of finished product stored for up to 12 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to ICH guidelines were provided. The manufacturing process used for the primary stability batches of medicinal product is representative of the process proposed for marketing and the batches were manufactured at the manufacturing sites proposed for marketing. The batches were manufactured using at least two different batches of each active substance. Each batch was at least one-tenth the scale of the largest proposed production batch size.

The container closure system proposed for glecaprevir/pibrentasvir 50 mg/20 mg coated granules is sachet laminate (from outer to inner layer: polyethylene terephthalate (PET) / aluminium / polyethylene (PE). The layer in contact with finished product is polyethylene. The container closure used in the stability studies is representative of the one proposed for marketing.

Tests performed to assess stability include assay, degradation products, description, water content, and dissolution. Microbial testing was performed at selected intervals. The stability indicating character of the methods for assay and degradation impurities was demonstrated.

No meaningful changes were detected to any of the parameters tested during long-term and accelerated stability studies.

The hold time for the extrudates has been approved for the Maviret tablets. A shelf-life of 9 months for the glecaprevir extrudate and 10 months for pibrentasvir extrudate intermediates is claimed. The applicant states that the shelf-life of the finished product is started when the extrudates are milled together. This is in line with what was justified for the tablets and is accepted given the similar formulations and same excipients.

Two batches of finished product manufactured with glecaprevir and pibrentasvir extrudates that were aged between 6 to 11 months, were placed on stability. Twelve months of stability data are available for these batches. No meaningful change was observed in any attribute studied under long-term storage conditions (30 °C /75% RH) for 12 months and under accelerated storage conditions (40 °C / 75% RH) for 6 months.

Supportive stability data is also available from clinical batches of intermediate bulk glecaprevir coated granules (24 months) and of pibrentasvir coated granules (24 months) which were packaged in high density polyethylene (HDPE) bottles with desiccant. Stability studies were conducted under long-term storage conditions (30 °C /75% RH) and under accelerated storage conditions (40 °C / 75% RH) and no meaningful change was detected.

In addition, two batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Based on the results, no special storage conditions to control exposure to light are needed.

Temperature excursion studies and temperature cycling studies were also conducted which support any temperature excursions which may occur during shipping or storage.

Based on available stability data, the proposed shelf-life of 2 years as stated in the SmPC (section 6.3) is acceptable. No special storage conditions are required.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

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 the product should have a satisfactory and uniform performance in clinical use.

The CHMP initially raised a major objection in relation to the GMP compliance status of the finished product manufacturing site AbbVie Chicago USA. This was addressed by the applicant in a satisfactory way. During the procedure and additional major objection was raised in relation to the nitrosamine risk assessment presented in this procedure. This was resolved by the applicant in a satisfactory way. Please refer also to the finished product section of this report.

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. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Pharmacology

No new non-clinical studies have been submitted in this procedure to support the line extension into the paediatric population, which is considered acceptable by the CHMP.

2.3.2. Pharmacokinetics

No new non-clinical pharmacokinetics studies have been submitted in this application, which is acceptable.

2.3.3. Toxicology

No new non-clinical studies have been submitted. The applicant provided a justification concerning the lack of juvenile animal studies which were deemed not needed before initiation of the paediatric program since there were no toxicologic findings that would be considered to be more severe or to manifest differently in an adult compared to a paediatric population. Additionally, there are no expected differences in metabolism between an adult and a paediatric population for the DAAs. The PDCO review did not raise any non-clinical issues.

2.3.4. Ecotoxicity/environmental risk assessment

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.

During the initial marketing authorisation application in adults, the applicant had already performed Phase I studies for glecaprevir and pibrentasvir that revealed PECSURFACEWATER 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 PECSURFACEWATER values for these compounds will be the same as the value calculated for the adult and adolescent indications as: 1) the recommended doses for glecaprevir and pibrentasvir for paediatrics are less than the adult / adolescent doses, and therefore the highest recommended doses (the adult and adolescent doses) were used to calculate the initial PEC values in accordance with EMA guidance, 2) the Fpen will not change as the default (conservative) Fpen was used in the original calculation.

Secondly, it was highlighted that the PECSURFACEWATER 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. No additional studies are required for the requested extension and revisions to the ERAs for glecaprevir and pibrentasvir are not warranted.

2.3.5. Conclusion on the non-clinical aspects

No new non-clinical studies have been submitted in this application, which is acceptable to the CHMP. Based on the updated data submitted in this application, no additional studies would be required for this extended indication.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The MAH 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

Clinical data submitted in support of the application are the followings:

• M16-123 Clinical Study Report. An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety and Efficacy of Glecaprevir/Pibrentasvir in Paediatric Subjects with Genotypes 1-6 Chronic Hepatitis C Virus (HCV) Infection (DORA). All Part 1 and Part 2 IPK PTW12 Primary Data were submitted in the initial submission. Within its response document to the List of Question, the MAH submitted all Part 1 and Part 2 PTW12 Primary data; i.e. post-treatment W12 data for the full 3->12y age cohorts.

• M17-142 Clinical Study Report - Bioavailability and Food Effect of Experimental Glecaprevir +Pibrentasvir Paediatric Formulation in Healthy Adult Subjects

• Population Pharmacokinetic Report (Part 2) - Population Pharmacokinetic Analysis of Glecaprevir and Pibrentasvir in Paediatric Subjects 3 to < 12 Years of Age with Genotypes 1 – 6 Chronic Hepatitis C Virus (HCV) Infection (Phase 2/3 Study M16-123, Part 2)

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	Study Status; Type of Report
BA	M17-142	5.3.1.1	PK, Bioavailability and Food Effect	Open-label	Adult Formulation GLE/PIB tablet; (300/120 mg, 3 × 100/40 mg tablets); Single-dose; PO. and Pediatric Formulation GLE + PIB as separate 15.67% and 8.25% film-coated pellets/granules; (300 mg and 120 mg in pellets); Single-dose; PO.	39	Heatlhy subjects 18 – 55 years of age	Part 1: 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIBadult formulation with washout interval ≥ 4 days between doses. Part 2: 3 doses of GLE + PIB pediatric formulations with washout interval of 5 days between doses.	Completed/ Final CSR

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	Study Status; Type of Report
Efficacy and safety	M16-123 (Part 1)	5.3.5.2	PK, Efficacy and Safety	Open-label	Adult Formulation GLE/PIB tablet; 300 mg/120 mg QD; PO.	48	≥ 12 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	Ongoing; All Part 1 Primary analysis Interim CSR
Efficacy and safety	M16-123 (Part 2 IPK Portion)	5.3.5.2	PK, Efficacy and Safety	Open-label	Pediatric Formulation GLE + PIB as separate 15.67% and 8.25% coated pellets/granules; dosed based on body weight/age-band; PO.	48	≥ 3 to < 12 years of age, HCV GT1 – GT6, treatment naïve, with or without compensated cirrhosis	8 or 12 weeks depending on cirrhosis status	Ongoing; Part 2 IPK Primary analysis Interim CSR

2.4.2. Pharmacokinetics

Glecaprevir (ABT-493, GLE)/ pibrentasvir (ABT-530, PIB), formulated as a fixed dose film-coated bilayer tablet (100 mg/40 mg tablet) is currently approved for the treatment of chronic HCV infection (genotype 1 to 6) in adult and adolescents (12 to < 18 years of age) patients.

A new paediatric formulation, comprised of coated granules of GLE/PIB (50 mg/20 mg) in a sachet for a convenient QD oral administration with a soft-food dosing vehicle, has been developed for use in children 3 to < 12 years of age and is the subject of the current application.

In children aged 3 to < 12 years and weighing less than 45 kg, the recommended dosage is presented in Table 2.

Table 2: Recommended dosage for children aged 3 to < 12 years

Weight of child (kg)	Number of sachets once daily (glecaprevir + pibrentasvir)
≥12 to < 20 kg	3 sachets (150 mg + 60 mg)
≥20 to <30 kg	4 sachets (200 mg + 80 mg)
≥30 to < 45 kg	5 sachets (250 mg + 100 mg)

This paediatric formulation has been investigated in two studies, Study M16-123 (Part 2) and Study

M17-142 (bioavailability and food effect). Dosing recommendation were guided by the development of Population PK models (PPK) of each compound (GLE and PIB).

Study M17-142

Design

Study M17-142 was a Phase 1, single center, open label, randomized study conducted in two parts with the aim to evaluate the bioavailability of the experimental GLE+PIB paediatric formulation relative to the approved adult formulation (Part 1) and the effect of high-fat and low-fat meals (Part 2) on the experimental GLE+PIB formulation relative to fasting conditions.

Part 1 was a four sequence, four-period crossover design to evaluate the bioavailability of the experimental GLE+PIB paediatric formulation relative to the Phase 3 adult formulation in fast and non-fasting conditions as presented in Table 3.

Table 3: Sequence groups for Part 1

		Regimens			
Sequence Group	N	Period 1	Period 2	Period 3	Period 4
1	6	A	B	C	D
2	6	B	D	A	C
3	6	C	A	D	B
4	6	D	C	B	A

Regimen A = Single dose of GLE + PIB pediatric formulations administered under fasting conditions (300 mg + 120 mg in pellets) (Test 1).

Regimen B = Single dose of GLE + PIB pediatric formulations administered under non-fasting conditions (300 mg + 120 mg in pellets) (Test 2).

Regimen C = Single dose of GLE/PIB adult formulation administered under fasting conditions (300/120 mg, 3 × 100/40 mg tablets) (Reference 1).

Regimen D = Single dose of GLE/PIB adult formulation administered under non-fasting conditions (300/120 mg, 3 × 100/40 mg tablets) (Reference 2).

Part 2 was a three-sequence, three-period cross-over design to evaluate the effect of a high or low fat meal as presented in Table 4 below.

Table 4: Sequence groups for Part 2

		Regimens		
Sequence Group	N	Period 1	Period 2	Period 3
1	5	E	F	G
2	5	F	G	E
3	5	G	E	F

Regimen E = Single dose of GLE + PIB pediatric formulations administered under high-fat conditions (300 mg + 120 mg in pellets) (Test 3).

Regimen F = Single dose of GLE + PIB pediatric formulations administered under low-fat conditions (300 mg + 120 mg in pellets) (Test 4).

Regimen G = Single dose of GLE + PIB pediatric formulations administered under fasting conditions (300 mg + 120 mg in pellets) (Reference 3 and Reference 4).

A wash-out period of 4 days (Part 1) or 5 days (Part 2) was considered. Blood samples for assay of

GLE or PIB were collected for up to 48 hours after dosing in each period.

At Day 1, subjects allocated in Regimen A, C and G were not served breakfast (fasting) whereas subjects in Regimen B, D, E and F received a breakfast with different fat contents at approximately 30 min prior to dosing.

Investigational drug product are presented in Table 5.

Table 5: Investigational drug products

	GLE (Test/Reference)	PIB (Test/Reference)	GLE/PIB (Reference)
Dosage Form	Film-coated pellets	Film-coated pellets	Film-coated tablets
Formulation	Pediatric	Pediatric	Adult
Strength	15.67% (w/w) film-coated pellets	8.25% (w/w) film-coated pellets	100 mg/40 mg per tablet
MMID	20017950	20017949	20003641
Bulk Product Lot Number	1000207309	1000207308	15-006595
Retest Date	31 August 2019	31 August 2019	31 August 2018

MMID = Material Master Identification

PK sampling consisted of pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 post-dose.

Results

Adult male and female subjects (N=39) were enrolled in the study, and 23/24 completed all four periods of Part 1 and 15/15 for Part 2. One subject discontinued Part 1 after receiving study drug in Period 2 due to an adverse event of upper respiratory infection.

Part 1

The mean plasma concentration-time profiles of GLE and PIB Part 1 are presented in Figure 1 on log-linear scales, a summary of PK parameters in Table 6 and a summary statistics for Part 1 in Table 7.

Figure 1: Mean GLE and PIB plasma concentration-time profiles (Part 1)

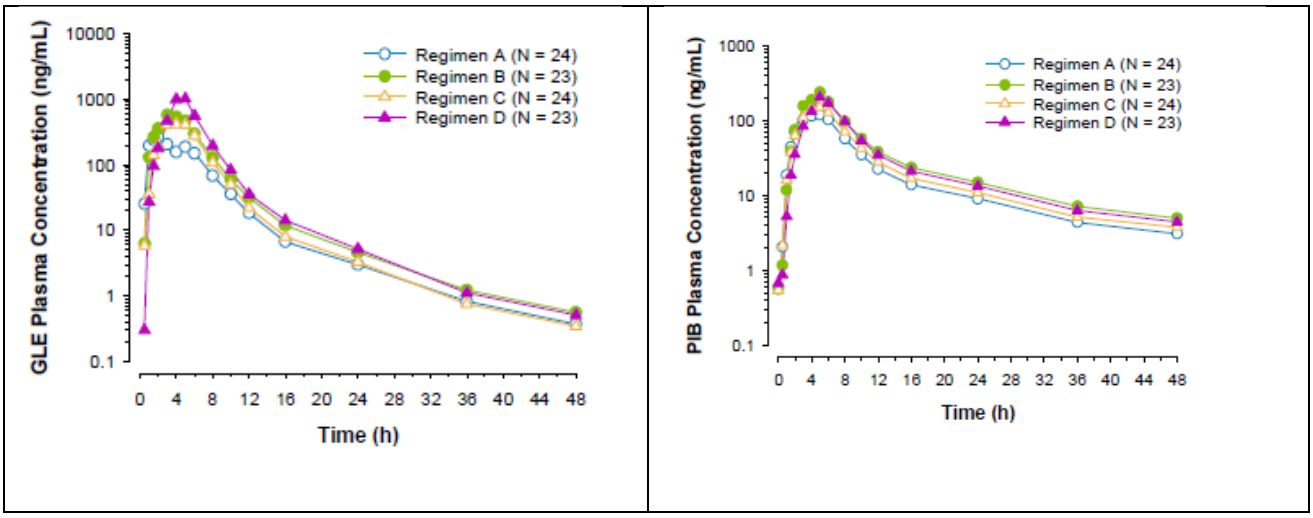


Table 6: Summary geometric mean PK parameters of GLE and PIB (Part 1)

Pharmacokinetic Parameters (units)	Regimen A (N = 24)	Regimen B (N = 23)	Regimen C (N = 24)	Regimen D (N = 23)
	GLE			
C_{max} (ng/mL)	236 (356, 144)	621 (721, 51)	399 (583, 97)	946 (1300, 83)
T_{max}[a] (h)	1.5 (1.0 – 6.0)	3.0 (1.5 – 6.0)	3.0 (2.0 – 6.0)	4.0 (2.0 – 6.0)
$t_{1/2}$[b] (h)	6.98 (2.58)	6.85 (1.45)	6.63 (1.58)	6.26 (1.55)
AUC_t (ng•h/mL)	1110 (1540, 118)	2700 (3060, 50)	1830 (2330, 78)	3410 (4290, 76)
AUC_{inf} (ng•h/mL)	1110 (1540, 118)	2710 (3060, 50)	1830 (2340, 78)	3420 (4300, 76)
	PIB			
C_{max} (ng/mL)	102 (125, 61)	213 (247, 51)	124 (153, 63)	189 (224, 58)
T_{max}[a] (h)	4.0 (3.0 – 5.0)	5.0 (3.0 – 6.0)	5.0 (2.0 – 6.0)	5.0 (2.0 – 8.0)
$t_{1/2}$[b] (h)	14.4 (1.89)	14.1 (1.38)	14.1 (1.63)	13.9 (1.57)
AUC_t (ng•h/mL)	869 (1070, 65)	1490 (1760, 52)	1010 (1270, 67)	1240 (1490, 60)
AUC_{inf} (ng•h/mL)	924 (1140, 64)	1580 (1870, 52)	1070 (1340, 68)	1310 (1580, 59)

Regimen A = Single dose of GLE + PIB pediatric formulations administered under fasting conditions (300 mg + 120 mg in pellets) (Test 1).

Regimen B = Single dose of GLE + PIB pediatric formulations administered under non-fasting conditions (300 mg + 120 mg in pellets) (Test 2).

Regimen C = Single dose of GLE/PIB adult formulation administered under fasting conditions (300/120 mg, 3 × 100/40 mg tablets) (Reference 1).

Regimen D = Single dose of GLE/PIB adult formulation administered under non-fasting conditions (300/120 mg, 3 × 100/40 mg tablets) (Reference 2).

a. Median (minimum through maximum).

b. Harmonic mean (pseudo-standard deviation).

Table 7: Relative bioavailability and 90% CI for GLE and PIB (Part 1)

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
				GLE	
A vs. C (Pediatric vs. Adult formulation under fasting conditions)	C_{max}	236	399	0.591	(0.447, 0.782)
	AUC_t	1110	1830	0.606	(0.478, 0.768)
	AUC_{inf}	1110	1830	0.607	(0.479, 0.769)
B vs. D (Pediatric vs. Adult formulation under non-fasting conditions)	C_{max}	631	949	0.664	(0.524, 0.842)
	AUC_t	2720	3420	0.794	(0.664, 0.949)
	AUC_{inf}	2730	3430	0.795	(0.665, 0.950)
				PIB	
A vs. C (Pediatric vs. Adult formulation under fasting conditions)	C_{max}	102	124	0.822	(0.659, 1.025)
	AUC_t	869	1010	0.859	(0.690, 1.070)
	AUC_{inf}	924	1070	0.862	(0.695, 1.070)
B vs. D (Pediatric vs. Adult formulation under non-fasting conditions)	C_{max}	211	186	1.137	(0.908, 1.424)
	AUC_t	1480	1210	1.223	(0.977, 1.531)
	AUC_{inf}	1570	1290	1.219	(0.978, 1.520)

Regimen A = Single dose of GLE + PIB pediatric formulations administered under fasting conditions (300 mg + 120 mg in pellets) (Test 1).

Regimen B = Single dose of GLE + PIB pediatric formulations administered under non-fasting conditions (300 mg + 120 mg in pellets) (Test 2).

Regimen C = Single dose of GLE/PIB adult formulation administered under fasting conditions (300/120 mg, 3 × 100/40 mg tablets) (Reference 1).

Regimen D = Single dose of GLE/PIB adult formulation administered under non-fasting conditions (300/120 mg, 3 × 100/40 mg tablets) (Reference 2).

Cross reference: Table 14.2__4.1.1, Table 14.2__4.1.2, Appendix 16.1__9.2.1.1, Appendix 16.1__9.2.1.2

Under fasting conditions, administration of GLE 300 mg + PIB 120 mg pellets (paediatric formulations; Regimen A) compared to GLE/PIB 300/120 mg tablets (adult formulation; Regimen C) resulted in slightly lower exposures (AUC) of GLE (39% decrease) and PIB (14% decrease). Under non-fasting conditions, administration of GLE 300 mg + PIB 120 mg pellets (paediatric formulations; Regimen B) compared to GLE/PIB 300/120 mg tablets (adult formulation; Regimen D) resulted in comparable exposures (AUC) of GLE and PIB (≤ 22% difference).

Part 2

The mean plasma concentration-time profiles of GLE and PIB Part 2 are presented in Figure 2 on log-linear scales, a summary of PK parameters in
Table **8** and a summary statistics for Part 1 in Table 9.

Figure 2: Mean GLE and PIB plasma concentration-time profiles (Part 2)

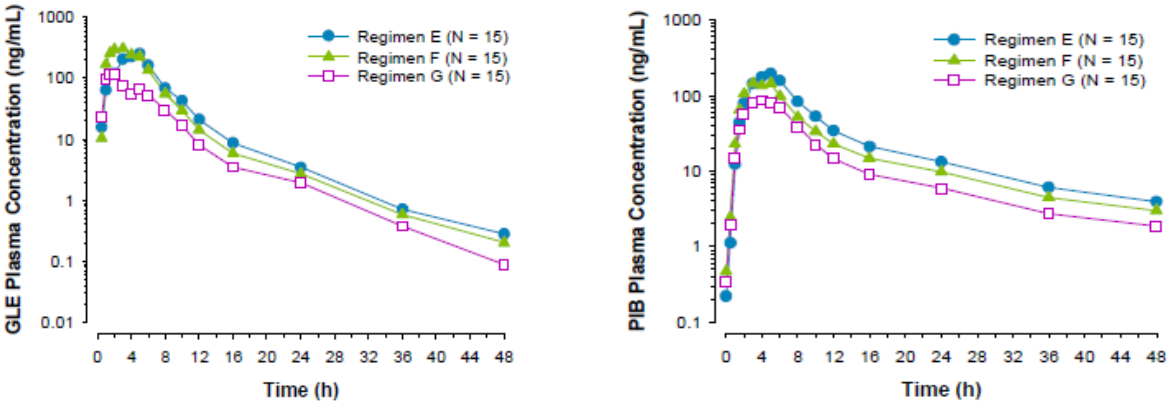


Table 8: Summary geometric mean PK parameters of GLE and PIB (Part 2)

Pharmacokinetic Parameters (units)	Regimen E (N = 15)	Regimen F (N = 15)	Regimen G (N = 15)
		GLE	
C_{max} (ng/mL)	284 (327, 64)	387 (437, 50)	134 (143, 40)
T_{max} [a] (h)	4.0 (1.5 – 6.0)	3.0 (1.0 – 6.0)	1.5 (1.0 – 2.0)
$t_{1/2}$ [b] (h)	5.59 (1.80)	6.26 (1.21)	5.28 (1.94)
AUC_t (ng•h/mL)	1350 (1500, 48)	1560 (1720, 46)	585 (643, 48)
AUC_{inf} (ng•h/mL)	1360 (1500, 48)	1570 (1720, 46)	589 (647, 48)
		PIB	
C_{max} (ng/mL)	189 (210, 54)	151 (173, 58)	82.2 (91.4, 46)
T_{max} [a] (h)	5.0 (2.0 – 6.0)	3.0 (2.0 – 5.0)	4.0 (2.0 – 5.0)
$t_{1/2}$ [b] (h)	12.7 (1.22)	13.0 (1.53)	13.4 (1.30)
AUC_t (ng•h/mL)	1400 (1560, 52)	1020 (1190,63)	653 (748, 49)
AUC_{inf} (ng•h/mL)	1470 (1640, 52)	1070 (1250, 63)	686 (785, 49)

Regimen E = Single dose of GLE + PIB pediatric formulations administered under high-fat conditions (300 mg + 120 mg in pellets) (Test 3).

Regimen F = Single dose of GLE + PIB pediatric formulations administered under low-fat conditions (300 mg + 120 mg in pellets) (Test 4).

Regimen G = Single dose of GLE + PIB pediatric formulations administered under fasting conditions (300 mg + 120 mg in pellets) (Reference 3 and Reference 4).

a. Median (minimum through maximum).

b. Harmonic mean (pseudo-standard deviation).

Table 9: Relative bioavailability and 90% CI for GLE and PIB (Part 2)

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
				GLE	
E vs. G (Pediatric formulation under high-fat vs. fasting conditions)	C_{max}	284	134	2.119	(1.732, 2.592)
	AUC_t	1350	585	2.310	(1.985, 2.688)
	AUC_{inf}	1360	589	2.305	(1.981, 2.681)
F vs. G (Pediatric formulation under low-fat vs. fasting conditions)	C_{max}	387	134	2.888	(2.361, 3.533)
	AUC_t	1560	585	2.676	(2.299, 3.114)
	AUC_{inf}	1570	589	2.666	(2.292, 3.101)
				PIB	
E vs. G (Pediatric formulation under high-fat vs. fasting conditions)	C_{max}	189	82.2	2.300	(1.867, 2.834)
	AUC_t	1400	653	2.145	(1.750, 2.629)
	AUC_{inf}	1470	686	2.138	(1.750, 2.613)
F vs. G (Pediatric formulation under low-fat vs. fasting conditions)	C_{max}	151	82.2	1.834	(1.489, 2.260)
	AUC_t	1020	653	1.566	(1.277, 1.919)
	AUC_{inf}	1070	686	1.562	(1.278, 1.908)

Regimen E = Single dose of GLE + PIB pediatric formulations administered under high-fat conditions (300 mg + 120 mg in pellets) (Test 3).

Regimen F = Single dose of GLE + PIB pediatric formulations administered under low-fat conditions (300 mg + 120 mg in pellets) (Test 4).

Regimen G = Single dose of GLE + PIB pediatric formulations administered under fasting conditions (300 mg + 120 mg in pellets) (Reference 3 and Reference 4).

Following a high-fat breakfast (Regimen E), administration of GLE 300 mg + PIB 120 mg pellets (paediatric formulations) resulted in GLE and PIB exposures (AUCs) that were 2.3-fold and 2.1-fold, respectively, of those under fasting conditions (Regimen G).

Following a low-fat breakfast (Regimen F), administration of GLE 300 mg + PIB 120 mg pellets (paediatric formulations) resulted in GLE and PIB exposures (AUCs) that were 2.7-fold and 1.6-fold, respectively, of those under fasting conditions (Regimen G).

Pharmacokinetics in Children (3 to < 12 years)

Study M16-123 (Part 2)

Design

Study M16-123 is an open-label, multicenter Phase 2/3 study to evaluate the PK, efficacy and safety of GLE/PIB in chronic HCV infected paediatric subjects, divided two parts, according to the formulation administered. Part 1 of the study was performed in adolescent patients (12 to < 18 years) with the tablet formulation and was already presented previously (EMEA/H/C/004430/II/0012). Part 2, HCV infected patients were divided in three cohorts, cohort 2 (9 to < 12 years), cohort 3 (6 to < 9 years) and cohort 4 (3 to < 6 years). During Part 2 the coated granule formulation of GLE + PIB based on body weight dosing regimen, using soft food as dosing vehicle was administered.

Investigational drug product are presented in Table *10*.

Table 10: Investigational drug product (Study M16-123)

Study Part	Investigational Product	Manufacturer	Mode of Administration	Dosage Form[b]	Strength	Bulk Lot Number
1	GLE/PIB	AbbVie	Oral	Film-coated Tablet	100 mg/ 40 mg	16-001002 16-001003 16-005216
2	GLE	AbbVie	Oral	Film-coated pellets in bottles	15.67%	1000207309
2	PIB	AbbVie	Oral	Film-coated pellets in bottles	8.25%	1000207308
2[a]	GLE/PIB	AbbVie	Oral	Film-coated granules in sachets	50 mg/ 20 mg unit dose	--

GLE = glecaprevir; PIB = pibrentasvir

a. The sachet packaging will be used for subjects enrolling in the non-IPK portion of Part 2.

b. Film-coated pellets and granules are the same formulation, and the terminology is considered interchangeable. They are listed separately, however, to reflect the changes in the packaging and labeling from "pellets" in bottles to "granules" in sachets.

Selected doses of GLE and PIB for the paediatric population are presented in Table 11. Briefly 17 subjects were administered the initial doses. These doses were determined based on modeling from data available from the adult formulation, result from Study M17-142 and Study M16-123 (Part 1, Adolescent). After the first 17 subjects from the IPK analysis, the dose was adjusted to the final proposed dose.

Table 11: GLE and PIB doses for the paediatric population

Formulation	Age Group (yrs) & Weight Band (kg)	Initial Doses (mg)		Final Proposed Doses (mg)	
		GLE	PIB	GLE	PIB
Pediatric formulation	3 to < 6 yr 12 to < 20 kg	120	45	150	60
	6 to < 9 yr ≥ 20 to < 30 kg	160	60	200	80
	9 to < 12 yr ≥ 30 to < 45 kg	200	75	250	100
Adult formulation	12 to < 18 yr ≥ 45 kg	--	--	300	120

GLE = glecaprevir; PIB = pibrentasvir; yr = year

PK sampling consisted of sparse sampling at Day 1, week 4, 8 and 12 and intensive PK (IPK) sampling at week 2 at pre-dose, 2, 4, 6, 12 hours after drug intake.

The primary PK endpoint was the steady state AUC of GLE and PIB at week 2 estimated by NCA or by PPK.

Results

Pharmacokinetic results following the initial dose regimen of 40 mg GLE + 15 mg PIB is presented in Table 12.

Table 12: Geometric mean (mean, CV%) PK parameters of GLE and PIB (Week 2 IPK) in paediatric subjects of Part 2 of Study M16-123 following the initial dosing regimens

		GLE + PIB QD Pediatric Formulation Week 2	
PK Parameters	**(Units)**	**GLE**	**PIB**
		Cohort 2 (N = 6), GLE/PIB Dose 200 mg/75 mg	
C_{max}	(ng/mL)	853 (2180, 166)	154 (169, 48)
AUC_{24}	(ng•h/mL)	4080 (9130, 148)	1250 (1580, 85)
C_{trough}	(ng/mL)	7.37 (36.9, 208)	20.6 (38.4, 151)
		Cohort 3 (N = 6), GLE/PIB Dose 160 mg/60 mg	
C_{max}	(ng/mL)	377 (451, 68)	142 (166, 58)
AUC_{24}	(ng•h/mL)	1680 (2100, 64)	987 (1220, 64)
C_{trough}	(ng/mL)	2.35 (2.54, 90)	8.07 (9.77, 60)
		Cohort 4 (N = 5), GLE/PIB Dose 120 mg/45 mg	
C_{max}	(ng/mL)	638 (775, 58)	117 (140, 65)
AUC_{24}	(ng•h/mL)	3030 (3320, 46)	871 (1010, 65)
C_{trough}	(ng/mL)	6.28 (7.76, 68)	9.60 (13.1, 100)

AUC_{24} = area under the plasma concentration-time curve from time 0 to 24 hours; C_{max} = maximum observed plasma concentration; C_{trough} = pre-dose trough plasma concentration; CV = coefficient of variation; GLE = glecaprevir; h = hour; IPK = intensive pharmacokinetic; PIB = pibrentasvir; PK = pharmacokinetic; QD = once daily

After analysis of the pharmacokinetic data following the initial proposed dosing regimen in each cohort of Part 2, both GLE and PIB geometric mean exposures were lower than the targeted adult exposures (geometric mean GLE and PIB AUC24 values of 4800 ng•hr/mL and 1430 ng•hr/mL, respectively). Therefore, both GLE and PIB doses were modified to the final proposed dose ratio of 50 mg GLE + 20 mg PIB. A summary of PK parameters of GLE and PIB at the Week 2 visit after subjects received the final proposed dosing regimens, including the primary PK endpoint (steady-state AUC) and secondary PK endpoints (Cmax and CL/F) in addition to predicted exposures in adolescents and adults is presented in Table 13.

Table 13: Geometric mean (mean, CV%) PK parameters of GLE and PIB (Week 2 IPK) in paediatric subjects of Part 2 of Study M16-123 following the final proposed dosing regimens compared to adolescent subjects of Part 1 (M16-123) and non-cirrhotic adults subjects.

		GLE + PIB QD Pediatric Formulation Week 2	
PK Parameters	**(Units)**	**GLE**	**PIB**
		Cohort 2 (N = 10), GLE/PIB Dose 250 mg/100 mg	
C_{max}	(ng/mL)	1440 (233, 19800)	219 (70.9, 567)
AUC_{24}	(ng•h/mL)	8630 (1130 ,175000)	2290 (539, 8900)
C_{trough}	(ng/mL)	17.0 (1.77, 2630)	40.8 (6.89, 363)
		Cohort 3 (N = 9), GLE/PIB Dose 200 mg/80 mg	
C_{max}	(ng/mL)	1320 (207, 17800)	179 (69.1, 362)
AUC_{24}	(ng•h/mL)	5920 (999, 79000)	1510 (470, 3490)
C_{trough}	(ng/mL)	8.16 (1.44, 404)	20.0 (4.69, 77.6)
		Cohort 4 (N = 10), GLE/PIB Dose 150 mg/60 mg	
C_{max}	(ng/mL)	1280 (185, 13800)	211 (115, 383)
AUC_{24}	(ng•h/mL)	6720 (1080, 55500)	1650 (679, 4050)
C_{trough}	(ng/mL)	6.94 (0.00, 144)	17.5 (2.45, 76.7)
		GLE/PIB QD Adult Formulation Week 2	
		Cohort 1 (N = 14) [a], GLE/PIB Dose 300 mg/120 mg	
C_{max}	(ng/mL)	1040 (245, 3400)	174 (72.2, 248)
AUC_{24}	(ng•h/mL)	4790 (1580, 16300)	1380 (530, 2090)
C_{trough}	(ng/mL)	3.79 (0.00, 8.89)	15.0 (4.69, 27.7)
		Non-Cirrhotic Adults (N=1804), GLE/PIB Dose 300 mg/120 mg	
C_{max}	(ng/mL)	597 (9.98, 25800)	110 (10.2, 678)
AUC_{24}	(ng•h/mL)	4800 (123, 297000)	1430 (148, 14200)
C_{trough}	(ng/mL)	13.0 (0.417, 8770)	18.9 (1.78, 477)

AUC_{24} = area under the plasma concentration-time curve from time 0 to 24 hours; C_{max} = maximum observed plasma concentration; C_{trough} = pre-dose trough plasma concentration; CV = coefficient of variation; GLE = glecaprevir; h = hour; IPK = intensive pharmacokinetic; PIB = pibrentasvir; PK = pharmacokinetic; QD = once daily

a. Summaries of PK parameters based on results from 14 subjects, including 4 Japanese subjects who participated in Japan-specific IPK sampling. Three subjects [redacted] were excluded from the non-compartmental analyses due to unusually low GLE and PIB concentrations at the Week 2 visit.

The results demonstrated that the Week 2 IPK geometric mean exposures of GLE and PIB at the final proposed dosing regimens in HCV-infected non-cirrhotic paediatric subjects in Cohorts 2 – 4 were 1.2 to 1.8 fold and 1.2 to 1.6 fold higher than the GLE and PIB targeted adult exposures (geometric mean GLE and PIB AUC24 values of 4800 ng•hr/mL and 1430 ng•hr/mL, respectively). The range of GLE and PIB exposure in HCV-infected non-cirrhotic paediatric subjects in Cohorts 2 - 4 were within the range of model-predicted exposures in HCV-infected noncirrhotic adult subjects (AUC24 values range from 123 – 297000 ng•hr/mL and 148 – 14200 ng•hr/mL, respectively, for GLE and PIB).

Population PK model

Objective

The objective of this analysis was to characterize the population PK of GLE and PIB when administered in combination in paediatric subjects aged 3 to < 12 years and to identify demographic, physiologic and treatment factors that may contribute to the variability in the PK of GLE and PIB. The results of this analysis will provide justification for selection of the final dose regimens of GLE and PIB in HCV Genotypes 1-6 infected peditaric subjects.

PK dataset

The PPK analysis included PK data from study M16-123 Part 1 (adolescent) and Part 2 (paediatric) only. No PK data from adult subject were included. An overview of the available PK data is presented in

Table 14. Plasma concentrations of GLE and PIB in both populations (adolescent and paediatric) were determined using the same validated assay method.

Table 14: Summary of study included in the PPK

Study (N)	Phase	Study Design and Population	Dose Range and Pharmacokinetic Sampling
M16-123 Part 1 (N = 47)	2/3	A randomized, multicenter, open-label, multiple dose, study of GLE and PIB in pediatric subjects with HCV GT1 – GT6 infection.	**Dose Evaluated in HCV GT1- to GT6-Infected Pediatric Subjects:** GLE/PIB 300 mg/120 mg QD for 8, 12 or 16 weeks. **Intensive Pharmacokinetic (PK) Sampling:** Day 1 at 4 hours post-dose, and Week 2 at 0 (immediately prior to dose), 2, 4, 6 and 12 hours post the dose administered during the visit. **Sparse PK Sampling:** Weeks 4, 8, 12 and 16 (if applicable): single samples during the visit without regard to the time since the last dose.
M16-123 Part 2 (N = 47)	2/3	A randomized, multicenter, open-label, multiple dose, study of GLE and PIB in pediatric subjects with HCV GT1 – GT6 infection.	**Doses Evaluated in HCV GT1- to GT6-Infected Pediatric Subjects*:** **Subject Group** / **GLE + PIB**: **9 - < 12 yr, ≥ 30 to < 45 kg**: 200 mg + 75 mg (Period 1) or 250 mg + 100 mg (Period 2); **6 - < 9 yr, ≥ 20 to < 30 kg**: 160 mg + 60 mg (Period 1) or 200 mg + 80 mg (Period 2); **3 - < 6 yr, 12 to < 20 kg**: 120 mg + 45 mg (Period 1) or 150 mg + 60 mg (Period 2). The above doses were evaluated QD for 8, 12 or 16 weeks. **Intensive Pharmacokinetic (PK) Sampling:** Day 1 at 4 hours post-dose, and Week 2 at 0 (immediately prior to dose), 2, 4, 6 and 12 hours post the dose administered during the visit. **Sparse PK Sampling:** Weeks 4, 8, 12 and 16 (if applicable): single samples during the visit without regard to the time since the last dose.

PK data from 94 subjects who received GLE/PIB in combination that had least one measurable GLE or PIB concentration were included in the PPK analyses. No subjects were excluded. All 47 subjects of Part 1 received the GLE/PIB 300/120 mg tablet formulation QD, whereas the other subjects from Part 2 received GLE/PIB dosing by body weight groups. A summary of the demographic and potential covariates are presented in Table 15.

Table 15: Summary of demographic and intrinsic factors for subjects included in the PPK analyses

Characteristic		Cohort 1 (N = 47)	Cohort 2 (N = 16)	Cohort 3 (N = 16)	Cohort 4 (N = 15)	Total (N = 94)
Age (years)	Mean (SD)	14.3 (1.51)	10.0 (0.89)	7.13 (0.89)	3.60 (0.63)	10.6 (4.27)
	Median	14.0	10.0	7.00	4.00	11.5
	Min – Max	12 – 17	9 – 11	6 – 8	3 – 5	3 – 17
BSA (m^2)	Mean (SD)	1.62 (0.20)	1.21 (0.10)	0.92 (0.07)	0.64 (0.05)	1.28 (0.41)
	Median	1.62	1.21	0.91	0.64	1.33
	Min – Max	1.1 – 2.3	1.1 – 1.4	0.81 – 1.0	0.56 – 0.73	0.56 – 2.3
Body Weight (kg)	Mean (SD)	59.2 (14.1)	37.5 (4.47)	24.5 (3.20)	15.3 (1.45)	42.6 (20.6)
	Median	57.7	36.9	23.6	15.2	43.0
	Min – Max	32.0 – 108.9	29.6 – 44.3	20.0 – 29.4	12.7 – 18.0	12.7 – 108.9
Genotype	1, N (%)	37 (78.7%)	12 (75%)	13 (81.3%)	11 (73.3%)	73 (77.7%)
	2, N (%)	3 (6.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.2%)
	3, N (%)	4 (8.5%)	4 (25%)	2 (12.5%)	4 (26.7%)	14 (14.9%)
	4, N (%)	3 (6.4%)	0 (0.0%)	1 (6.2%)	0 (0.0%)	4 (4.2%)
	5, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	6, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nationality	Non-Japanese, N (%)	43 (91.5%)	16 (100%)	16 (100%)	15 (100%)	90 (95.7%)
	Japanese, N (%)	4 (8.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (4.3%)
Race	White, N (%)	35 (74.5%)	12 (75%)	13 (81.3%)	11 (73.3%)	71 (75.5%)
	Black, N (%)	4 (8.5%)	1 (6.3%)	0 (0.0%)	1 (6.7%)	6 (6.4%)
	Asian, N (%)	6 (12.8%)	1 (6.3%)	2 (12.5%)	1 (6.7%)	10 (10.6%)
	Other, N (%)	2 (4.2%)	2 (12.5%)	1 (6.2%)	2 (13.3%)	7 (7.5%)
Sex	Male, N (%)	21 (44.7%)	7 (43.8%)	5 (31.3%)	6 (40.0%)	39 (41.5%)
	Female, N (%)	26 (55.3%)	9 (56.2%)	11 (68.7%)	9 (60.0%)	55 (58.5%)
Treatment Experience	Naive, N (%)	36 (76.6%)	16 (100%)	16 (100%)	15 (100%)	83 (88.3%)
	Experienced, N (%)	11 (23.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (11.7%)

HIV Co-infection	No HIV-infection, N (%)	45 (95.7%)	16 (100%)	16 (100%)	15 (100%)	92 (97.9%)
	HIV co-infection, N (%)	2 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
Cirrhosis	Without cirrhosis, N (%)	47 (100%)	16 (100%)	16 (100%)	15 (100%)	94 (100%)
	With compensated cirrhosis, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal Function	Normal, N (%)	46 (97.9%)	16 (100%)	16 (100%)	15 (100%)	93 (98.9%)
	Mild impairment, N (%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
	Moderate impairment, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe impairment, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

SD = standard deviation; Min = minimum; Max = maximum; BSA = Body Surface Area; HIV = Human Immunodeficiency Virus

Results

PK data handling

PPK analyses

All HCV-infected subjects who received GLE/PIB combination as part of treatment in Part 1 and Part 2 from study M16-123, and who had at least one measurable concentration of GLE or PIB were included in the PPK analyses.

However several PK samples were flagged and excluded from the PPK analysis:

- Observed plasma concentrations (≥ LOQ) that were observed prior to the first dose

- 1 subject from cohort 4 (3 to <6 y) was partially dosed, discontinued from the study, and had no GLE or PIB plasma concentration measurements

- Visit week 2 PK data of 3 subjects from cohort 1 (Adolescent), due to unusual PK profiles

These 3 subjects along with 1 subject from Cohort 3 which received a double dose on the day of week 2 was excluded for both PPK and NCA analyses.

- Observed concentrations below the LLOQ

- Outlying measurements

Overall, a total of 34 out 95 subjects were excluded for the NCA analysis. Out of these 34 subjects, 30 had only sparse PK samples (Cohort 1), 3 subjects have unusual PK concentrations (Cohort 1) and 1 subject received twice the designated dose on week 2 day 1.

BQL data

All the plasma concentration below LLOQ that was observed prior to the first dose were flagged and excluded (4 GLE and 4 PIB concentrations).

The first individual plasma concentration below the LLOQ following a non-BLQ observation between two consecutive doses was set to half the LOQ (LLOQ/2), and included in the dataset (25 GLE and 3 PIB).

All subsequent observation BLQ:

- prior to the next non-BLQ observations and prior to the next dose

- with time since last dose > 7 days were set to LLOQ/2 and excluded (1 GLE and 1 PIB).

Outlying measurement

On the basis of visual inspection of concentration and time since last dose relationship, trough plasma concentrations (recorded at times greater than 21.6 hours (0.9 days) after the administration of dose) measured 45 days or more after the start of the study were excluded from analysis (26 out of 262 (PART 1) and 24 out of 375 (PART 2) for both GLE and PIB observations).

In total, 11% of the overall observed concentrations were discarded. Moreover, given the small number of BQL (less than 5%), it is agreed with the applicant that there is limited insight when exploring additional BLQ handling methods.

Based on the Nonmem code GLE and PIB PK dataset consisted of 94 patients and 567 observations.

GLE PPK model development

A one-compartment PK model with first-order absorption and elimination adequately described the GLE concentration-time data. A two-compartment model was not supported by the data. The model was parameterized in terms of CL/F, V2/F, and absorption rate constant (KA). Based on the results from the Study M17-142, differences in the relative bioavailability (F1) between the adult and paediatric formulations was parameterized and fixed for paediatric subjects in Part 2 and for adolescent subjects in Part 1. In order to avoid flip-flop behavior, the absorption rate constant was parameterized to constrain it to be greater than the elimination rate constant (K = CL/V2). Body weight (BW) allometric scaling of clearance and volume was treated as part of the structural base model. Using body surface area instead of body weight for allometric scaling of CL/F and V2/F led to indifferent results. As body weight is a more convenient body measure, it was kept as part of the base model. All structural parameters were estimated with acceptable precision (RSE <30%). Correlated random effects were included for CL/F and V2/F to describe inter-individual variability. A proportional error model was used to describe the residual error. The summary of model selection is presented in **Error! Reference s ource not found.** and final PK parameter estimates in Table 16.

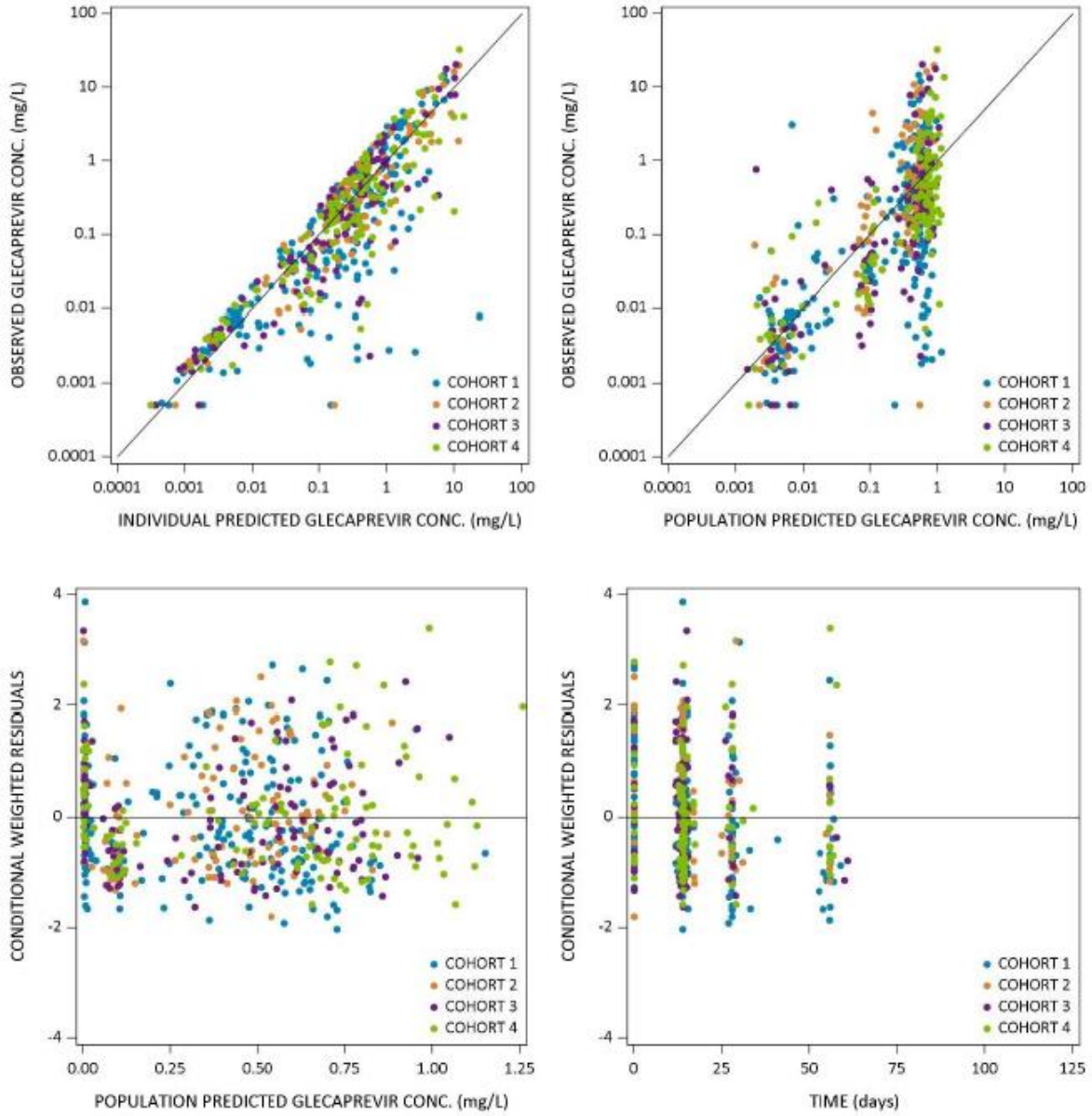
The CV of IIV for CL/F and V2/F were 194% and 200% with ETA-shrinkage of 2 and 2.9% respectively. Except BW which was considered in the base structure PK model, no other covariates was found significant. BW exponent on CL/F and V2/F were estimated respectively at 0.944 and 1.04.

Table 16: Parameter estimates and variability of GLE PK: Base and Final PK model

	Population Value (θ)			Inter-Individual Variability (ω^2)		
Parameter	**Estimate (SEE)**	**%RSE**	**95% Confidence Interval**	**Variance (%CV)**	**% RSE**	**95% Confidence Interval**
CL/F (L/day)[a]	1850 (394)	21.4	1230 - 2770	1.56 (194)	16.9	1.04 - 2.08
V2/F (L)[a]	344 (87.7)	25.5	213 - 555	1.61 (200)	15.7	1.11 - 2.11
Absorption Factor[b]	3.66 (0.482)	13.2	2.72 - 4.60	--	--	--
Formulation (Part 2) on F1	0.800 (FIX)	-	-	--	--	--
Body Weight on CL/F	0.944 (0.217)	23.0	0.519 - 1.37	--	--	--
Body Weight on V2/F	1.04 (0.242)	23.3	0.566 - 1.51	--	--	--
Derived Absorption Rate Constant KA (1/day)[b]	19.6 (NA)	-	-	--	--	--
	Residual Variability (σ^2)					
Parameter	**Estimate (SEE)**	**%RSE**	**95% Confidence Interval**			
σ_1^2 (Proportional)	0.580 (0.0366)	6.31	0.508 - 0.652	--	--	--

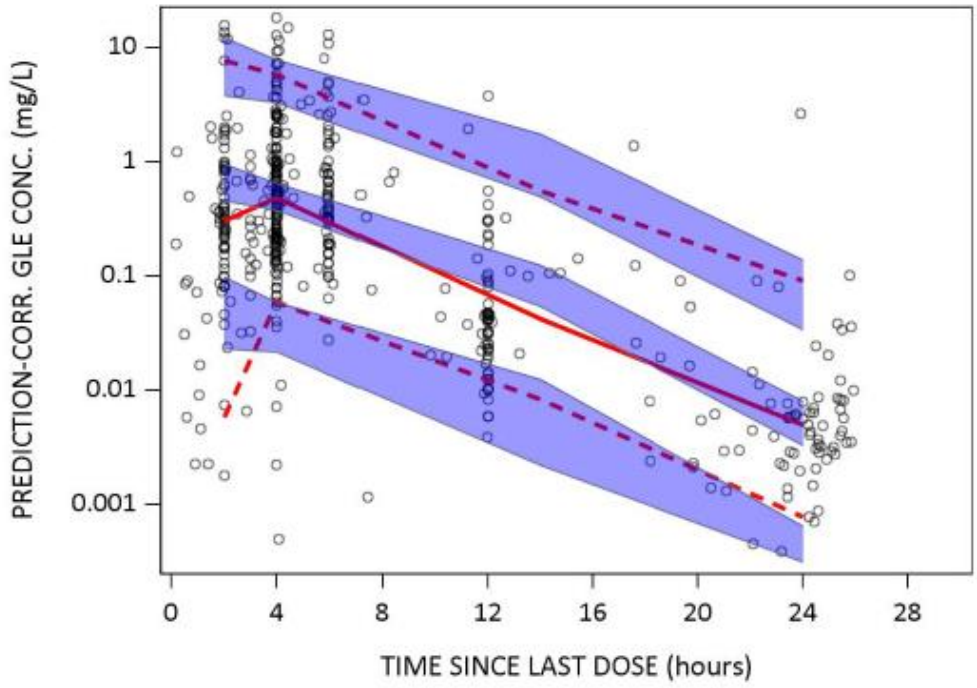
The GOF for the final model are presented in Figure 3. On a log-scale, DV vs IPRED show that most values lay near the line of identity, indicating that the model adequately described the observations over the entire GLE plasma concentration range (and by cohort). The CWRES vs PRED or vs TIME does not show a particular trend.

Figure 3: Goodness-of-fit plots of final GLA PK model



Model evaluation was performed using a pcVPC, presented in Figure 4. Overall the variability in the observed data is described with reasonable accuracy and the central tendency of the data is well described. Finally, a bootstrap analysis was performed with satisfactory results.

Figure 4: pcVPC of GLE concentration vs time since last dose

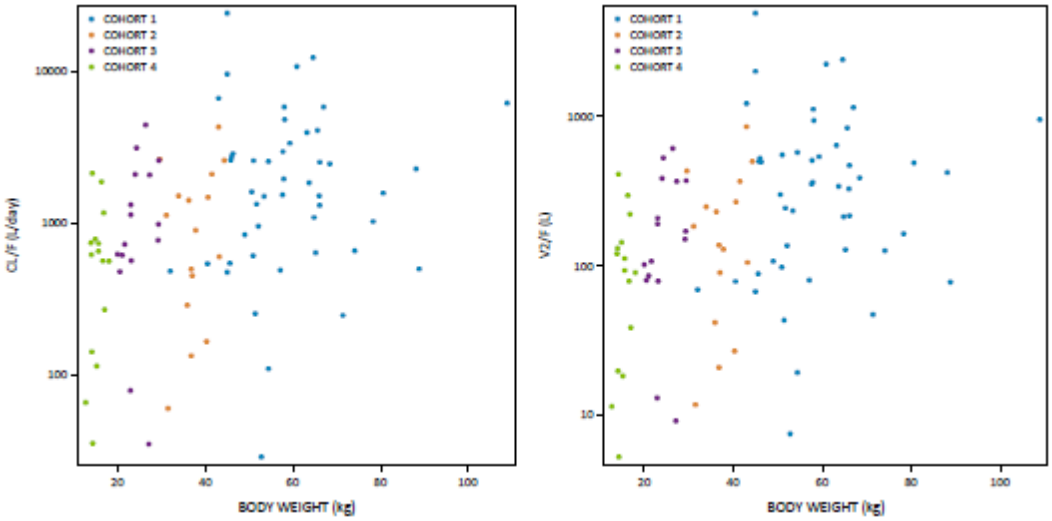


The shaded blue areas represent the 90% prediction interval of the 5th, 50th and 95th percentiles of simulated GLE concentrations, the solid red line represents median of observed GLE concentrations and dashed red lines represent the 5th and 95th percentile of the observed GLE concentrations. The open circles represent observed GLE concentrations.

Note: VPCs are cut at 24 hours after last dose, as data are too sparse beyond.

Body weight ranged 12.7 – 108.9 kg across all subjects included in this analysis, with a median of 43 kg. Body weight based allometric scaling of apparent clearance (CL/F) and apparent volume of distribution of the central compartment (V2/F) was included as a structural covariate as part of the base model. The scatterplots for the correlations between CL/F and V2/F vs. body weight are showed in Figure 5. The lack of any trends in ETA plots for CL/F and V2/F vs. body weight showed that adding body weight in the model did not introduce any bias.

Figure 5: scatterplot of the Post hoc CL/F and V2/F vs BW for GLE



PIB PPK model development

A two-compartment PK model with first order absorption and elimination, including a lag in absorption time adequately described the PIB concentration-time data. A two-compartment model was more appropriate in describing the observed data than a one compartment model. The model was parameterized in terms of CL/F, V2/F, KA, apparent inter-compartmental clearance (Q/F), apparent volume of distribution of the peripheral compartment (V3/F) and absorption lag time (ALAG1). Based on the results from Study M17-142, the difference in the relative bioavailability (F1) between the two formulations was parameterized and fixed for paediatric subjects (Part 2) and for adolescent subjects (Part 1). In order to avoid flip-flop behavior, the absorption rate constant was parameterized to constrain it to be greater than the elimination rate constant (K = CL/V2). Body weight allometric scaling of clearance and volume was treated as part of the structural base model. Using body surface area instead of body weight for allometric scaling of CL/F and V2/F led to indifferent results. As body weight is a more convenient body measure, it was kept as part of the base model. All structural parameters were estimated with acceptable precision. Correlated random effects were included for CL/F and V2/F to describe inter-individual variability. A proportional error model was used to describe the residual error. Final PK parameter estimates are provided in Table 17.

The CV of IIV for CL/F and V2/F were 64.4% and 45.9% with ETA-shrinkage of 4.6% and 8.3% respectively. Except BW which was considered in the base structure PK model, no other covariates was found significant. BW exponent on CL/F and V2/F were estimated respectively at 0.402 and 0.728.

Table 17: Parameter estimates and variability for PIB PK: Base and Final Model

	Population Value (θ)			Inter-Individual Variability (ω^2)		
Parameter	Estimate (SEE)	%RSE	95% Confidence Interval	Variance (%CV)	%RSE	95% Confidence Interval
CL/F (L/day)[a]	2170 (236)	10.9	1750 - 2680	0.347 (64.4)	22.1	0.196 - 0.498
V2/F (L)[a]	503 (92.2)	18.3	354 - 714	0.191 (45.9)	31.3	0.0738 - 0.308
Q/F (L/day)[a]	829 (113)	13.6	637 - 1080	--	--	--
V3/F (L)[a]	4920 (2070)	42.1	2340 - 10300	--	--	--
ALAG1 (days)	0.0550 (0.00261)	4.74	0.0502 - 0.0604	--	--	--
Absorption Factor[b]	2.16 (0.450)	20.8	1.28 - 3.04	--	--	--
Formulation (Part 2) on F1	1.20 (FIX)	-	-			
Body Weight on CL/F	0.402 (0.119)	29.6	0.169 - 0.635	--	--	--
Body Weight on V2/F	0.728 (0.128)	17.6	0.477 - 0.979	--	--	--
Derived Absorption Rate Constant KA (1/day)[b]	9.30 (NA)	-	-	--	--	--
	Residual Variability (σ^2)					
Parameter	Estimate (SEE)	%RSE	95% Confidence Interval			
σ_1^2 (Proportional)	0.236 (0.0189)	8.01	0.199 - 0.273	--	--	--

The GOF for the final model are presented in Figure 6. On a log-scale, DV vs IPRED show that most values lay near the line of identity, indicating that the model adequately described the observations over the entire GLE plasma concentration range (and by cohort). The CWRES vs PRED or vs TIME does not show a particular trend.

Model evaluation was performed using a pcVPC, presented in Figure 7. Overall the variability in the observed data is described with reasonable accuracy and the central tendency of the data is well described. Finally a bootstrap analysis was performed with satisfactory results.

Figure 6: GOF of Final PIB PK model

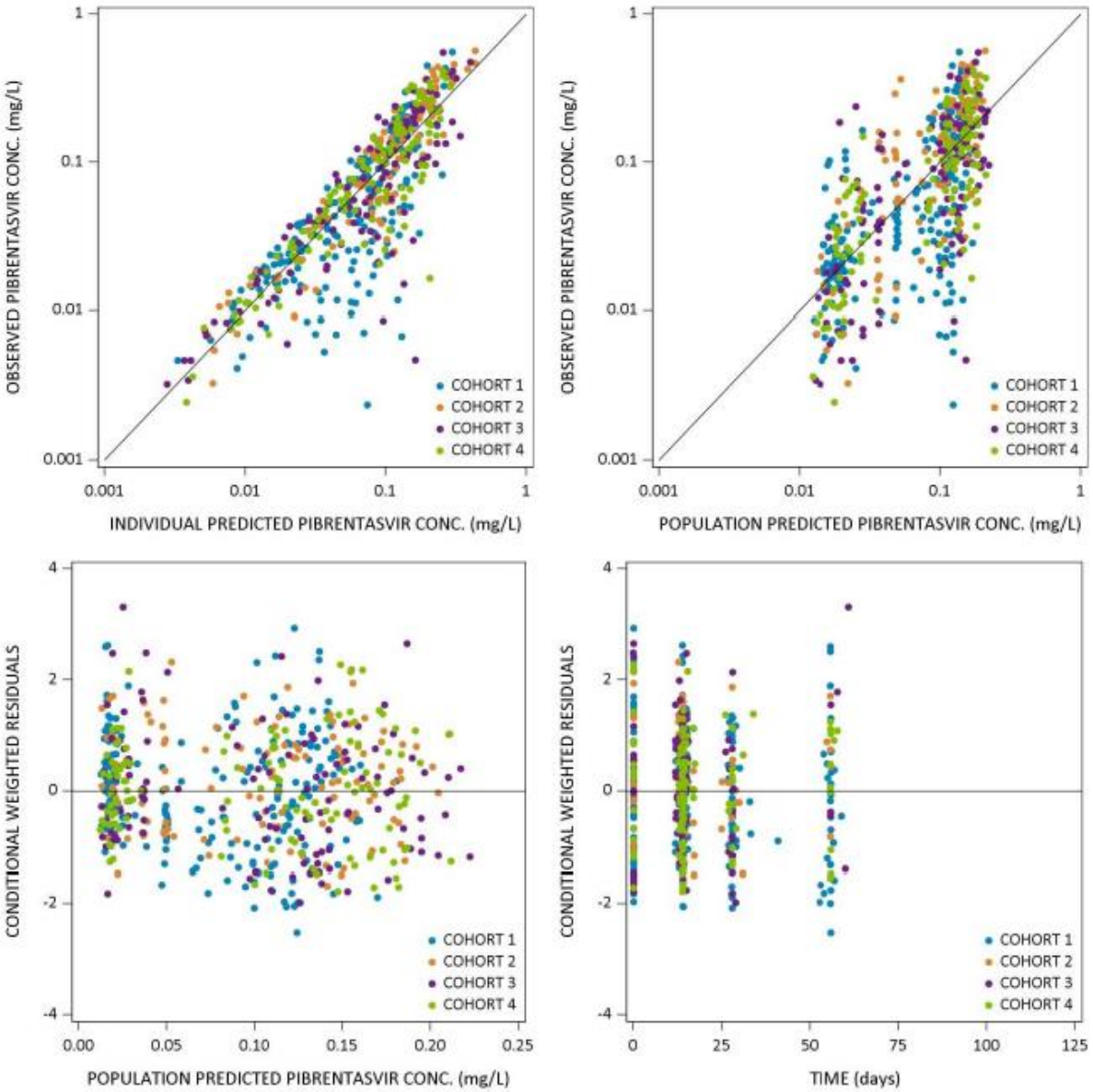
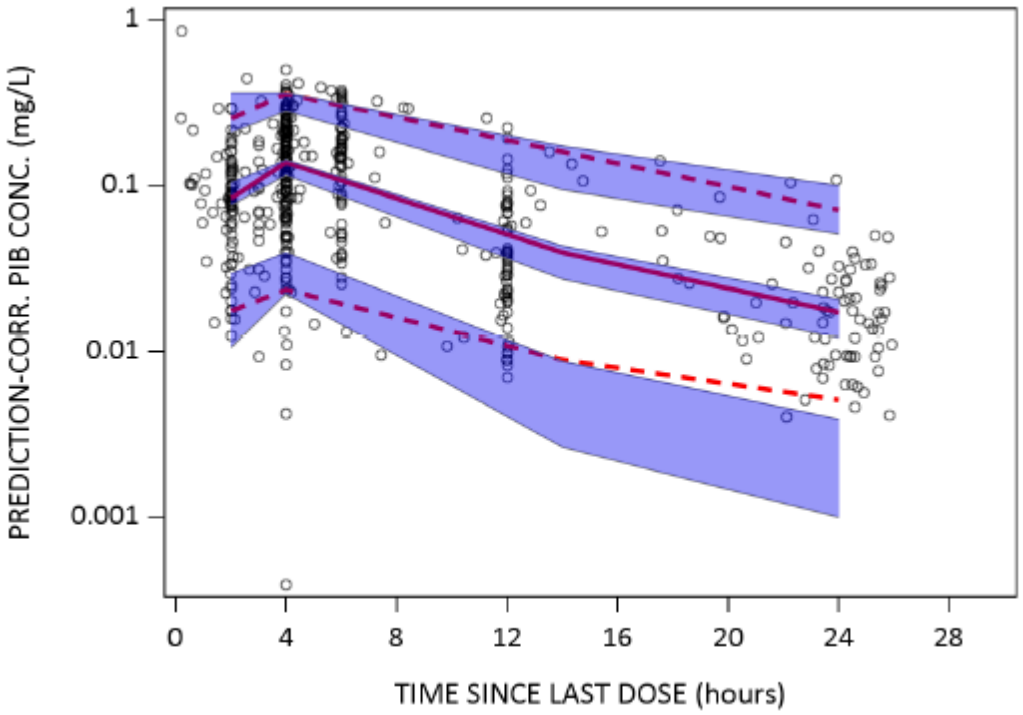
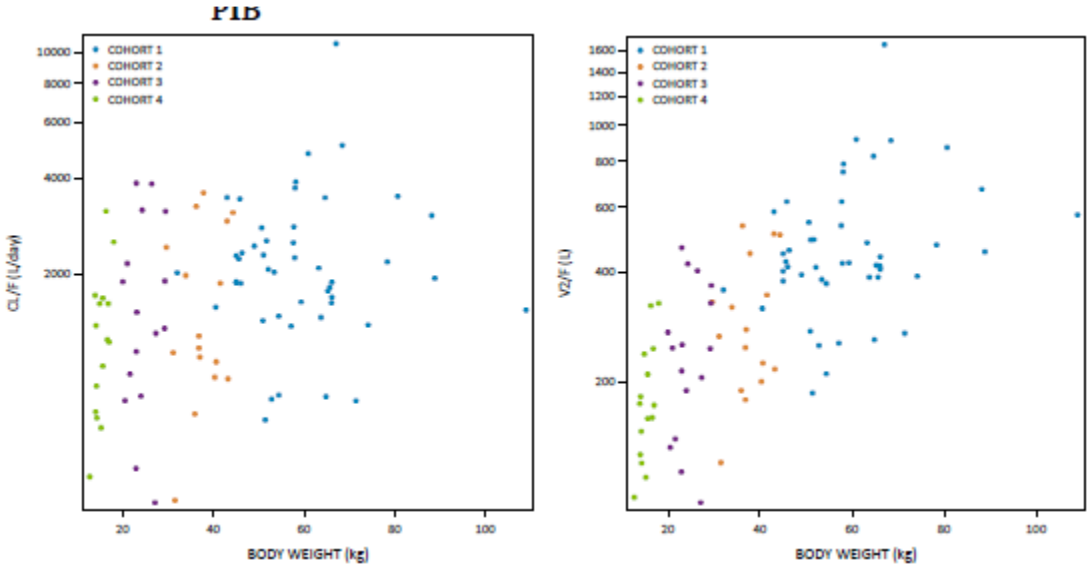


Figure 7: pcVPC of PIB concentration vs time since last dose



Body weight ranged 12.7 – 108.9 kg across all subjects included in this analysis, with a median of 43 kg. Body weight based allometric scaling of apparent clearance (CL/F) and apparent volume of distribution of the central compartment (V2/F) was included as a structural covariate as part of the base model. The scatterplots for the correlations between CL/F and V2/F vs. body weight are shown in Figure 8. The lack of any trend in ETA plots for CL/F and V2/F vs. body weight showed that adding body weight in the model did not introduce any bias.

Figure 8: Scatterplot of the Post-hoc CL/F and V2/F vs BW



Two PPK models for GLE and PIB were developed based on PK data from study M16-123 only, from which derived PK parameters (AUC24 at week 2) were compared a) to AUC24 adult targets, b) to AUC24 estimated by NCA. Then PK simulations were performed considering GLE and PIB body weight

based dosing to justify the selected dose. To this end adequate PPK models for both compounds are needed.

An update of both PPK models was requested in order to solve many issues (dose non-linearity, flip-flop kinetics, inadequate structural PK model, estimation of relative bioavailability…), however even if significant efforts were provided, the PPK models were not updated, therefore results from the simulation exercise are still not considered reliable. As a consequence, the PK similarity based on exposures between children and adult/adolescent, as claimed by the Applicant in the SmPC cannot be endorsed on this basis.

Comparison of GLE and PIB exposures in paediatric, in adolescent and adults

Based on *post hoc* final model pharmacokinetic parameters, the GLE and PIB geometric mean exposures (steady-state area under the plasma concentration-time curve from time zero to 24 hours post-dose [AUC24]) were derived for the 46 HCV-infected paediatric and 14 HCV-infected adolescent subjects with intensive PK sampling. Here, 29 out of 46 subjects that were administered the adjusted dosing (Period 2) are discussed. Geometric mean AUC24 for subjects from 3 to < 6 years of age were 8990 ng•hr/mL and 1760 ng•hr/mL, for subjects from 6 to < 9 years of age were 5160 ng•hr/mL and 1730 ng•hr/mL and for subjects from 9 to < 12 years of age were 8120 ng•hr/mL and 2360 ng•hr/mL, for GLE and PIB respectively. The GLE and PIB geometric mean AUC24 estimated for the adolescent subjects, using the final PK model that included body weight based allometric scaling and relative bioavailability to compensate for different formulation, were 4940 ng•hr/mL and 1530 ng•hr/mL and comparable to the previously obtained 4380 ng•hr/mL and 1440 ng•hr/mL using a PK model based on adolescent subjects only.

The paediatric geometric mean AUC24 values are somewhat higher by (≤ 87% for GLE, ≤ 65% for PIB) than the reported geometric mean GLE and PIB AUC24 values of 4800 ng•hr/mL and 1430 ng•hr/mL, respectively, in HCV-infected non-cirrhotic adults receiving 300 mg/120 mg approved formulation (R&D/16/0234). Since GLE has high variability in exposures and PIB has moderate to high variability in exposures, the estimated GLE and PIB geometric mean exposures for paediatric subjects are still acceptable. Moreover, the predicted GLE and PIB exposure ranges in HCV-infected paediatric subjects were within the exposure ranges of GLE and PIB in HCV-infected noncirrhotic adults (Table 18).

Table 18: Model-predicted GLE and PIB steady-state AUC24 in HCV infected paediatric (Period 2 only), adolescent and adults

Population	GLE/PIB 300 mg/120 mg QD Adult Formulation Geometric Mean (%CV) [Range]	
	GLE AUC_{24} (ng•hr/mL)	PIB AUC_{24} (ng•hr/mL)
	Results of the Updated Model	
HCV-infected adolescents Cohort 1 (12 – < 18 years, ≥ 45 kg, N = 44)	4940 (195) [303 - 262000]	1530 (53.6) [304 - 4360]
HCV-infected pediatric in Cohort 2, Period 2 (9 – < 12 years, 30 - < 45 kg, N = 10)	8120 (189) 1140 – 82600	2360 (77.5) [904 - 7700]
HCV-infected pediatric in Cohort 3, Period 2 (6 – < 9 years, 20 < 30 kg, N = 9)	5160 (141) [1230 - 49500]	1730 (71.8) [677 - 4960]
HCV-infected pediatric in Cohort 4, Period 2 (3 – < 6 years, 12 < 20 kg, N = 10)	8990 (244) [1380 - 81200]	1760 (55.2) [626 - 3960]
	Results of the Previous Model	
HCV-infected adolescents (12 to < 18 years, N = 47)	4370 (157) [268 – 70300]	1440 (47.3) [428 – 3380]
HCV-infected non-cirrhotic adults (N = 1804)	4800 (122) [123 – 297000]	1430 (57.2) [148 – 14200]

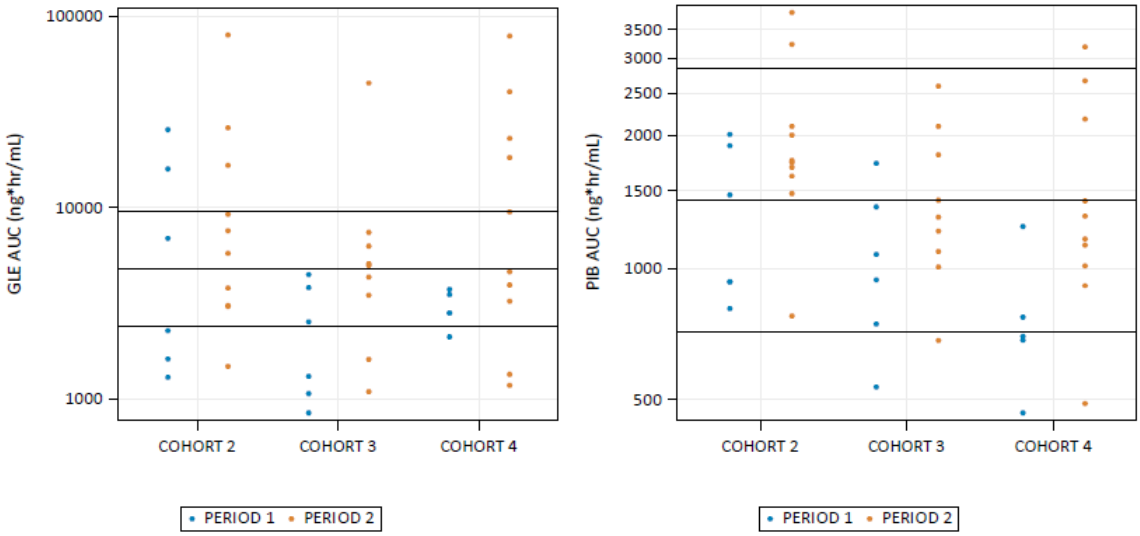
AUC_{24} = area under the plasma concentration-time curve from time 0 to 24 hours at steady-state; CV = coefficient of variation, calculated as $\%CV = 100 \cdot \sqrt{e^{[\sigma\,(\ln(P))]^2} - 1}$, where σ is the standard deviation and P is the pharmacokinetic parameter of interest; QD = once daily; Range = minimum to maximum value of the pharmacokinetic parameter of interest. Subjects 112001, 112002, 112003 had unusual PK profiles, and 311605 had duplicate dosing on Day 2. All of these four subjects were excluded from the calculations.

In addition comparison between model predicted steady state GLE and PIB AUC24 values from subjects in Period 1 (initial dose) that were administered GLE+PIB dose of 200/75 mg (Cohort 2), 160/60 mg (Cohort 3) and 120/45 mg (Cohort 4) and subjects in Period 2 which received GLE/PIB dose 250/100 mg, 200/80 mg and 150/60 mg, respectively, are provided in Figure 9.

Subjects in Period 2, in general, show higher exposures as compared to the subjects in Period 1. GLE exposures in Period 2 lie within the target AUC range of 2400-9600 ng.h/mL, however they are some rather high exposures predicted in Cohort 2 and Cohort 4.

PIB exposures in Period 2 lie within the target AUC range of 715-2860 ng.h/mL, with only a few lying outside the range.

Figure 9: Comparison between model-predicted GLE and PIB steady-state AUC24 by period



Dashed lines show the target GLE AUC range of (2400-9600) ng•hr/mL and target PIB AUC range of (715 – 2860) ng•hr/mL

Comparison of GLE and PIB exposures from NCA and PPK in paediatrics and in adolescents

Individual predicted GLE and PIB exposures (steady-state area under the plasma concentration-time curve from time zero to 24 hours post-dose [AUC24]) based on *post-hoc* final model pharmacokinetic parameters for subjects with intensive pharmacokinetic sampling were comparable to the observed individual GLE and PIB AUC24 based on non-compartmental analysis (NCA) (Figure 10 and Table 19).

Figure 10: Comparison between model-predicted and NCA GLE and PIB steady-state AUC24

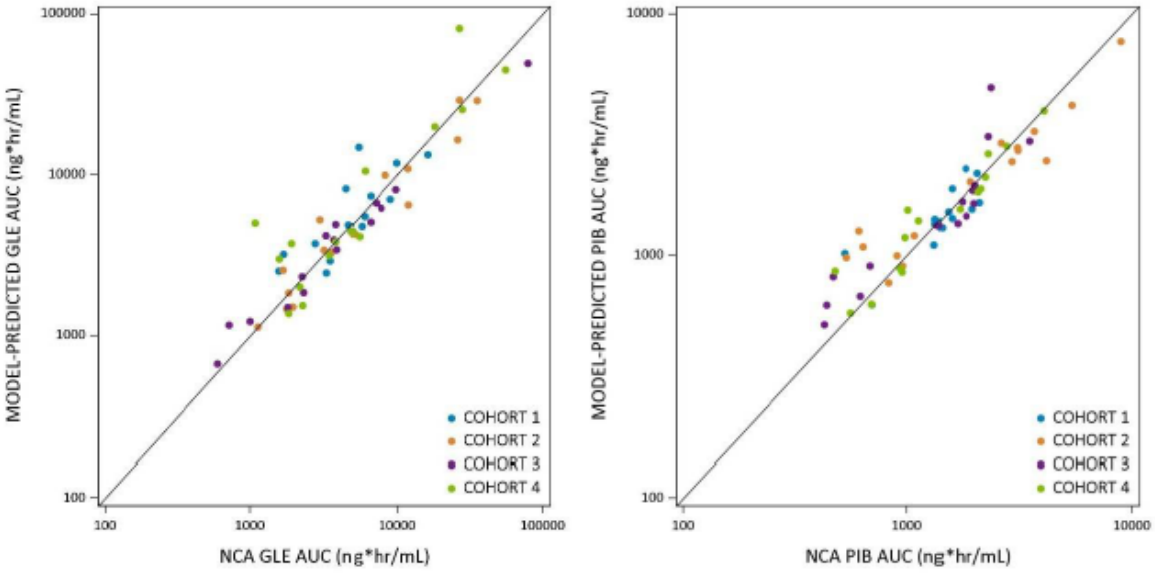


Table 19: NCA AUC24 in HCV-infected paediatric and adolescent patients

	Dose(mg) GLE/PIB	N	GLE AUC_{24} (ng•hr/mL) Geometric Mean (%CV) [Range]	PIB AUC_{24} (ng•hr/mL) Geometric Mean (%CV) [Range]
HCV-infected adolescents Cohort 1 with IPK (12 – < 18 year, ≥ 45 kg)	300/120	14	4790 (67.1) [1580 - 16300]	1380 (30.6) [530 - 2090]
HCV-infected pediatric in Cohort 2 (9 – < 12 year, 30 - < 45 kg)	200/75	6	4080 (148) [1680 - 35500]	1250 (84.7) [611 - 4160]
	250/100	10	8630 (201) [1130 - 175000]	2290 (79.2) [539 - 8900]
HCV-infected pediatric in Cohort 3 (6 – < 9 year, 20 - < 30 kg)	160/60	6	1680 (63.6) [596 - 3870]	987 (63.7) [430 - 1990]
	200/80	9	5920 (185) [999 - 79000]	1510 (52.4) [470 - 3490]
HCV-infected pediatric in Cohort 4 (3 – < 6 year, 12 - < 20 kg)	120/45	5	3030 (46.0) [1580 - 5490]	871 (64.8) [479 - 2110]
	150/60	10	6720 (121) [1080 – 55500]	1650 (54.5) [679 - 4050]

IPK = Intensive PK

Simulated GLE and PIB exposures in paediatrics

10000 virtual subjects were simulated with GLE and PIB body weight-based dosing. The GLE and PIB exposures (steady-state AUC24) for each individual were simulated using the final adolescent and paediatric PK models. The geometric mean of the simulated GLE and PIB AUC24 for paediatrics (Table 20) is ≤ 15% higher for both GLE and PIB than the reported geometric mean GLE and PIB AUC24 values of 4800 ng•hr/mL and 1430 ng•hr/mL, respectively, in HCV-infected non-cirrhotic adults receiving 300 mg/120 mg approved formulation (R&D/16/0234).

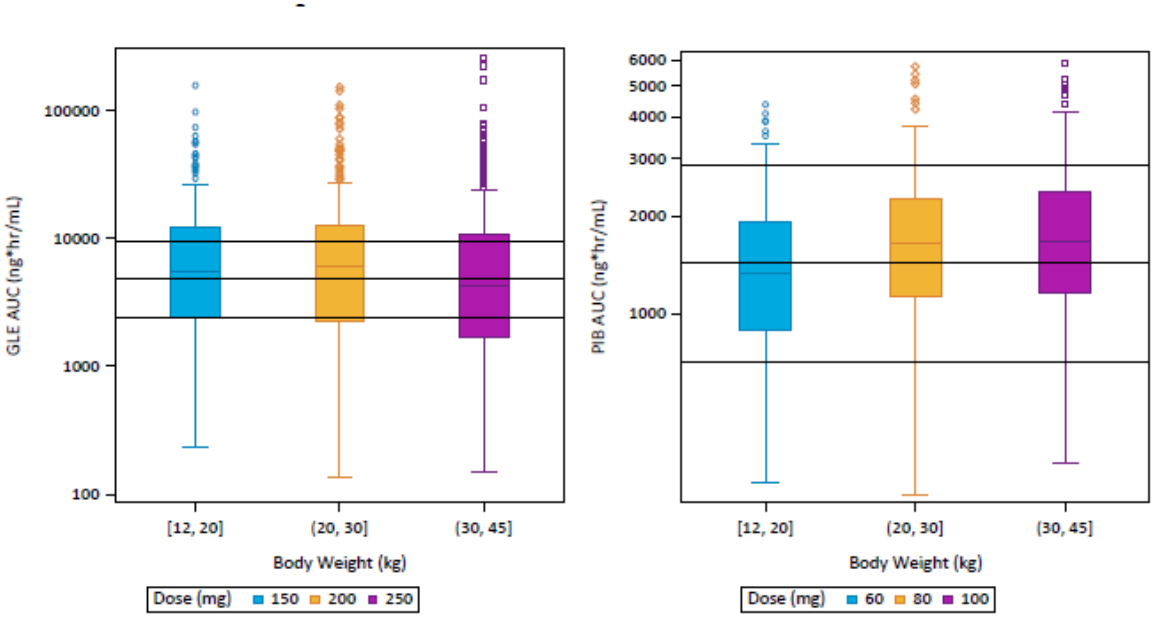
Table 20: Simulated GLE and PIB steady-state AUC24 by BW

Body Weight (kg)	Dose (mg)	Geometric Mean (P5, P95)	%Subjects	
		GLE AUC_{24ss} (ng•hr/mL)	GLE AUC_{24ss} < 2400 ng•hr/mL	GLE AUC_{24ss} > 9600 ng•hr/mL
[12, 20]	150	5520 (669, 43200)	26.3	33.2
[20, 30]	200	5440 (640, 42100)	26.0	34.3
[30, 45]	250	4300 (522, 35600)	33.0	27.2
		PIB AUC_{24ss} (ng•hr/mL)	PIB AUC_{24ss} < 715 ng•hr/mL	PIB AUC_{24ss} > 2860 ng•hr/mL
[12, 20]	60	1300 (523, 2740)	14.2	3.64
[20, 30]	80	1580 (674, 3250)	7.92	10.0
[30, 45]	100	1630 (661, 3580)	5.58	12.8

Cross reference: Table 14.10__1.2, Table 14.10__2.2

The distribution of AUC24 by body weight groups in Figure 11 shows that most of the simulated individuals show exposure within the range of (0.5 × AUC24adult, 2 × AUC24adult). Thus, the selected body weight group-based dosing is most likely to result in paediatric exposures similar to the exposures that are shown to be safe and efficacious in adults.

Figure 11: Simulated GLE and PIB steady-state AUC24 by body weight group

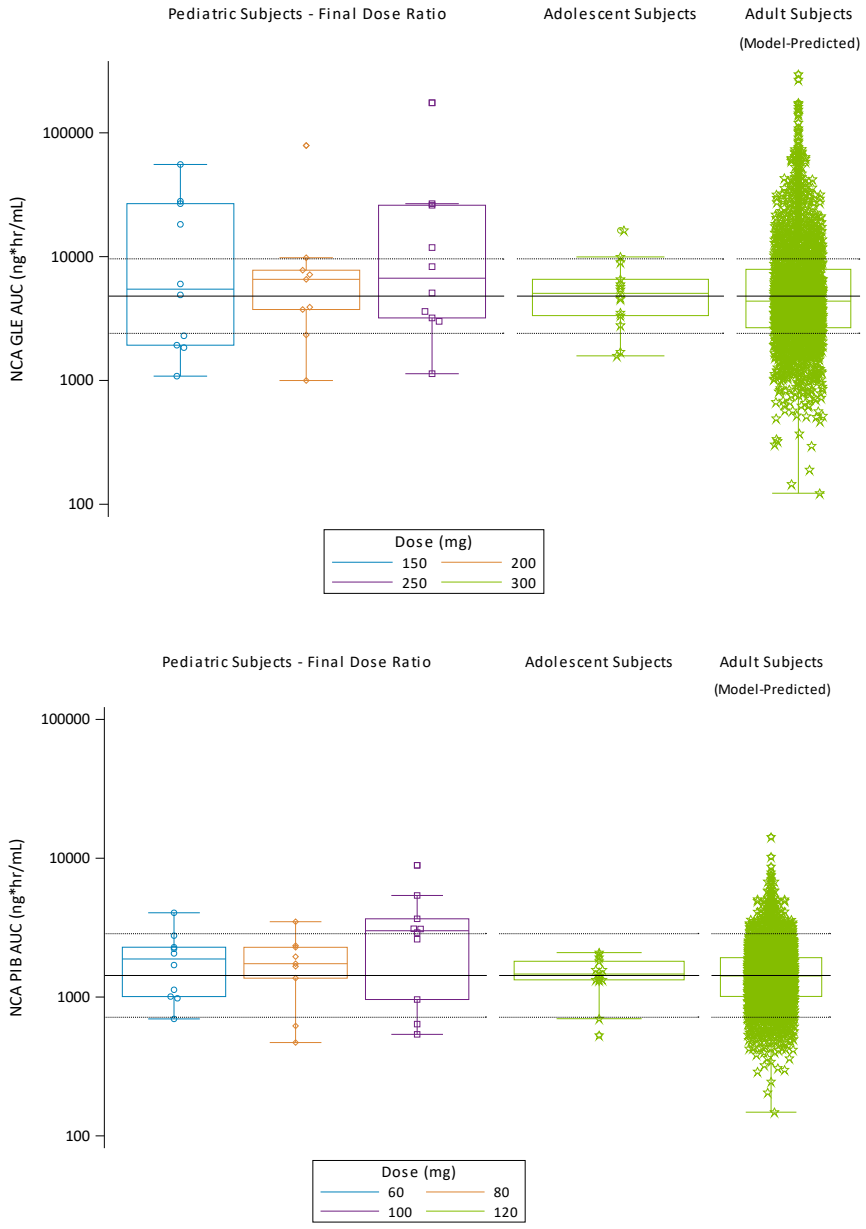


Dashed lines show the target GLE AUC range of (2400 – 9600) ng•hr/mL and target PIB AUC range of (715 – 2860) ng•hr/mL.

Observed exposure metrics (paediatric) vs Predicted exposure metrics (adults)

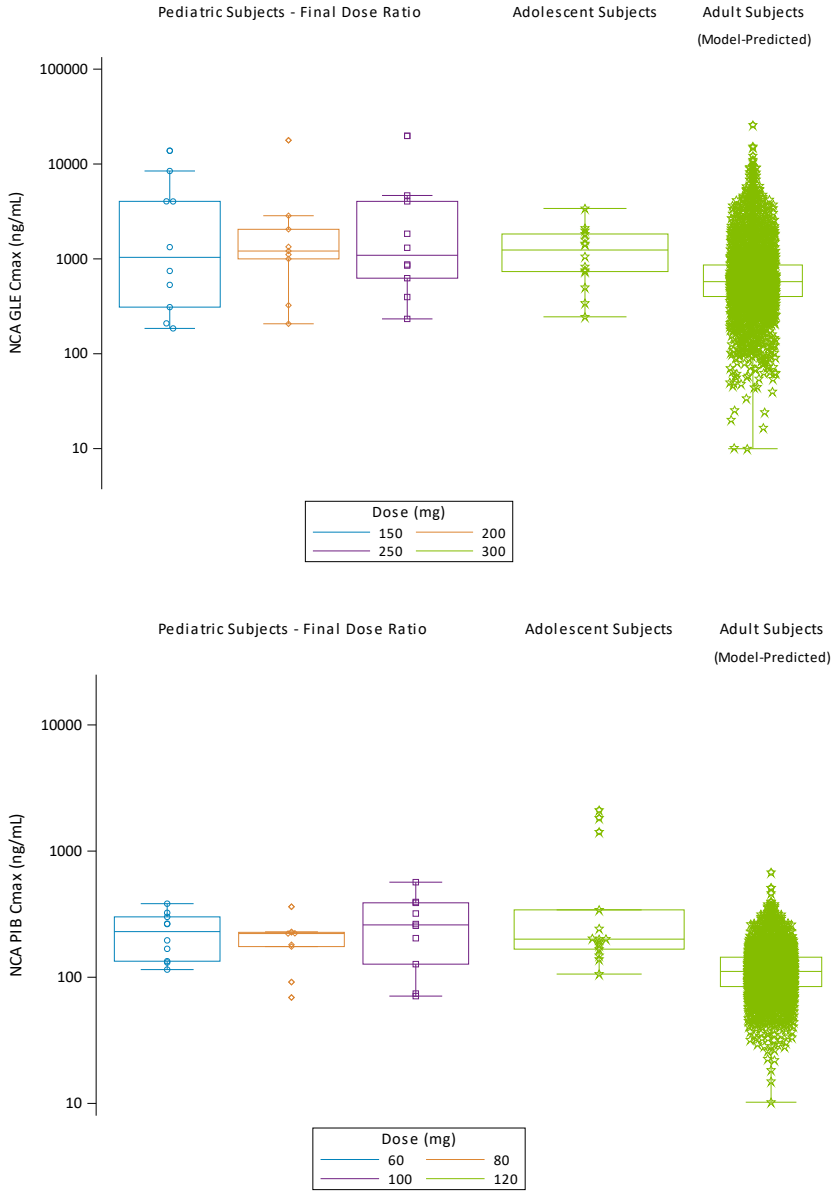
Results from the observed GLE and PIB exposures in children aged 3 to < 12 years range fall within the safe and efficacious exposure range seen in adults (as illustrated in the requested boxplots in Figure 12, Figure 13, and Figure 14 below; there was sparse-sampling in adults, accordingly model-predicted PK parameters are provided), and there were no safety concerns observed in the paediatric subjects. In addition, there was no observed virologic failure in children aged 3 to < 12 years treated with the proposed dosing regimen.

Figure 12: Comparison of Observed NCA GLE and PIB AUC_{24} in Paediatrics and Adolescents with Model-Predicted AUC_{24} in Adults



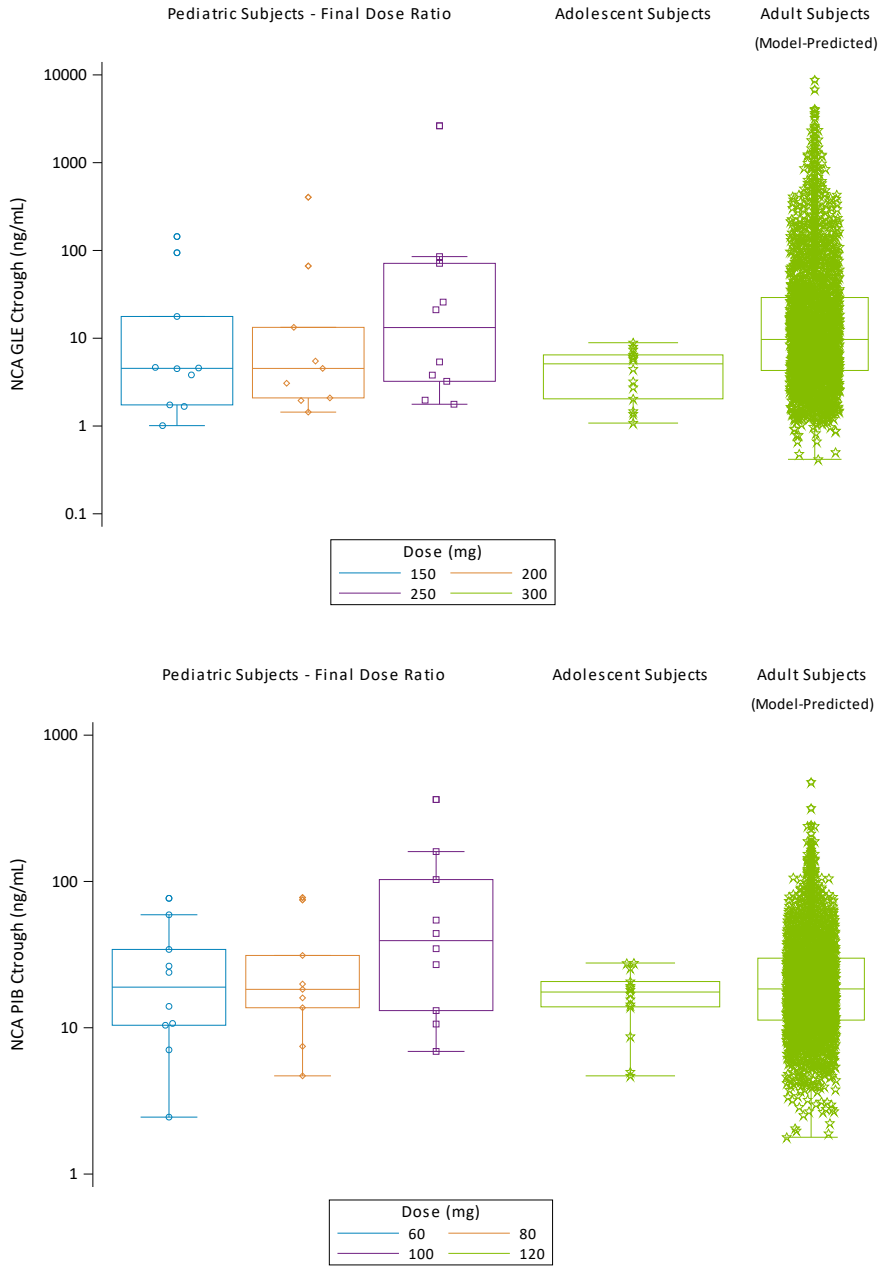
Boxplots show the distribution of observed NCA AUC_{24} in paediatrics and adolescents and model-predicted AUC_{24} in adults overlaid by individual data. Dashed lines show the target GLE AUC range of (2400 - 9600) ng•hr/mL and target PIB AUC range of (715 – 2860) ng•hr/mL.

Figure 13: Comparison of Observed NCA GLE and PIB C_{max} in Paediatrics and Adolescents with Model-Predicted C_{max} in Adults



Boxplots show the distribution of observed NCA Cmax in paediatrics and adolescents and model predicted Cmax in adults overlaid by individual data.

Figure 14: Comparison of Observed NCA GLE and PIB C_{trough} in Paediatrics and Adolescents with Model-Predicted C_{trough} in Adults



Boxplots show the distribution of observed NCA C_{trough} in paediatrics and adolescents and model predicted C_{trough} in adults overlaid by individual data.

2.4.3. Discussion on clinical pharmacology

Glecaprevir / pibrentasvir, formulated as a fixed dose film-coated bilayer tablet (100 mg/40 mg tablet) is currently approved for the treatment of chronic HCV infection (genotype 1 to 6) in adult and adolescents (12 to < 18 years of age) patients. The pharmacokinetics of both compounds have been well characterized in adult patients and particularly for both non-linear PK behaviour have been already described.

The current Type II variation of extension of the indication of GLE/PIB in the paediatric population (3 to < 12 years) have been addressed according to the paediatric investigation part of GLE/PIB clinical development. In support of expanding the treatment of HCV infection using an extrapolation of adult PK to patients aged 3 to < 12 years, Abbvie conducted an exploratory Phase 2/3 study (Study M16-123, Part 2 with three cohorts) in patients aged 3 to <12 years. A new paediatric formulation, comprised of coated granules of GLE/PIB (50mg/20 mg, commercial formulation) in a sachet has been developed. However it is important to note that no PK data with the commercial formulation GLE/PIB ("/"for combined in the same formulation) are available. During the development program experimental formulation of GLE+PIB ("+" for separated compounds) were used in two studies (Study M17-142 and M16-123), this was accepted by the PDCO.

Study M17-142 was designed to study the relative bioavailability of the experimental paediatric formulation of GLE/PIB supplied separately as GLE+PIB film-coated pellet (not the commercial formulation where GLE and PIB are in the same sachet) vs the adult commercial formulation of GLE/PIB tablet (100/40 mg) in fast and fed states (Part 1: non-fasting; Part 2: high and low fat meal). The GLE and PIB single dose investigated was 300/120 mg.

Result from the Part 1 indicated that:

a) Under fasting conditions, administration of GLE+PIB vs GLE/PIB resulted in slightly low exposure with an AUCinf GMR (90%CI) of 0.607 (0.479-0.769) for GLE and 0.862 (0.695-107) for PIB

b) Under non-fasting conditions, administration of GLE+PIB vs GLE/PIB resulted in slightly low exposure with an AUCinf GMR (90%CI) of 0.795 (0.665-0.950) for GLE and 1.219 (0.978-1.52) for PIB

Overall, these results suggest that the paediatric and the adult formulations do not perform similarly and are not considered interchangeable, this have been highlighted in the SmPC.

Results from the Part 2 indicated that:

c) the administration of GLE+PIB (high fat meal) vs GLE+PIB (fast) resulted in 2.3-fold and 2.1-fold higher exposure of GLE and PIB, respectively, compared to fasting conditions

d) the administration of GLE+PIB (low fat meal) vs GLE+PIB (fast) resulted in 2.6-fold and 1.5-fold higher exposure of GLE and PIB, respectively, compared to fasting conditions.

In addition based on the results from Part 1, by considering the administration of GLE+PIB (non-fasting) vs GLE+PIB (fasting) (Table 5, regimen B vs regimen A), resulted in a 2.4-fold (2710/1110) and 1.7-fold (1580/924) higher exposure of GLE and PIB respectively, compared to fasting conditions.

Overall, these results suggest that whatever the content of the meal (breakfast, high or low fat), the exposure of both compounds is approximately two-fold increase compared to fasting conditions.

Initially a GLE+PIB experimental formulation (40 mg+ 15 mg) was investigated in a cohort of 17 paediatric patients from which AUC24 estimated by NCA was far from the GLE and PIB adult target (4800 and 1430 ng.h/mL). Therefore the 50 mg+20 mg formulation was investigated in 29 additional paediatric patients. In the three cohorts a slight increase of 25% of the initial dose of GLE and 30% of PIB was associated to approximately a 2.1-3.52-fold increase of GLE AUC24, and a 1.5-1.9-fold increase of PIB AUC24 respectively. These results could be explained by the known non-linear PK behaviour of both compounds. Importantly, even if the observed AUC24 in the paediatric population appears 1.2-1.8-fold greater for GLE and 1.06-1.6-fold greater for PIB than the adult target, it should be noted that no major safety signal was observed, and the efficacy endpoint (SVR12) was observed in 46/47 patients (please refer to the efficacy and safety parts). Based on these preliminary PK results (without modelling & simulation), the applicant claimed weight –based dosing regimen can be supported.

However, for the extension of indication in the paediatric population, a population PK analysis was developed for each compound from which a simulation exercise was performed to support the comparability of exposure between adult and paediatric patients with the claimed weight-based dosing regimen. Overall the applicant claimed that both PPK models are fit for purpose and this is not endorsed particularly for the GLE PPK model.

Final GLE PPK model consisted of a one compartment PK model with first order absorption and first order elimination from the central compartment parameterized with CL/F, V2/F, ka, and IIV terms on CL/F, Vc/F only. To avoid flip-flop kinetics ka was constraint to be greater than ke (ke=CL/Vé). BW allometric scaling was considered with estimated exponents. Since two formulations were used tablet for adolescent and granule for children, relative bioavailability (F1) was fixed for the granule formulation based on the results from Study M17-142.

PK parameters were estimated with good precision for both fixed and random effects (RSE <26%). CL/F and V2/F IIV were particularly high 194% and 200% (CV%). CL/F and V2 was highly correlated (>0.98) and this was accounted with an omega block. Eta-shrinkage was particularly low <3%. RUV modeled as a proportional error model was estimated at 0.58 (variance) which turns to 76% suggests a refinement of the PPK model.

Such inflated RUV (76%) and the inflated IIV of CL/F (194%) can be explained with regards to the several assumptions made by the applicant. Four parameters are expected to be estimated (Ka, CL/F, V2/F and FR) and in state one, CL/F is of interest (to derive the AUC24), since FR is fixed, Ka is fixed (flip-flop assumption) and V2/F is highly correlated to CL/F (>0.98).

GOF plots were provided without any local regression line to allow easy detection of potential misspecification. A pcVPC was provided, showing clearly that the absorption phase is not well captured, whereas the terminal elimination phase appears slightly over-predicted.

The applicant concludes that the model fit for purpose, however this is not endorsed.

Indeed based on the initial PPK model in adults (initial MAA in 2016, report RD160234), GLE PPK model consisted of a two compartment PK model where the non-linear behavior of GLE was accounted for and no parameterization to avoid flip flop kinetics was performed. IIV was estimated on CL/F and F.

The final PIB PPK model consisted of a two compartment PK model with first order absorption with lag time (ALAG1) and first order elimination from the central compartment parameterized with CL/F, V2/F, Q/F and V3/F ka, and IIV terms on CL/F, Vc/F only. To avoid flip-flop kinetics ka was constraint to be greater than ke (ke=CL/V2). BW allometric scaling was considered with estimated exponents. Since two formulations were used tablet for adolescent and granules for children, relative bioavailability (F1) was fixed for the granule formulation based on the results from Study M17-142.

PK parameters were estimated with good precision for both fixed and random effects (RSE <30%), except for V3/F (RSE of 42.1%). CL/F and V2/F IIV were moderate 64.4% and 45.9% (CV%). CL/F and V2 was highly correlated (>0.91) and this was accounted with an omega block. Eta-shrinkage was particularly low <10%. RUV modelled as a proportional error model was estimated at 0.236 (variance) which turns to 48.5% suggests a refinement of the PPK model. GOF plots were provided without any local regression line to allow easy detection of potential misspecification. A pcVPC was provided, showing that the model adequately represents the observed data in the paediatric population.

The applicant concludes that the model fit for purpose, which is partially endorsed.

In both PPK models the non-linearity PK behaviour for each compound was not handled, this remains the critical issue which hampers the reliability of the results from the simulation exercise. Indeed overall simulated AUC24 appears clearly under-predicted compared to the observed AUC24 (estimated by NCA) for GLE and PIB.

An update of both PPK models was requested in order to solve the raised issues (dose non-linearity, flip-flop kinetics, inadequate structural PK model, estimation of relative bioavailability…), however even if significant efforts were provided, the PPK models were not updated, therefore results from the simulation exercise are still not considered reliable.

Consequently, the PK similarity based on exposures between children and adult/adolescent, claimed in the SmPC cannot be endorsed. Additional data were requested particularly, boxplots of the observed exposure metrics (AUC, Cmax and Cmin) in the paediatric population (Cohort 2, 3 and 4) and those from adolescents (Cohort 1) and adults, and their associated tables. These boxplots were provided (Figure 12 to Figure 14), without the associated tables.

In the three paediatric age cohorts (Cohort 2, 3, and 4), observed Cmin distribution fell within the predicted Cmin distribution in adults for both compounds. It should be noted that median observed Cmin appears for both compounds particularly increased in Cohort 2 compared to all other groups. The same comments can be made for AUC0-24 for both compounds.

In the three paediatric age cohort (Cohort 2, 3, and 4), observed Cmax distribution fell within the predicted Cmax distribution in adolescent (Cohort 1) for both compounds. It should be noted that median observed Cmax appears for both compounds slightly increased compared to adults.

Therefore, for cohort 2 only, both Cmin and Cmax for both compounds are increased compared to adults suggesting that a reduced dose would have been more suitable. However as shown in Study M16-23 (initial phase) where tested dose of GLE/PIB of 200/75 mg were investigated in cohort 2, observed AUC0-24 is for both compounds approximately 20% decreased compared to the AUC0-24 targets of adults. And since efficacy should be promote and presently observed (no virological failure) without no major safety concerns at the tested doses in all three cohorts, the applicant's proposal in the SmPC that "exposures of glecaprevir and pibrentasvir in children aged 3 to < 12 years fell within the efficacious exposure range in adults from Phase 2/3 studies" in the SmPC can be considered acceptable.

More importantly it was predicted than more than 25% of the patients will fell below the 0.5XAUC24 target of 2400 ng.h/mL for GLE and less than 15% for PIB and this is a source of particular concern for GLE, since HCV resistance development should be avoided. However, according to the applicant none of the 5 paediatric subjects, for which observed AUC24 was below this target, experienced a virological failure.

2.4.4. Conclusions on clinical pharmacology

Exposure expressed as AUC0-24 of GLE and PIB in paediatric patients aged 3-<12 years, receiving the paediatric commercial formulation following a weight-based dose regimen has been estimated by intensive PK in 29 patients using a NCA and a PopPK approach. Due to the non-linear PK behavior of both compounds, both methods have limitations to conclude on PK similarity solely on AUC0-24 between children (3-<12 years) and, adolescents (12-<18 years) or adults (>=18 years). Additional exposure metrics as Cmin and Cmax were generally similar compared to those from adults and fells within the efficacious exposure range of adults. The proposed weight-based dose for GLE/PIB can be considered acceptable.

2.5. Clinical efficacy

2.5.1. Main study(ies)

M16-123: An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Paediatric Subjects with Genotypes 1 - 6 Chronic Hepatitis C Virus (HCV) Infection (DORA)

Steps of assessment of M16-123 in paediatric patients

The first interim analysis occurred once all subjects participating in the IPK portion of Part 1 completed PT Week 12 or prematurely discontinued from the study. A second interim analysis occurred once all subjects in Part 1 completed PT Week 12 or prematurely discontinued from the study. Both analysis were assessed during the procedure of extension of the indication in adolescents (see Maviret Type II/12 variation).

A third interim analysis occurred once all subjects participating in the IPK portion of Part 2 completed PT Week 12 or prematurely discontinued from the study. The data from these analyses were the basis of the current application.

During the assessment review, the Applicant submitted within the response to the LoQ the fourth interim analysis that occurred once all subjects in Parts 1 and 2 completed PT Week 12 or prematurely discontinued the study.

The final analysis will occur after all subjects have completed the study (through PT Week 144).

Methods

Study M16-123 is a Phase 2/3, open-label, multicenter study to evaluate the PK, efficacy, and safety of GLE/PIB for 8, 12, or 16 weeks in HCV GT1 – GT6-infected paediatric subjects ≥ 3 to < 18 years of age, with or without compensated cirrhosis, with or without HIV-1 coinfection, who were either TN, TE to IFN with or without RBV, or TE with SOF plus RBV with or without pegIFN.

The study was designed to enroll approximately 125 subjects to meet scientific, regulatory, and clinical objectives without enrolling an undue number of subjects in alignment with ethical considerations.

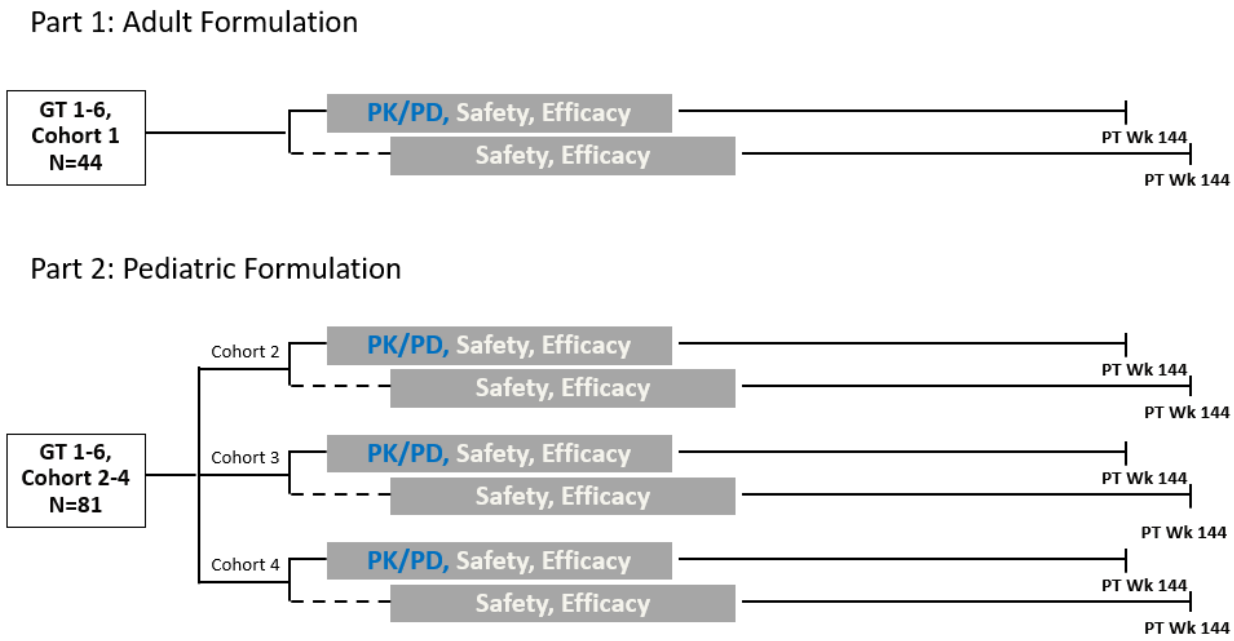
The study is divided into 2 parts:

Part 1 of the study allowed for enrollment 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 allowed for enrollment of approximately 81 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. Subjects in Part 2 received the paediatric formulation of GLE + PIB.

Each cohort was expected to enroll approximately 12 HCV-infected subjects in the IPK portions to adequately characterize the PK of a particular age group. In each cohort, subjects were enrolled first into the IPK portion, followed by the non-IPK safety/efficacy portion, with sparse PK sampling in all subjects. In Part 2, subjects in each age cohort were enrolled in parallel.

Figure 15: Study M16-123 Schematic



GT = genotype; PK = pharmacokinetic; PD = pharmacodynamic; PT Wk = Post-Treatment Week

The paediatric study is a phase 2/3 non comparative study evaluating PK, safety and efficacy in TN or TE [prior IFN, RBV, or SOF exposure], with or without HIV-1 coinfection, without cirrhosis or with compensated cirrhosis. The overall design is acceptable. At the time of the study design development, no IFN-free regimens were approved in children less than 12 years. Exploration of further regimen/duration was deemed not warranted this paediatric population as the same duration and regimens used in adults were anticipated to be similarly successful in children as long as the drug exposures were comparable, which is agreed.

In support of the current application to extend the indication of Maviret to children aged 3 years and older, the MAH is submitting the clinical data from the 3rd interim analysis of M16-123, which occurred once all subjects for the cohorts in Part 2 (3 to < 6 years old, 6 to < 9 years old, and 9 to < 12 years old) undergoing IPK analysis completed the Post-Treatment (PT) Week 12 or prematurely discontinued from the study (n=48). The approach of submitting paediatric extension on the basis of a paediatric study whose primary endpoint is PK exposure was agreed in the PIP in accordance with the feedback from EU experts calling for an accelerated access to DAA in children.

However, the FDA recommended to include an expanded number of patients for safety and non-IPK cohorts were included in the paediatric study to fulfil FDA requirement. Those data are part of the 4th interim analysis. During the assessment of the procedure, this 4th interim analysis was made available and the Applicant submitted, in response to the LoQ, the study report which includes all efficacy/safety data from the non-IPK safety/efficacy portion, i.e on the full 3-<12 years age cohorts (n=80).

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 enrollment.

- 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 coinfected 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.

To be noted that patients undergoing Intensive PK analysis had to be HCV Treatment-naïve and HIV-negative, with determined genotype while the non-IPK safety/efficacy portions included paediatric patients with or without compensated cirrhosis who were TN or TE (prior IFN [alpha, beta, or pegIFN], RBV or SOF exposure), with or without HIV-1 coinfection, and could include subjects with mixed or indeterminate HCV genotype.

Treatments

For the IPK portion of Part 2 of Study M16-123, the paediatric GLE and PIB coated granules were packaged separately (noted as "GLE + PIB") for administration to allow for dose adjustments to determine the final paediatric dose. The study drug was dosed based on body weight/age. The IPK portion of Part 2 of the study evaluated 2 dose ratios.

The initial dose ratio of 40 mg/15 mg was determined based on modelling using available results from the bioavailability Study M17-142 that compared the paediatric formulation to the adult bilayer tablets, and the adolescent PK results from Part 1 of Study M16-123. An IPK analysis was then conducted on the initial dose ratio, which included 17 subjects dosed across the Part 2 age cohorts. After this initial IPK analysis and review of available efficacy and safety data, the doses of the paediatric formulation were then adjusted to the GLE + PIB 50 mg/20 mg final proposed dose ratio. The dose adjustments were made to ensure safe and efficacious exposures, while not exceeding those of the adult dose of 300 mg/120 mg of GLE/PIB.

The final proposed 50 mg/20 mg dose ratio of GLE/PIB was administered to a total of 30 subjects across all 3 age cohorts in the IPK portion of Part 2.

Based on current modelling and available PK data at the completion of the IPK portion of Part 2, the above Final Proposed Doses (Table 21 below) of the paediatric formulation are the target doses for use in children < 12 years of age. The PK and clinical data will be used to confirm appropriate exposure in each of the ≥ 3 to < 12 years old age groups.

Table 21. Glecaprevir and Pibrentasvir doses for the paediatric population

Formulation	Age Group (yrs) & Weight Band (kg)	Initial Doses (mg)		Final Proposed Doses (mg)	
		GLE	PIB	GLE	PIB
Pediatric formulation	3 to < 6 yr 12 to < 20 kg	120	45	150	60
	6 to < 9 yr ≥ 20 to < 30 kg	160	60	200	80
	9 to < 12 yr ≥ 30 to < 45 kg	200	75	250	100
Adult formulation	12 to < 18 yr ≥ 45 kg	--	--	300	120

GLE = glecaprevir; PIB = pibrentasvir; yr = year

The dosing instructions given to subjects and their caregivers specified mixing the granules with soft food. To be noted that the same GLE and PIB coated granules were co-filled into one sachet at the final paediatric dose ratio of 50 mg GLE + 20 mg PIB for administration in the non-IPK safety/efficacy portion of the study, for greater patient/care giver convenience.

Treatment duration was 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.

Overall, a paediatric formulation, comprised of coated granules of glecaprevir and pibrentasvir in a sachet for oral administration has been developed for use in children from 3 to <12 years of age. While the children in the IPK part received GLE and PIB coated granules packaged separately, the same GLE and PIB coated granules were co-filled into one sachet for greater patient/care giver convenience and

were further used in paediatric patients participating in non-IPK part of the study. The coated granules in sachet is the paediatric formulation that is proposed for children 3 to <12 years and is the subject of the current line extension. None of the children from the IPK part received the final co-packaged formulation but it is not anticipated to be of any concern insofar as the only difference is separated versus combined coated granules.

A total of 18 children aged 3 to <12 years received the initial dose ratio of 40mg/15mg GLE/PIB that was determined on modeling and 30 received the adjusted paediatric dose ratio 50mg/20mg GLE/PIB, in the intensive PK portion of the study. Clinical data from these 48 paediatric patients from the IPK part of the study were the initial basis of the efficacy/safety demonstration to support the extension of the indication to children <12 years. Further children received the final paediatric dose ratio 50/20 mg GLE/PIB in the non-IPK part of the study. The 4th interim report including data from the non-IPK part was submitted during the assessment of the procedure.

Treatment duration was the same as that recommended in adults.

Outcomes/endpoints

The primary endpoint was the steady state AUC values for GLE and PIB to be 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 were:

● Cmax and clearance of GLE and PIB at Week 2;

● The percentage of subjects with SVR12 by age group and overall (primary efficacy variable for the US FDA);

● The percentage of subjects with on-treatment virologic failure (i.e., breakthrough or failure to suppress at EOT) by age group and overall;

● The percentage of subjects with PT 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 by age group and overall.

Sample size

It was planned to enrol a total of approximately 125 subjects into this study. The proposed sample size of 48 subjects (approximately 12 subjects for each age cohort) for IPK sampling (separate from sampling performed in subjects in Japan) was expected to adequately characterize the PK of GLE and PIB to enable dose selection in paediatric subjects. Approximately 10 subjects will undergo additional PK sampling to support characterization of GLE and PIB exposures in children from Japan. Additional subjects will be enrolled to reach the proposed total of 125 subjects to provide safety and efficacy information. As per the PIP agreement, EMA has required that a minimum of 9 patients are to be enrolled in each IPK age cohort. A total of 16 children in each 3 age bands (3-<6, 6-<9, 9-<12) were enrolled in the IPK portion part 2 of the study.

Results

While in the 3rd interim report submitted in the initial application, 96 children were enrolled and 95 received at least 1 dose of study drug (see D80 AR), data from the full cohort (IPK and non-IPK part, including 32 additional children aged 3 to <12 y.o) were subsequently available and are presented below:

Disposition (4th interim report)

A total of 129 subjects were enrolled and 127 subjects received at least 1 dose of study drug. One paediatric subject (Cohort 4) who received the initial dose prematurely discontinued study drug due to refusal to swallow the study drug granule formulation and one subject (Cohort 2) experienced a study drug related AE of rash erythematous.

Table 22: Study participants

	Number of Subjects GLE/PIB					
	Cohort 1 ≥ 12 to < 18 years old N = 48	Cohort 2 ≥ 9 to < 12 years old N = 29	Cohort 3 ≥ 6 to < 9 years old N = 27	Cohort 4 ≥ 3 to < 6 years old N = 25	Cohorts 2 - 4 ≥ 3 to < 12years old N = 81	Total N = 129
Enrolled	48	29	27	25	81	129
Treated	47	29	27	24	80	127
Study drug disposition						
Completed study drug	47	28	27	23	78	125
Discontinued study drug	0	1	0	1	2	2
Study disposition						
Completed study	2	1	0	0	1	3
Discontinued study[a]	1	0	0	2	2	3
Ongoing[b]	45	28	27	23	78	123

GLE = glecaprevir; PIB = pibrentasvir

a. Subject [redacted] (Cohort 1) and Subject [redacted] (Cohort 4) were enrolled but were never dosed. Subject [redacted] (Cohort 4) was enrolled and partially dosed; subject refused to swallow entire dose and then discontinued from the study.

b. Ongoing refers to subjects who had not completed or prematurely discontinued the study at the time of database lock for this CSR.

Conduct of the study

Protocol amendments

The original protocol (dated 15 December 2016; 27 subjects enrolled) was amended 6 times (3 global and 3 country-specific) and had 2 administrative changes. A total of 24 subjects were enrolled under Amendment 1 and 45 subjects were enrolled under Amendment 2, 31 subjects were enrolled under

Amendment 3. One additional subject was incorrectly entered in the clinical database as enrolled under Amendment 4, which was a site data entry error, and should have been entered as enrolled under Amendment 3. The protocol changes described in the amendments (inclusion of specific changes for Japanese patients, information in support of the proposed paediatric dosing, increased number of subjects to be enrolled from 110 to 125 subjects, due to change in dosing) did not affect the interpretation of the results in this study.

Protocol deviations

None of the deviations was considered to have affected the study outcome or interpretation of the study results or conclusions.

Baseline data

Demographics and baseline disease characteristics of the study population in Study M16-123 are summarized the tables below.

All subjects were non-cirrhotic and the majority of subjects were HCV GT1-infected. Only 2 adolescent subjects (Cohort 1) and 1 subject from Cohort 3 (paediatric) was HCV/HIV-1 coinfected.

Table 23: Demographic Characteristics

Variable	Cohort 1 ≥ 12 to < 18 years old (N = 47) n (%)	Cohort 2 ≥ 9 to < 12 years old (N = 29) n (%)	Cohort 3 ≥ 6 to < 9 years old (N = 27) n (%)	Cohort 4 ≥ 3 to < 6 years old (N = 24) n (%)	Cohorts 2 – 4 ≥ 3 to < 12 years old (N = 80) n (%)	Total (N = 127) n (%)
Sex						
Female	26 (55.3)	15 (51.7)	17 (63.0)	12 (50.0)	44 (55.0)	70 (55.1)
Male	21 (44.7)	14 (48.3)	10 (37.0)	12 (50.0)	36 (45.0)	57 (44.9)
Race						
White	35 (74.5)	21 (72.4)	18 (66.7)	16 (66.7)	55 (68.8)	90 (70.9)
Black or African American	4 (8.5)	1 (3.4)	1 (3.7)	1 (4.2)	3 (3.8)	7 (5.5)
Asian	6 (12.8)	5 (17.2)	5 (18.5)	4 (16.7)	14 (17.5)	20 (15.7)
American Indian or Alaska Native	0	1 (3.4)	0	1 (4.2)	2 (2.5)	2 (1.6)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (4.2)	1 (1.3)	1 (0.8)
Multiple	2 (4.3)	1 (3.4)	3 (11.1)	1 (4.2)	5 (6.3)	7 (5.5)
Age (Years)						
≥ 12 to < 18	47 (100)	0	0	0	0	47 (37.0)
≥ 9 to < 12	0	29 (100)	1 (3.7)	0	30 (37.5)	30 (23.6)
≥ 6 to < 9	0	0	26 (96.3)	0	26 (32.5)	26 (20.5)
≥ 3 to < 6	0	0	0	24 (100)	24 (30.0)	24 (18.9)
Weight (kg)						
≥ 12 to < 20	0	0	1 (3.7)	23 (95.8)	24 (30.0)	24 (18.9)
≥ 20 to < 30	0	2 (6.9)	25 (92.6)	1 (4.2)	28 (35.0)	28 (22.0)
≥ 30 to < 45	3 (6.4)	27 (93.1)	1 (3.7)	0	28 (35.0)	31 (24.4)
≥ 45	44 (93.6)	0	0	0	0	44 (34.6)
Geographic region						
Europe	21 (44.7)	10 (34.5)	6 (22.2)	5 (20.8)	21 (26.3)	42 (33.1)
Japan	4 (8.5)	3 (10.3)	3 (11.1)	3 (12.5)	9 (11.3)	13 (10.2)
North America	22 (46.8)	16 (55.2)	18 (66.7)	16 (66.7)	50 (62.5)	72 (56.7)

Table 24: Baseline Disease Characteristics

Variable	Cohort 1 ≥ 12 to < 18 years old (N = 47) n (%)	Cohort 2 ≥ 9 to < 12 years old (N = 29) n (%)	Cohort 3 ≥ 6 to < 9 years old (N = 27) n (%)	Cohort 4 ≥ 3 to < 6 years old (N = 24) n (%)	Cohorts 2 – 4 ≥ 3 to < 12 years old (N = 80) n (%)	Total (N = 127) n (%)
HCV genotype[a]						
1	37 (78.7)	19 (65.5)	22 (81.5)	17 (70.8)	58 (72.5)	95 (74.8)
2	3 (6.4)	2 (6.9)	0	0	2 (2.5)	5 (3.9)
3	4 (8.5)	8 (27.6)	3 (11.1)	7 (29.2)	18 (22.5)	22 (17.3)
4	3 (6.4)	0	2 (7.4)	0	2 (2.5)	5 (3.9)
5	0	0	0	0	0	0
6	0	0	0	0	0	0
HCV genotype subtype[a]						
1a	24 (51.1)	11 (37.9)	12 (44.4)	14 (58.3)	37 (46.3)	61 (48.0)
1b	13 (27.7)	8 (27.6)	10 (37.0)	3 (12.5)	21 (26.3)	34 (26.8)
2a	1 (2.1)	0	0	0	0	1 (0.8)
2b	1 (2.1)	2 (6.9)	0	0	2 (2.5)	3 (2.4)
2q	1 (2.1)	0	0	0	0	1 (0.8)
3	0	0	0	1 (4.2)	1 (1.3)	1 (0.8)
3a	4 (8.5)	7 (24.1)	3 (11.1)	5 (20.8)	15 (18.8)	19 (15.0)
3b	0	1 (3.4)	0	1 (4.2)	2 (2.5)	2 (1.6)
4a	0	0	1 (3.7)	0	1 (1.3)	1 (0.8)
4d	2 (4.3)	0	0	0	0	2 (1.6)
4f	1 (2.1)	0	0	0	0	1 (0.8)
4k	0	0	1 (3.7)	0	1 (1.3)	1 (0.8)
Cirrhosis Status						
Cirrhotic	0	0	0	0	0	0
Non-cirrhotic	47 (100)	29 (100)	27 (100)	24 (100)	80 (100)	127 (100)
Prior HCV Treatment History						
Naive	36 (76.6)	27 (93.1)	27 (100)	24 (100)	78 (97.5)	114 (89.8)
Experienced	11 (23.4)	2 (6.9)	0	0	2 (2.5)	13 (10.2)
Type of Previous Regimen[c]						
IFN-based	11 (23.4)	2 (6.9)	0	0	2 (2.5)	13 (10.2)
SOF-based	0	0	0	0	0	0
Baseline HCV RNA Level (IU/ml)						
< 1,000,000	21 (44.7)	10 (34.5)	15 (55.6)	14 (58.3)	39 (48.8)	60 (47.2)
≥ 1,000,000 to < 2,000,000	4 (8.5)	8 (27.6)	4 (14.8)	1 (4.2)	13 (16.3)	17 (13.4)
≥ 2,000,000	22 (46.8)	11 (37.9)	8 (29.6)	9 (37.5)	28 (35.0)	50 (39.4)
Baseline Fibrosis Stage						
F0 – F1	45 (95.7)	28 (96.6)	26 (96.3)	24 (100)	78 (97.5)	123 (96.9)
F2	1 (2.1)	1 (3.4)	1 (3.7)	0	2 (2.5)	3 (2.4)
F3	1 (2.1)	0	0	0	0	1 (0.8)
F4	0	0	0	0	0	0
HCV/HIV Co-Infected Subjects						
Yes	2 (4.3)	0	1 (3.7)	0	1 (1.3)	3 (2.4)
No	45 (95.7)	29 (100)	26 (96.3)	24 (100)	79 (98.8)	124 (97.6)

The paediatric population aged 3 to <12 years enrolled in cohort 2-4 mainly consisted in female (55%), white (69%) patients. While all children were enrolled in US (included Puerto Rico) or Canada for the IPK part, patients from other countries participated to the non-IPK part and overall Europe account for 26% of the 3-<12 y paediatric population included in the study (North America: 63% and Japan 11%).

Most of the children were infected by HCV GT1 (72.5%), mainly GT1a. There were 18 patients with GT3 (22.5%), and 2 patients each with GT2 or GT4. As expected for a paediatric population, the children had a mild disease. None of the 80 children aged 3-<12 years had cirrhosis and all had F0-F1 fibrosis, apart from 2 children who had fibrosis F2 (1 each in cohort 9-<12y and cohort 6-<9y). It would have been of interest to have baseline ALT value to appreciate the proportion of patients with active disease/elevated ALT.

The baseline and disease characteristics between adolescents and paediatric patients <12 years were roughly comparable, besides a larger proportion of GT3 enrolled in part 2 (22.5% vs 8.5% in part 1). A larger proportion of GT3 patients is welcomed to assess the efficacy of Maviret in paediatric patients given GT3-infected patients were known to be harder to treat patients based on adult experience. All but 2 children 3-<12 y.o. were treatment-naïve and therefore were assigned to the 8 week treatment duration regimen as per EU SmPC. There were 2 children in the >9-<12y cohort who were IFN-experienced. None had history of depression or bipolar disorders and none use concomitant PPI or statins.

In the study, dosing was based on age. However, per inclusion criteria, subject must have a weight consistent with the recommended weight band for their age at the time of Screening. As a consequence, all but 1 children aged 3-<6 y.o weighed 12 to <20kg, all but 2 children aged 6-<9 y.o weighed 20-<30kg and all but 1 children in cohort 9 to <12 years weighted 30-<45kg. The dosing schedule proposed in the SmPC is based on weight, which is appropriate; weight-based dosing has been recognised on previous Hep C paediatric extension as a more adequate approach than age-based posology. In line with the clinical population included in the study, the lower limit weight cut-off is clearly mentioned.

Because the formulations have different pharmacokinetic profiles, the tablets and the coated granules are not interchangeable. This is mentioned in section 4.2 and has also been detailed in section 5.2.

Outcomes and estimation

As a reminder, In Part 1 (adolescent), three GT3-infected, TE and noncirrhotic subjects were assigned to 16 weeks of GLE/PIB treatment; the remaining 44 subjects were assigned to 8 weeks of treatment per protocol.

Sustained virologic response 12 weeks post-treatment was achieved by 100% (47/47) of subjects in the ITT population.

Cohorts 2 – 4 Paediatric Subjects ≥ 3 to < 12 Years of Age

All but 2 were TN and were assigned to 8 weeks of treatment per protocol. The two IFN-experienced patients from the >9-<12 years cohort were treated one with a 12w regimen and the other with a 16w regimen (according to the local labelling recommendation).

In the third interim report, sustained virologic response 12 weeks post-treatment was achieved by 95.8% (46/48) of paediatric subjects in the ITT population. In the full cohort, SVR was achieved by **96.3% (77/80)** of paediatric subjects in the ITT population.

Three subjects were considered SVR12 non-responders:

- one due to virologic failure (relapse by PT Week 12)

A 9-year-old, TN male infected with GT 3b in Cohort 2 relapsed by PT Week 4. The subject received the initial dose ratio (GLE 200 mg + PIB 75 mg) QD for 8 weeks. The subject had HCV RNA < 15 IU/mL at Treatment Day 26 with no HCV RNA detected at Treatment Day 56; at PT Day 29, HCV RNA was detected. Study drug was completed and there were no reports of non-compliance. Palatability results show successful administration of the coated granules formulation. This subject had no baseline polymorphism or treatment-emergent substitutions in nonstructural viral protein 3 (NS3), and had K30R and V31M in nonstructural viral protein 5A (NS5A) at baseline and treatment-emergent substitution Y93H in NS5A at the time of failure.

Reason Cohort	Sex/ Age/ Race	HCV Subtype[a]	HCV Treatment Experience	Baseline Polymorphisms in NS3[b]	Substitutions at the time of failure in NS3[b]	Baseline Polymorphisms in NS5A[b]	Substitutions at the time of failure in NS5A[b]	Baseline HCV RNA (log_{10} IU/mL)	Treatment Duration (Days)	≥ 80% Compliant[c]
Relapse by Post-Treatment Week 12										
Cohort 2	Male/9/ Asian	3b	naïve	none	none	K30R V31M	K30R V31M Y93H	7.14	56	Yes

HCV = hepatitis C virus; IRT = interactive response technology; ITT = intention-to-treat; IU = International Unit; NGS = next-generation sequencing; NS3 = nonstructural viral protein 3; NS5A = nonstructural viral protein 5A; RNA = ribonucleic acid; SVR_{12} = sustained virologic response 12 weeks post-treatment

a. Performed by phylogenetic analysis.

b. The following are considered signature amino acid positions in GT3b: 36, 43, 54, 55, 56, 80, 155, 156, 168 in NS3/4A, and 24, 28, 29, 30, 31, 32, 58, 92, and 93 in NS5A. Baseline polymorphisms detected by NGS at 15% detection threshold are listed. "None" indicates that baseline polymorphisms or treatment-emergent substitutions at signature amino acid positions were not detected.

c. Treatment compliance was calculated from accountability data recorded in the IRT system. Treatment compliance was calculated as the percentage of dosing units taken relative to the total number of dosing units expected to be taken.

- two due to non-virologic reasons.

One paediatric subject (Cohort 4, 40/15mg ratio), a 3-year-old TN male infected with GT 3a, was enrolled and partially dosed on Treatment Day 1; the subject refused to swallow the entire dose and then discontinued from the study on Treatment Day 1. There is no HCV RNA data available for this subject after Treatment Day 1.

The other paediatric subject (Cohort 2, 50/20mg ratio), an 11-year-old TN female with HCV GT1b infection, experienced rash erythematous on Treatment Day 1 which was considered by the investigator as having a reasonable possibility of being study drug related. The subject discontinued study drug on Treatment Day 4.

	Cohort 1 ≥ 12 to < 18 years old (N = 47) n (%)	Cohort 2 ≥ 9 to < 12 years old (N = 29) n (%)	Cohort 3 ≥ 6 to < 9 years old (N = 27) n (%)	Cohort 4 ≥ 3 to < 6 years old (N = 24) n (%)	Cohorts 2 – 4 ≥ 3 to < 12 years old (N = 80) n (%)	Total (N = 127) n (%)
SVR_{12}, n/N (%)	47/47 (100)	27/29 (93.1)	27/27 (100)	23/24 (95.8)	77/80 (96.3)	124/127 (97.6)
95% CI[a]	92.4, 100.0	78.0, 98.1	87.5, 100.0	79.8, 99.3	89.5, 98.7	93.3, 99.2
Non-responders, n/N (%)	0/47	2/29 (6.9)	0/27	1/24 (4.2)	3/80 (3.8)	3/127 (2.4)
Reasons for non-response						
Virologic failure	0/47	1/29 (3.4)	0/27	0/24	1/80 (1.3)	1/127 (0.8)
On-treatment virologic failure	0/47	0/29	0/27	0/24	0/80	0/127
Breakthrough	0/47	0/29	0/27	0/24	0/80	0/127
EOT failure	0/47	0/29	0/27	0/24	0/80	0/127
Relapse by post-treatment Week 12	0/47	1/28 (3.6)	0/27	0/23	1/78 (1.3)	1/125 (0.8)
Non-virologic failure	0/47	1/29 (3.4)	0/27	1/24 (4.2)	2/80 (2.5)	2/127 (1.6)
Premature study drug discontinuation	0/47	1/29 (3.4)	0/27	1/24 (4.2)	2/80 (2.5)	2/127 (1.6)
HCV reinfection	0/47	0/29	0/27	0/24	0/80	0/127
Missing SVR_{12} data	0/47	0/29	0/27	0/24	0/80	0/127
Other	0/47	0/29	0/27	0/24	0/80	0/127

CI = confidence interval; EOT = end of treatment; HCV = hepatitis C virus; ITT = intention-to-treat; SVR_{12} = sustained virologic response 12 weeks post-treatment

No paediatric subject who received the final dose ratio experienced virologic failure.

Overall, the SVR rate in children was high (96.3%), in line with results observed with Maviret in adolescents and in adults. Only 1 child relapsed; the child had pejorative GT3b genotype and received a lower than the final recommended dose/ratio. A non virological failure was also reported in a 3 years old child who refused to swallow the entire dose (of note, there were 10 children of 3 years of age successfully treated in the study). No other major palatability concerns were reported in this study and the children overall well accepted the granules formulation despite some resistance to taste and texture (see safety). The other non-virological failure pertains to a child who prematurely discontinued treatment due to occurrence of rash erythematous on treatment D1 that was considered as possibly drug related (see safety part).

To be noted that 2/3 non responders received the initial 40/15mg ratio dose. The MAH initially proposed to reflect in section 5.1 of the SmPC only the results for patients receiving the final recommended dose. However, as requested by the CHMP, the virological failure reported in the apparent compliant GT3b child with pejorative mutation at baseline who received the initial lower dose has also been reflected.

Efficacy Subgroup Analyses

The number and percentage of subjects with SVR12 were analyzed by demographic and baseline characteristics. Overall, there was an SVR12 rate of 100% among all subjects in Cohort 1 and 96.3% in Cohorts 2 – 4 (ITT population).

In Cohorts 2 – 4, the ITT SVR12 rates were 88.9% (16/18) for subjects who received the initial 40 mg/15 mg dose ratio and 95.8% (23/24) for the GLE 250 mg + PIB 100 mg dose, 100% (21/21) for the GLE 200 mg + PIB 80 mg dose, and 100% (17/17) for the GLE 150 mg + PIB 60 mg dose.

As only 1 subject, on the initial 40 mg/15 mg dose ratio, exhibited virologic failure, no negative baseline predictors/trends could be identified, including demographics, baseline HCV RNA level, genotype, presence of baseline polymorphisms in NS3 and/or NS5A, or common comorbidities.

Thus, among the 62 children aged 3-<12 years old who received the final 50/20mg dose ratio, none experienced virological failure.

A 9 years old subject (29.6kg) from Cohort 2 was dosed with 200 mg/75 mg initial dose. Estimated GLE and PIB AUC24 by NCA approach were 1780 ng.h/mL and 903 ng.h/mL, respectively. In this cohort with the tested dose it should be noted that, for GLE, 4 out of 6 (including this 9 year old subject) was below the 0.5xAUC24 adult target of 2400 ng.h/mL and for PIB 1 out of 6 (excluding this 9 year old subject) was below the 0.5XAUC24 adult target of 715 ng.h/mL. Therefore GLE or PIB AUC24 level cannot explain such relapse.

GLE

TRT: GLE+PIB 200 mg+75 mg once daily (QD) for 8 weeks FORMULATION:PELLET

[redacted] COHORT: COHORT 2 AGE:9 SEX:[redacted] RACE:[redacted] WEIGHT:29.6 KG

TRT	1 TO 56	1	1	15:25	4 HOURS POST	0.00	<(1.01)*	650707928618
		14	14	7:13	PRIOR	2.33		650707928014
				9:31	2 HOURS POST	487.00		650707928016
				11:31	4 HOURS POST	221.00		650707928018
				13:31	6 HOURS POST	65.80		650707928020
				19:23	12 HOURS POST	9.15		650707928022
		26	26	14:12		234.00		650707928916
		56	56	14:00		0.00	<(1.01)*	650767420518

PIB

TRT: GLE+PIB 200 mg+75 mg once daily (QD) for 8 weeks FORMULATION:PELLET

[redacted] COHORT: COHORT 2 AGE:9 SEX:[redacted] RACE:[redacted] WEIGHT:29.6 KG

	TRT	1 TO 56	1	1	15:25	4 HOURS POST	650707928618
			14	14	7:13	PRIOR	650707928014
					9:31	2 HOURS POST	650707928016
					11:31	4 HOURS POST	650707928018
					13:31	6 HOURS POST	650707928020
					19:23	12 HOURS POST	650707928022
			26	26	14:12		650707928916
			56	56	14:00		650767420518

25.00		
11.20		
143.00		
106.00		
45.50		
16.10		
145.00		
6.96		

Ancillary analyses

Baseline polymorphisms in NS3 were not detected at amino acid positions 155, 156, or 168 in any of the 124 HCV GT1 – GT4-infected subjects with available sequence. The prevalence of NS3 Q80K in GT1a-infected subjects was high.

Baseline polymorphisms at amino acid positions 24, 28, 30, 31, 58, 92, or 93 in NS5A were detected in 23.2% (29/125) of the HCV GT1 – GT4-infected subjects with available sequence. A30K/T and Y93H in NS5A were each detected in 10.5% (2/19) and 5.3% (1/19) of the HCV GT3a-infected subjects, respectively. One of the 2 HCV GT3b infected subjects experienced virologic failure. The subject experiencing virologic failure (Cohort 2) had no baseline polymorphism or treatment emergent substitutions in NS3 and had K30R and V31M in NS5A at baseline and treatment-emergent substitution Y93H in NS5A at the time of failure. All other subjects in the mITT-VF population achieved SVR12 and there was no evidence that baseline polymorphisms had an impact on treatment outcome.

To be noted that the only child who experienced virological failure had GT3b infection and was of Asian origin. Prevalence of GT3b is very low in Europe (<1%). In this study, conducted in US and Canada, 2 children with GT3b were however included. Phase III studies conducted in China already showed that Maviret had lower efficacy in GT3b adult patients as compared to GT3a due to the presence of naturally occurring K30 and M31 in NS5A with reduced susceptibility to PIB. This has been reflected in the SmPC (following Maviret Var II/26). Even though the GT3b child received the initial lower dose of Maviret, this virological failure has also been highlighted in the paediatric paragraph in section 5.1

In the remaining children, baseline polymorphism had no impact on treatment outcome in this interim analysis.

2.5.2. Discussion on clinical efficacy

Study M16-123 is a Phase 2/3, open label study conducted in paediatric patients from 3 to <18 years of age. Part 1 of the study enrolled 47 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). On the basis of these data, the indication of Maviret were extended in adolescents.

Part 2 of the study enrolled 80 HCV GT1 - GT6-infected paediatric subjects divided into the ≥ 9 to < 12 (Cohort 2, n=29), ≥ 6 to < 9 (Cohort 3, n=27), and ≥ 3 to < 6 (Cohort 4, n=24) years old age groups. Subjects in Part 2 receive the paediatric formulation of GLE + PIB.

The overall design is acceptable. At the time of the study design development, no IFN-free regimens were approved in children less than 12 years. Exploration of further regimen/duration in children was

deemed not warranted as the same duration and regimens used in adults were anticipated to be similarly successful in children as long as the drug exposures were comparable.

In support of its request to extend the indication of Maviret in children from 3 years of age, the Applicant initially provided the interim data of study M16-123 including the PK, efficacy and safety from the 48 children aged 3 to <12 years included in the Intensive PK part of the study. In its response to the LoQ, the Applicant further provided the 4th interim report of study M16-123 including the data up to W12 post-treatment of all children included in the study.

All children aged 3 to <12 years old were treatment-naïve and received 8 weeks GLE/PIB duration as recommended in adults, except 2 IFN-experienced children who received 12 or 16w regimen (according to their local labelling recommendation). None had cirrhosis (or advanced fibrosis). The majority (72.5%) were infected by GT1 but 18 (22.5%) had GT3 infection.

The initial dose ratio of 40mg/15mg GLE/PIB that was determined on modelling and was received by 18 children (1 patient discontinued early); then 62 children received the adjusted paediatric dose ratio 50mg/20mg GLE/PIB (1 patient discontinued early). While the children in the IPK part received GLE and PIB coated granules packaged separately, the same GLE and PIB coated granules were co-filled into one sachet for greater patient/care giver convenience and were further used in paediatric patients participating in non-IPK part of the study. The coated granules in sachet is the commercial paediatric formulation that is proposed for children 3 to <12 years and is the subject of the current line extension.

SVR12 was achieved by 77/80 (96.3%) of paediatric subjects in the ITT population. A 9-year-old, TN male infected with GT3b, relapsed. This patient received the lower initial dose ratio (GLE 200 mg + PIB 75 mg) QD for 8 weeks. In adults, Maviret has been shown to have lower efficacy in GT3b patients (prevalent in Asian region) due to the presence of naturally occurring K30 and M31 in NS5A with reduced susceptibility to PIB; this has been reflected in the SmPC. The virological failure reported in this study in the GT3b child has also been reflected in section 5.1 even though he received the initial lower dose.

Moreover, 2 patients were non-responder due to non-virologic reason: a 3-year-old TN male refused to swallow the entire dose and then discontinued from the study on Treatment Day 1. No other palatability concerns were reported in this study and the children overall well took the granule formulation. An 11-year-old TN female with HCV GT1b infection, experienced rash erythematous on Treatment Day 1 which was considered by the investigator as having a reasonable possibility of being study drug related and discontinued study drug on Treatment Day 4.

The MAH requests the extension of the approved indication in adult and adolescent to children from 3 years of age, whatever the genotypes, TN or TE (DAA-naïve) status, presence or not of cirrhosis or HIV co-infection.

There is no obvious reason that the efficacy would differ between children and adults or adolescents as long as there is no concern of too low exposure. As a reassuring finding, there were 15 children with GT3a infection and all achieved SVR.

A weight-based posology is proposed in the SmPC for children, which is appropriate. The lower limit weight cut-off is clearly mentioned in the SmPC for the coated granule and it has been made clear that children who are less than 12 years old but who weigh at least 45 kg should take the tablet. It has been agreed upon that adolescents (regardless of weight) should take the tablet.

2.5.3. Conclusions on the clinical efficacy

The SVR rate of 96.3% in the 80 children aged >3-<12 years old from study M16-123 support the use of Maviret in children from 3 years of age.

2.6. Clinical safety

Patient exposure

The safety population comprises 47 adolescents in Cohort 1 (Part 1) and 80 paediatric patients in Cohorts 2 to 4 (Part 2).

The safety data derived from the Part 1 of the study in adolescents have already been provided and assessed as part of the type II Variation II/0012 of Maviret and will not be further discussed in this report.

All paediatric subjects in Cohorts 2 – 4 were within 3 to < 12 years of age. There were 44 females (55%) and 36 males (45%) and were white in majority. They were all non-cirrhotic and all but 2 were naïve of treatment. HCV genotype was G3 in 18 subjects (22.5%), G1 in 58 subjects (72.5%) and G4 in 5 subjects. There was 1 HCV/HIV co-infected subject.

All but 2 were treated with Maviret for 8 weeks (the 2 TE patients were treated with Maviret 12 or 16 weeks according to their local labelling recommendation).

The 18 first included paediatric subjects received the initial 40mg/15mg dose ratio. After an initial PK analysis and review of efficacy and safety data, the other 62 subjects received the final 50mg/20mg dose ratio.

Adverse events

Table 25: Overview of adverse events

	Cohort 1 ≥ 12 to < 18 years old (N = 47) n (%)	Cohort 2 ≥ 9 to < 12 years old (N = 29) n (%)	Cohort 3 ≥ 6 to < 9 years old (N = 27) n (%)	Cohort 4 ≥ 3 to < 6 years old (N = 24) n (%)	Cohorts 2 – 4 ≥ 3 to < 12 years old (N = 80) n (%)	Total (N = 127) n (%)
Subjects with:						
Any adverse event (AE)	41 (87.2)	20 (69.0)	16 (59.3)	21 (87.5)	57 (71.3)	98 (77.2)
Any AE with a reasonable possibility of being related to DAAs (glecaprevir/pibrentasvir)[a]	9 (19.1)	6 (20.7)	9 (33.3)	8 (33.3)	23 (28.8)	32 (25.2)
Any AE with a Grade 3 or higher	1 (2.1)	1 (3.4)	0	0	1 (1.3)	2 (1.6)
Any DAA related AE with a Grade 3 or higher	0	1 (3.4)	0	0	1 (1.3)	1 (0.8)
Any serious AE	0	0	0	0	0	0
Any DAA related serious AE	0	0	0	0	0	0
Any AE leading to discontinuation of study drug	0	1 (3.4)	0	0	1 (1.3)	1 (0.8)
Any DAA related AE leading to discontinuation of study drug	0	1 (3.4)	0	0	1 (1.3)	1 (0.8)
Any serious AE leading to discontinuation of study drug	0	0	0	0	0	0
Any AE leading to interruption of study drug	0	1 (3.4)	0	0	1 (1.3)	1 (0.8)
Any fatal AE	0	0	0	0	0	0
Deaths[b]	0	0	0	0	0	0

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

a. As assessed by investigator.

b. Includes non treatment-emergent deaths.

Table 26: Most frequently reported (⩾ 5% of subjects) AEs

MedDRA 23.0 Preferred Term	Cohort 1 ≥ 12 to < 18 years old (N = 47) n (%)	Cohort 2 ≥ 9 to < 12 years old (N = 29) n (%)	Cohort 3 ≥ 6 to < 9 years old (N = 27) n (%)	Cohort 4 ≥ 3 to < 6 years old (N = 24) n (%)	Cohorts 2 - 4 ≥ 3 to < 12 years old (N = 80) n (%)	Total (N = 127) n (%)
Any adverse event	41 (87.2)	20 (69.0)	16 (59.3)	21 (87.5)	57 (71.3)	98 (77.2)
Headache	8 (17.0)	2 (6.9)	6 (22.2)	3 (12.5)	11 (13.8)	19 (15.0)
Nasopharyngitis	11 (23.4)	4 (13.8)	1 (3.7)	1 (4.2)	6 (7.5)	17 (13.4)
Vomiting	5 (10.6)	1 (3.4)	6 (22.2)	4 (16.7)	11 (13.8)	16 (12.6)
Upper respiratory tract infection	9 (19.1)	1 (3.4)	3 (11.1)	2 (8.3)	6 (7.5)	15 (11.8)
Fatigue	5 (10.6)	1 (3.4)	3 (11.1)	3 (12.5)	7 (8.8)	12 (9.4)
Diarrhoea	3 (6.4)	2 (6.9)	4 (14.8)	2 (8.3)	8 (10.0)	11 (8.7)
Pyrexia	5 (10.6)	2 (6.9)	2 (7.4)	2 (8.3)	6 (7.5)	11 (8.7)
Cough	2 (4.3)	1 (3.4)	1 (3.7)	5 (20.8)	7 (8.8)	9 (7.1)
Nausea	4 (8.5)	2 (6.9)	2 (7.4)	1 (4.2)	5 (6.3)	9 (7.1)
Oropharyngeal pain	5 (10.6)	2 (6.9)	1 (3.7)	0	3 (3.8)	8 (6.3)

The most frequently reported (⩾ 10% subjects) AEs for paediatric subjects (Cohorts 2 – 4 combined) were headache, vomiting and diarrhoea.

Table 27: Number and percentage of subjects with drug-related AEs

MedDRA 23.0 Preferred Term	Cohort 1 (N=47) n (%)	Cohort 2 (N=29) n (%)	Cohort 3 (N=27) n (%)	Cohort 4 (N=24) n (%)	Cohorts 2-4 (N=80) n (%)	Total (N=127) n (%)
Any adverse event	9 (19.1)	6 (20.7)	9 (33.3)	8 (33.3)	23 (28.8)	32 (25.2)
Fatigue	3 (6.4)	1 (3.4)	2 (7.4)	3 (12.5)	6 (7.5)	9 (7.1)
Vomiting	1 (2.1)	1 (3.4)	3 (11.1)	2 (8.3)	6 (7.5)	7 (5.5)
Headache	0	1 (3.4)	2 (7.4)	3 (12.5)	6 (7.5)	6 (4.7)
Abdominal pain	2 (4.3)	0	1 (3.7)	0	1 (1.3)	3 (2.4)
Abdominal pain upper	0	1 (3.4)	1 (3.7)	1 (4.2)	3 (3.8)	3 (2.4)
Decreased appetite	2 (4.3)	0	1 (3.7)	0	1 (1.3)	3 (2.4)
Diarrhoea	0	0	1 (3.7)	2 (8.3)	3 (3.8)	3 (2.4)
Nausea	0	1 (3.4)	1 (3.7)	1 (4.2)	3 (3.8)	3 (2.4)
Rash	0	2 (6.9)	1 (3.7)	0	3 (3.8)	3 (2.4)
Malaise	0	0	1 (3.7)	1 (4.2)	2 (2.5)	2 (1.6)
Pruritus	0	1 (3.4)	1 (3.7)	0	2 (2.5)	2 (1.6)
Abdominal distension	1 (2.1)	0	0	0	0	1 (0.8)
Chills	1 (2.1)	0	0	0	0	1 (0.8)
Crystal urine present	1 (2.1)	0	0	0	0	1 (0.8)
Decreased activity	1 (2.1)	0	0	0	0	1 (0.8)
Dizziness	0	0	1 (3.7)	0	1 (1.3)	1 (0.8)
Hyperbilirubinaemia	1 (2.1)	0	0	0	0	1 (0.8)
Increased appetite	0	0	0	1 (4.2)	1 (1.3)	1 (0.8)
Irritability	0	0	1 (3.7)	0	1 (1.3)	1 (0.8)
Mood altered	0	0	0	1 (4.2)	1 (1.3)	1 (0.8)
Palpitations	0	0	1 (3.7)	0	1 (1.3)	1 (0.8)
Proteinuria	1 (2.1)	0	0	0	0	1 (0.8)

Overall, 23 (28.8%) paediatric subjects across Cohorts 2 – 4 experienced study drug-related AEs. The most frequently reported ADRs for paediatric subjects (reported in ⩾ 5% subjects overall) were fatigue, headache and vomiting.

The majority of paediatric subjects who experienced AEs across cohorts 2-4 combined (73.7%; 42/57) had AEs with a maximum severity of Grade 1 (mild). One subject prematurely discontinued study drug on Treatment Day 4 due to a non-serious Grade 3 AE, which was considered study-drug related by the investigator. An 11-year-old female subject, experienced rash erythematous on Treatment Day 1. The event resolved with cessation of study drug and treatment with cetirizine. No other paediatric subjects experienced a treatment-emergent Grade 3 AE or higher. A 9-year-old male subject, experienced a non-serious AE of respiratory tract infection on Treatment Day 29, which led to a brief interruption of

study drug. The event was considered not study-drug related by the investigator and the subject resumed study drug after 4 days.

Of note, paediatric subjects in cohort 2-4 experienced more drug-related AEs than adolescent in Cohort 1 (28.8% vs 19.1%). Diarrhoea, nausea and vomiting occurred at a slightly higher frequency in paediatric subjects compared to adolescents (adverse reactions: 3.8% vs. 0%, 3.8% vs. 0%, and 7.5% vs. 2.1% respectively). Regarding gastrointestinal symptoms, this trend is also observed whatever the relatedness with study drug. They were mostly reported in children aged 3 to <9 years old.

Even though those AEs are generally mild to moderate and did not lead to treatment discontinuation, the Applicant was requested to update section 4.8 to reflect this differential in terms of frequency of gastrointestinal disorders between paediatric and adolescents, for which a consistent trend is observed between paediatric and adolescent whatever the assessment of causality. The SmPC has been revised accordingly.

Four children in cohorts 2-4 experienced treatment-related rash, of which 1 grade 3 AE leading to treatment discontinuation. Although there is no obvious qualitative or quantitative difference between Maviret tablets or granules formulation that could explain occurrence of rash in children, the MAH has been requested to discuss the occurrence of treatment-related rash in children. Detailed information on the cases of drug-related rash were provided. Alternative aetiology or confounding factors were identified for 2 children. All cases were non serious and, except the case leading to study drug discontinuation, resolved without Maviret discontinuation. All occurred in children aged from 7 to 11-years old with no events reported in younger children. Moreover, no signal was identified for adolescent and adults in the recent review assessed by the PRAC. There is insufficient evidence for a causal association between Maviret and rash in paediatric patient at this stage. This issue will continue to be closely monitored in PSURs.

As this could be expected due to the higher dosage, paediatric subjects who received the higher final dose ratio 50mg/20mg had more AEs than those receiving the initial dose 40mg/15mg (75.8% vs 55.5%).

Serious adverse events and deaths

No treatment-emergent SAE and no deaths were reported during the study. In the post-treatment period, one 5-year-old female paediatric subject in Cohort 4 experienced a non-treatment emergent SAE of osteomyelitis of the hip and pelvic bone on post-treatment Day 171 which was not considered related to study drug by the investigator (event occurring around 6 months after the end of study treatment).

No hepatic decompensation/hepatic failures 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.

One subject in Cohort 4 (paediatric) had a single Grade 3 low neutrophil count on Treatment Day 14 that returned to within reference range by Treatment Day 32; the subject's neutrophil count remained within reference range at all other Treatment Period and PT period visits. The single Grade 3 low

neutrophil count was not considered clinically significant and was not reported as an AE. No other subjects had a Grade 3/4 haematology or chemistry value 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

One subject prematurely discontinued study drug due to a non-serious Grade 3 AE. An 11-year-old female, experienced a non-serious Grade 3 AE of rash erythematous on Treatment Day 1 which was considered as having a reasonable possibility of being study drug related. The subject discontinued the study drug on Treatment Day 4. The event resolved with cessation of study drug and treatment with cetirizine. No other subjects reported an AE leading to premature study drug discontinuation.

One paediatric subject (Cohort 4) prematurely discontinued study drug due to refusal to swallow the study drug pellet formulation. No subjects discontinued therapy due to taste.

Palatability

For each subject who took the paediatric formulation (Cohorts 2 – 4), the parent(s)/guardian(s) of the subject completed a Palatability Questionnaire to provide feedback on the perception of the dosage form. The questionnaire was completed by 77 subjects at Week 2, 68 subjects at Week 8, and 78 subjects at the Final Treatment Visit. Subjects did report a dislike for the taste (82.4%) or the texture (52.9%) of the medicine. Despite some resistance to taste and texture, most subjects reported successful administration of the whole dose with soft food (75.3%). Furthermore, most subjects reported that they took the dose within 5 minutes or less (84.6%).

Post marketing experience

There are no post-marketing data available for GLE/PIB in paediatric subjects $\leq$12 years old, as it is not currently indicated for use in this patient population.

2.6.1. Discussion on clinical safety

Overall, no major safety concern was identified in the paediatric subjects treated with the coated granules in a sachet dosed 50mg/20mg of GLE/PIB during this study. The main reported AEs were headache, vomiting and diarrhoea. Overall, those AEs were mild to moderate and were not associated with treatment discontinuation. However, as compared to adolescent, the frequency of gastrointestinal AEs tends to be higher in paediatric population, suggesting that Maviret coated granules has been overall less well tolerated in children than the film coated tablets in adolescents. This has been reflected in section 4.8.

Four children in cohorts 2-4 experienced treatment-related rash, of which 1 grade 3 AE leading to treatment discontinuation. Alternative aetiology or cofounding factors were identified for 2 children. All cases were non serious and, except the case leading to study drug discontinuation, resolved without Maviret discontinuation. All occurred in children aged from 7 to 11-years old with no events reported in younger children. Moreover, no signal was identified for adolescent and adults in the recent review

assessed by the PRAC. There is insufficient evidence for a causal association between Maviret and rash in paediatric patient at this stage. This issue will continue to be closely monitored in PSURs.

The observed AUC24 in the paediatric population appears 1.2-1.8-fold greater for GLE and 1.06-1.6-fold greater for PIB than the adult target. Even though there was no major safety signal in the paediatric study, there is currently a limited clinical experience in paediatric patients. Paediatric patients will be discussed through a dedicated section in future PSUR.

2.6.2. Conclusions on the clinical safety

The safety dataset of use of Maviret in paediatric subjects relies on 80 children aged from 3 to <12 years of age. Maviret has showed to have an overall favourable safety profile in this patient population with no severe AEs, no serious treatment-emergent AE. One child discontinued treatment due to occurrence of drug-related rash erythematous. The safety profile of GLE/PIB observed in children was overall consistent in nature with that reported in adults and adolescents. However, higher frequencies of gastrointestinal disorders have been reported in paediatric subjects, which has been reflected in the product information.

Cases of treatment-related rash, of which 1 grade 3 AE leading to treatment discontinuation, were reported in 4 children but there is insufficient evidence of a causal relationship with Maviret at this stage. This issue will continue to be closely monitored.

Furthermore, the safety in paediatric patients will be discussed through a dedicated section in future PSURs.

2.7. Risk Management Plan

Safety concerns

Table 28: Summary of 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 moderate inducers of P-gp/CYP3A (e.g., efavirenz, oxcarbazepine, eslicarbazepine, lumacaftor, crizotinib) – 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 patients with previous hepatocellular carcinoma

Pharmacovigilance plan

Table 29: Ongoing and Planned Additional Pharmacovigilance Activities

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
DAA-PASS (Study B16-959): A Post-Authorization Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy/Ongoing	The primary objective is to estimate the risk of early HCC recurrence (within 24 months after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort. The secondary objectives are to: 1. Compare the adjusted incidence of early HCC recurrence (within 24 months after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort; 2. Estimate the risk of early HCC recurrence (within 24 months after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC; 3. Compare the adjusted incidence of early HCC recurrence (within 24 months after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC. The exploratory objective is to describe in a non-comparative summary the cumulative risk of HCC recurrence over time for the historical cohort alone.	Potential risk of recurrence of hepatocellular carcinoma and the Missing Information for safety in patients with previous hepatocellular carcinoma.	Protocol approval by PRAC (v 4.2) Final report submission	11 June 2020 3Q2021

Table 29: Ongoing and Planned Additional Pharmacovigilance Activities (Continued)

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable.				
Category 3 – Required additional pharmacovigilance activities				
Study M13-576 A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral (DAA) Agent 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/Ongoing.	The primary objectives are to assess the durability of response for subjects who achieved SVR_{12} with a regimen including ABT-493 and/or ABT-530 and to assess the emergence and persistence of specific HCV amino acid substitutions associated with drug resistance in subjects who experienced virologic failure. The secondary objectives are to summarize medical events related to progression of liver disease including but not limited to: events of hepatic decompensation, change in Child-Pugh classification, liver transplantation, hepatocellular carcinoma and/or, death; to summarize results of the following laboratory tests and scores: FibroTest, APRI, IP-10, alpha fetoprotein (if collected under a previous protocol version), FibroScan, and liver biopsy.	Identified risk of resistance development	Interim report Final report	December 2016 January 2021

Table 29: Ongoing and Planned Additional Pharmacovigilance Activities (Continued)

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 – Required additional pharmacovigilance activities (continued)				
Study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C (Study B20-146)/ Planned.	The primary objectives are: 1. Estimate the risk of de novo HCC associated with DAA therapy exposure in cirrhotic HCV-infected patients compared to no anti-HCV therapy exposure in cirrhotic HCV-infected patients. 2. Estimate the risk of de novo HCC in cirrhotic HCV patients treated with DAA therapy compared to those treated with IFN-based therapy. The secondary objective is: Compare, in a subset of patients with available data recorded in the Veterans Affairs Clinical Case Registries (VA CCR), tumor characteristics (i.e., tumor size, tumor number, tumor stage, tumor type) of the de novo HCC cases observed following initiation of DAA therapy to those of de novo HCC cases observed (a) following initiation of IFN containing regimens and (b) in untreated patients.	Potential risk of emergence of hepatocellular carcinoma.	Feasibility assessment	Submitted June 2017
			Protocol submission	24 September 2018 (version 2).
			Protocol submission	01 April 2019 (version 3)
			Protocol approval by PRAC	14 June 2019 (version 3)

APRI = aspartate aminotransferase to platelet ratio index; DAA = Direct-acting antiviral; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IFN = interferon; IP-10 = interferon-gamma inducible protein 10; PASS = post-authorization safety study; SVR = sustained virologic response; SVR_{12} = sustained virologic response 12 weeks after treatment

Risk minimisation measures

Table 30: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Identified risk: HBV reactivation	Routine risk minimization measures: • SmPC Section 4.4 - Special warnings and precautions for use, includes information on HBV/HCV co-infected patients at risk, and recommendation for monitoring of patients for HBV reactivation. • PIL Section 2 - What you need to know before you take Maviret. • HBV screening should be performed in all patients before initiation of treatment. • HBV/HCV co-infected patients should be monitored and managed per current clinical guidelines. • Restricted medical prescription. ○ Use of treatment should be initiated and supervised by specialists. • Pack size. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Identified risk: Resistance development	Routine risk minimization measures: • SmPC Section 4.2 - Posology and method of administration, includes information on dosage and duration of treatment for patients without prior HCV therapy or patients with failed prior HCV therapies. • PIL Section 3 - How to take Maviret, advise to patients on appropriate dosing and administration to achieve maximal efficacy.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None.

Table 30: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern (Continued)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Identified risk: Resistance development (continued)	• SmPC Section 5.1 - Pharmacodynamic properties, provides information on HCV resistance-associated substitutions. • Maviret is not recommended for patients who failed a prior regimen containing an NS5A inhibitor and/or an NS3/4A PI. • Restricted medical prescription. ○ Use of treatment should be initiated and supervised by specialists • Pack size Additional risk minimization measures: None.	Additional pharmacovigilance activities: Study with long-term follow-up (36 months): Study M13-576 is evaluating durability of response (SVR) and development and/or persistence of resistance among subjects who do not achieve SVR in previous trials.
Potential risk: Recurrence of hepatocellular carcinoma	Routine risk minimization measures: • Restricted medical prescription. ○ Use of treatment should be initiated and supervised by specialists. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None. Additional pharmacovigilance activities: The MAHs shall conduct and submit the results of a joint prospective, observational PASS, "DAA-PASS (Study B16-959): A Post-Authorisation Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy" that will estimate the risk of early HCC recurrence associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with previous successfully treated HCC.

Table 30: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern (Continued)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Potential risk: Emergence of hepatocellular carcinoma	Routine risk minimization measures: • Restricted medical prescription. ○ Use of treatment should be initiated and supervised by specialists. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None. Additional pharmacovigilance activities: The MAH shall conduct and submit the results of a proposed joint retrospective cohort study, "A study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C (Study B20-146)."
Potential risk: 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)	Routine risk minimization measures: • SmPC Section 4.5 - Interaction with other medicinal products and other forms of interaction, provides information on drug – drug interactions with moderate and strong P-gp/CYP3A inducers or substrates; and OATP1B1 or OATP1B3 strong inhibitors and substrates. • SmPC Section 4.4 - Special warnings and precautions for use, and PIL Section 2 - What you need to know before you take Maviret, provide information on medicines patients should not take when on Maviret. • Medicinal products that are contraindicated with Maviret are listed in SmPC Section 4.3. • Specific dose adjustment and/or monitoring recommendations per SmPC Section 4.5.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None. Additional pharmacovigilance activities: None.

Table 30: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern (Continued)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Potential risk: Drug-drug interactions (continued): – Concomitant use with drugs that are moderate inducers of P-gp/CYP3A (e.g., efavirenz, oxcarbazepine, eslicarbazepine, lumacaftor, crizotinib) – 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)	• Medicinal products not recommended for co-administration with Maviret as detailed in SmPC Section 4.5. • List of medicines not to be taken with Maviret is included in PIL Section 2 - What you need to know before you take Maviret. • Restricted medical prescription. ○ Use of treatment should be initiated and supervised by specialists. Additional risk minimization measures: None.	
Missing information: Safety in patients with moderate hepatic impairment (Child-Pugh B)	Routine risk minimization measures: • SmPC Section 4.2 - Posology and method of administration, hepatic impairment section, provides information that advises that the use of GLE/PIB is not recommended in patients with moderate hepatic impairment (Child Pugh B). • SmPC Section 4.4 - Special warnings and precautions for use, advises that the use of Maviret is not recommended in patients with moderate hepatic impairment (Child-Pugh B).	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Use of Hepatic Questionnaire (see Annex 4). Additional pharmacovigilance activities: None.

Table 30: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern (Continued)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information: Safety in patients with moderate hepatic impairment (Child-Pugh B) (continued)	• Restricted medical prescription. ○ Use of treatment should be initiated and supervised by specialists. Additional risk minimization measures: None.	
Missing information: Safety in patients with previous hepatocellular carcinoma	Routine risk minimization measures: • Restricted medical prescription. ○ Use of treatment should be initiated and supervised by specialists. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None. Additional pharmacovigilance activities: A joint MAH PASS, "DAA-PASS (Study B16-959): A Post-Authorisation Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy," will provide safety information in this population, specifically regarding the potential risk of early HCC recurrence with the use of DAAs.

Conclusion

The CHMP and PRAC considered that the risk management plan version 5.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

Not Applicable

Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH 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.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Maviret (glecaprevir / pibrentasvir) is included in the additional monitoring list as an imposed PASS is listed in annex IID of the product information under obligation to conduct post-authorisation measures.

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

Hepatitis C viral infection is a global health problem, with over 71 million individuals chronically infected worldwide. In a recent systematic review, an estimated 13.2 million children aged 1 – 15 years are infected with chronic HCV, globally.

Within the US and Europe's paediatric population, the prevalence of HCV in children and adolescents ranges from 0.05% to 0.36%. New HCV infections among the 0 to 4 year-old age group constituted 0.4% of all new infections in EU/EEA during 2016, 5 – 14 year-olds 0.3%, and 15 – 19 year-olds 1.3%, equating to a rate of infection of 0.55, 0.21, and 1.92 per 100,000, respectively.

Within the paediatric population (< 18 years of age), mother-to-child transmission (MTCT) during the perinatal period is the most common reason for paediatric HCV infection, accounting for 60% of cases. The remaining paediatric/adolescent cases, acquired after the perinatal period, are attributable to intra-familial transmission and high risk behaviours such as intravenous drug abuse

There are 6 major HCV GTs, with prevalence varying by geographic region. Among the European paediatric population (≤ 14 years old) who tested positive for HCV between 2011 and 2015, genotype distribution was as follows: 15% GT1 (where not subtyped), 26.3% GT1a, 21.3% GT1b, 3.8% GT2, 18.8% GT3, 13.8% GT4, 1.3% GT5, and 0% GT6. The HCV genotype distribution in the paediatric population is similar to the HCV genotype pattern in adults.

Although the majority of children have a mild disease and do not need urgent treatment, advanced liver disease has been reported in children as young as 3 years of age. Disease progression also may occur many years after the initial infection. Guidance published by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2018 recommends that all children with chronic HCV infection should be considered for treatment,

considering that the rationale underlying the indications for treatment of adults with chronic infection is also valid for children. Guidance published by ESPGHAN also recommends that all children aged 3 to 17 years with chronic HCV infection may be considered candidates for treatment, and should be considered for treatment if they develop consistently elevated serum aminotransferase levels or liver fibrosis.

3.1.2. Available therapies and unmet medical need

Current approved treatment options for children aged 3 years and older remain limited although expanding. Recently, ledipasvir (LDV)/SOF and SOF + RBV have been approved for use (CHMP positive opinion on 30 April 2020), but they are not pangenotypic IFN-free and the recommended regimen for HCV GT2 and GT3 infection require co-administration with RBV. Moreover, during the assessment of this procedure, Epclusa received EU approval for an extension of the indication in children from 6 years of age.

3.1.3. Main clinical studies

This current application for an extension of the indication to children aged 3 years and older is supported by new clinical data from part 2 of Study M16-123 [An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir for 8, 12, or 16 weeks in HCV GT1 – GT6-infected paediatric subjects 3 to < 18 years of age (DORA)].

A paediatric formulation, comprised of coated granules of glecaprevir and pibrentasvir in a sachet for oral administration has been developed for use in children from 3 to <12 years of age. While the children in the IPK part received GLE and PIB coated granules packaged separately, the same GLE and PIB coated granules were co-filled into one sachet for greater patient/care giver convenience. This formulation was used in the non-IPK part and is the to-be marketed formulation.

Part 1 of the study evaluated the use of the adult bilayer tablets in adolescents (Cohort 1) and has been previously submitted and assessed to support the extension of the indication in paediatric patients from 12 years of age. Part 2 of the study is evaluating the use of the paediatric coated granules formulation of GLE + PIB in children 3 to < 12 years of age (Cohorts 2 – 4). In each cohort, subjects are enrolled first into the intensive pharmacokinetic (IPK) portion, followed by the non-IPK safety/efficacy portion.

Initially, the Applicant provided interim data including the PK, efficacy and safety from the 48 children aged 3 to <12 years included in the Intensive PK part of the study. During the assessment review, the Applicant submitted within the response to the LoQ the fourth interim analysis of study M16-523 that occurred once all subjects in Parts 1 and 2 completed PT Week 12 or prematurely discontinued the study.

All children aged 3-<12 years old were treatment-naïve and received 8 weeks GLE/PIB duration as recommended in adults, except 2 IFN-experienced children who received 12 or 16w regimen (according to their local labelling recommendation). None had cirrhosis (or advanced fibrosis). The majority (72.5%) were infected by GT1 but 18 (22.5%) had GT3 infection.

The initial dose ratio of 40mg/15mg GLE/PIB that was determined on modelling and was received by 18 children (1 patient discontinued early); then 62 children received the adjusted paediatric dose ratio 50mg/20mg GLE/PIB (1 patient discontinued early). While the children in the IPK part received GLE and PIB coated granules packaged separately, the same GLE and PIB coated granules were co-filled into one sachet for greater patient/care giver convenience and were further used in paediatric patients

participating in non-IPK part of the study. The coated granules in sachet is the commercial paediatric formulation that is proposed for children 3 to <12 years and is the subject of the current line extension

3.2. Favourable effects

SVR12 was achieved by 77/80 (96.3%) of paediatric subjects in the ITT population.

A 9-year-old, TN male infected with GT 3b, relapsed. This patient received the lower initial dose ratio (GLE 200 mg + PIB 75 mg) QD for 8 weeks; in adults, Maviret has been shown to have lower efficacy in GT3b patients (prevalent in Asian region) due to the presence of naturally occurring K30 and M31 in NS5A with reduced susceptibility to PIB; this has been reflected in the SPC. Whether the relapse is linked to under-exposure or pejorative mutations at baseline is not known but the failure with emergence of Y93H in this GT3b child is a cause for concern and has been highlighted in the SPC.

Moreover, 2 patients were non-responders due to non-virologic reason: a 3-year-old TN male refused to swallow the entire dose and then discontinued from the study on Treatment Day 1. No other palatability concerns were reported in this study and the children overall took the granule formulation well. An 11-year-old TN female with HCV GT1b infection, experienced rash erythematous on Treatment Day 1 which was considered by the investigator as having a reasonable possibility of being study drug related and discontinued study drug on Treatment Day 4.

GT1 was mainly represented in the study population but a non-negligible proportion of GT3 were enrolled in the study. Moreover, even though the children aged from 3 to <12 years in this study had a mild disease, as expected from a paediatric population, PK data support the extrapolation from adults

3.3. Uncertainties and limitations about favourable effects

The observed AUC24 in the paediatric population appears 1.2-1.8-fold greater for GLE and 1.06-1.6-fold greater for PIB than the adult target. However, it should be noted that no major safety signal was observed, and the efficacy endpoint (SVR12) was observed in all but 3 patients (including only 1 virologic failure).

A population PK analysis was developed for each GLE and PIB compound from which a simulation exercise was performed to support the comparability of exposure between adult and paediatric patients with the claimed weight-based dosing regimen. Overall, the applicant claimed that both PPK models are fit for purpose which is not endorsed particularly for the GLE PPK model. Indeed, in both PPK models the non-linearity PK behavior for each compound was not handled, this remains the critical issue which hampers the reliability of the results from the simulation exercise. Overall simulated AUC24 appears clearly under-predicted compared to the observed AUC24 (estimated by NCA) for GLE and PIB.

Based on these PK results (without modelling & simulation), the applicant claimed weight –based dosing regimen can be supported. However, since results from the simulation exercise are not considered reliable, the PK similarity based solely on AUC0-24 of GLE/PIB between children and adult/adolescent, as claimed by the Applicant in the SmPC was not endorsed. Additional PK data comparison (Cmin and Cmax) between populations were requested and showed that only one cohort of pediatric patients (9-<12 years) appears to be slightly over-exposed compared to adults.

Finally, given there is no data in adults using the granule formulation and in the light of the lack of interchangeability, the indication (section 4.1) has been revised to make it clear that the granule formulation is only indicated in paediatric patients from 3 years of age.

Of note, the tablet formulation SmPC indicated in adults and adolescents is now also indicated in children from 3 years of age to take into account the fact that children weighing at least 45kg could take the tablet. However, section 4.2 clearly specified that Maviret tablet is intended for children weighing at least 45kg and that Maviret coated granule formulation is intended for children aged 3 to less than 12 years weighing 12 kg to less than 45 kg.

3.4. Unfavourable effects

The safety profile of GLE/PIB observed in children was overall consistent in nature with that reported in adults and adolescents. However, the frequency of gastrointestinal disorders tends to be higher in paediatric subjects, which has been reflected in the product information. Moreover, 4 children in cohorts 2-4 experienced treatment-related rash, of which 1 grade 3 AE leading to treatment discontinuation. However, there is insufficient evidence of a causal relationship with Maviret based on these cases.

3.5. Uncertainties and limitations about unfavourable effects

The observed AUC24 in the paediatric population appears 1.2-1.8-fold greater for GLE and 1.06-1.6-fold greater for PIB than the adult target. Even though there was no major safety signal in the paediatric study, there is currently a limited clinical experience in paediatric patients. The safety in paediatric patients will be discussed through a dedicated section in future PSURs.

3.6. Effects Table

Table 31: Effects Table for Maviret in children aged 3 to 12 years old

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
SVR 12 At low and final doses	HCV RNA less than LLOQ at 12 weeks after the cessation of treatment	% (number)	96.3% (77/80)	-	1 virologic failure: relapse in a 9 year old child with HCV GT3b infection, who had received the initial lower dose. K30R and V31M at baseline and treatment-emergent Y93H at relapse.	DORA Part-2
SVR12 At the final recommended dose			98.4% (61/62)		No virological failure in children taking the final recommended dose	
Unfavourable Effects						
Study drug-related AEs	Incidence of	%	28.8%	-	Slightly higher compared to adolescents	DORA Part-2
Diarrhoea (drug-related)	Incidence of	%	3.8%			

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Nausea (drug-related)	Incidence of	%	3.8%			
Vomiting (drug-related)	Incidence of	%	7.5%			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Considering the natural course of chronic HCV infection, use of Maviret in children is associated with a very high cure rate without significant safety concern; overall, the favourable effects clearly outweigh the unfavourable effects.

A weight-based posology is proposed in the SmPC for children, which is appropriate. The lower limit weight cut-off is clearly mentioned in the SmPC for the coated granules and it has been made it clear in section 4.2 that children who are less than 12 years old but who weigh at least 45 kg should take the tablet. It has already been agreed upon that adolescents (regardless of weight) should take the tablet.

3.7.2. Balance of benefits and risks

The proposed dosing regimen does not raise major issues and the efficacy and safety data in children 3 years and older reported are overall acceptable.

3.8. Conclusions

The overall B/R of Maviret in children 3 years and older is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Maviret 50 mg / 20 mg coated granules in sachet is favourable in the following indication:

Maviret coated granules is indicated for the treatment of chronic hepatitis C virus (HCV) infection in children 3 years and older (see sections 4.2, 4.4. and 5.1).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Maviret 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).

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.

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):	Q3 2021

Description	Due date
In order to evaluate the recurrence of hepatocellular carcinoma associated with 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:	

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMEA-C-001832-PIP01-15-M02 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation to the terms of the marketing authorisation, concerning the following change(s):

Variations 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, II, IIIA and IIIB

Extension application to introduce a new strength and pharmaceutical form (50/20 mg coated granules in sachet), grouped with a type II extension of indication variation (C.I.6.a) to include the treatment of children from 3 to <12 years of age (weighing at least 45 Kg) for the approved Maviret 100 mg/40 mg film-coated tablets. As a consequence of the extended indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated accordingly. Furthermore, the MAH took the opportunity to implement several clarifications and editorial changes and to bring the product information in line with the latest QRD template version 10.2. The RMP (version 8) is updated in accordance.