21 May 2026
EMADOC-1700519818-3140847
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Maviret

International non-proprietary name: Glecaprevir / Pibrentasvir

Procedure No. EMA/VR/0000316551

Marketing Authorisation Holder (MAH): Abbvie Deutschland GmbH & Co. KG

Note

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

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List of abbreviations

AASLD	American Association for the Study of Liver Diseases
ADME	Absorption, Distribution, Metabolism, and Excretion
AESI	Adverse Events of Special Interest
ALT	Alanine transaminase
ART	Antiretroviral Therapy
AST	Aspartate transaminase
AUC24ss	GLE and PIB steady-state exposures
CL/F	Apparent clearance/Relative oral bioavailability
CHC	Chronic Hepatitis C
CTCAE	Common Terminology Criteria for Adverse Events
DAA	Direct-Acting Antiviral Agents
EASL	European Association for the Study of the Liver
EEA	European Economic Area
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLE	glecaprevir
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
ICH	International Conference on Harmonization
mITT-VF	modified ITT – virologic failure population
OST	Opioid Substitution Therapy
PIB	pibrentasvir
PK	Pharmacokinetics
PMQ	AbbVie Product MedDRA Query
PTC	Patient Treatment Course
PWID	People Who Inject Drugs
SVR12	Sustained Virologic Response at 12 weeks post treatment

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Abbvie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 2 December 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of acute HCV for Maviret, based on final results from study M20-350; this is a multicenter, single-arm prospective study to evaluate safety and efficacy of GLE/PIB 8-week treatment in adults and adolescents with acute hepatitis C virus (HCV) infection. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2, of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder took the opportunity to update the list of local representatives in the Package Leaflet.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMA/PE/0000252916 on the granting of a (product-specific) waiver for treatment of acute hepatitis C virus infection.

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 and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Nicolas Beix Co-Rapporteur: n.a.

Timetable	Actual dates
Submission date	02 December 2025
Start of procedure:	27 December 2025
CHMP Rapporteur's preliminary assessment report circulated on:	25 February 2026
PRAC Rapporteur's preliminary assessment report circulated on:	26 February 2026
Joint Rapporteur's updated assessment report circulated on:	20 March 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 March 2026
MAH's responses submitted to the CHMP on:	21 April 2026
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	24 April 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	06 May 2026
PRAC RMP advice and assessment overview adopted by PRAC	07 May 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	13 May 2026
CHMP opinion:	21 May 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Approximately 50 million people worldwide are infected with HCV. In 2022, there were an estimated 1 million new global infections, including 67,400 in the United States, with acute HCV infections doubling since 2015. In Canada, 7,535 cases (acute, chronic, and unspecified) were reported in 2021, at a rate of 19.7 per 100,000 people. In Europe, 23,273 new cases were reported in 2022, with a crude rate of 6.2 per 100,000 inhabitants. The rise in acute HCV infections is primarily linked to increased high-risk behaviours, such as injection drug use. Modelling studies suggest that each HCV-infected person who injects drugs may infect about 20 others within the first three years of infection. Globally, an estimated 3.5 million children and adolescents (ages 1 to 19) live with chronic HCV infection.

Currently available treatments are approved for chronic HCV infection.

Acute hepatitis C (HCV) infection is defined as the 6-month time period following exposure to the hepatitis C virus. After initial infection, the virus can be clear spontaneously but 60% to 80% of patients infected with HCV develop chronic HCV infection.

The European Association for the Study of the Liver practice guidelines (as well as the American Association for the Study of Liver Diseases) recommend treatment of acute HCV to prevent progression to chronic HCV. Treatment of HCV infection during the acute phase could decrease community transmission of the disease, help ensure that those individuals with acute HCV infection maintain their connection to care/intervention before their infection progresses to chronic infection, and prevent the

known complications of chronic HCV infection. The population most at risk of HCV transmission is primarily people who inject drugs (PWID).
Risk factors for developing an acute infection include men, people of older age, people with HIV-1 co-infection.

2.1.2. About the product

Maviret is a fixed-dose combination of two pan-genotypic, direct acting antiviral agents, glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor), targeting multiple steps in the HCV viral lifecycle.

Currently, Maviret is available as 100 mg glecaprevir/40 mg pibrentasvir film-coated tablets and 50 mg/20 mg coated granules in sachet.

Maviret is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults and children aged 3 years and older.

The present type II variation is an extension of indication of the same combination of glecaprevir and pibrentasvir in the treatment of acute hepatitis C in adults, adolescents and children from 3 years of age.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Submission	Indication	Approval date
Initial MAA	Adult chronic HCV indication	28 JUL 2017
Line Extension	Adolescent chronic HCV indication (patients 12 to less than 18 years of age)	13 MAR 2019
Line Extension	Pediatric chronic HCV indication (patients 3 to less than 12 years of age)	22 JUN 2021

2.1.4. General comments on compliance with GCP

The MAH confirms that all clinical trials included in this submission were performed in accordance with the principles of Good Clinical Practice, as defined by the International Conference on Harmonization (ICH).

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

The MAH provided an updated ERA report (20 November 2025) and reflected the cumulative environmental exposures resulting from use of glecaprevir (ABT-493) and pibrentasvir (ABT-530) for new indication, treatment of acute hepatitis C infection.

Table 1. Summary of main study results of glecaprevir (ABT-493)

Substance (INN/Invented Name): glecaprevir Established name: glecaprevir Other name: Maviret					
CAS-number (if available): CAS No. 1365970-03-1					
PBT screening not required	**Test protocol**		**Result**	**Conclusion**	
Bioaccumulation potential- log K_{ow}	OECD 107		2.50	Potential PBT: N	
Phase I					
Calculation			**Value**	**Unit**	**Conclusion**
$PEC_{SURFACEWATER}$ = (DOSEai * Fpen)/(WASTEWinhab * DILUTION) DOSEai maximum daily dose consumed per inhabitant 300 mg/(inh-d) Fpen market penetration 0.01 [Default] WASTEWinhab amount of wastewater per inhabitant per day 200 L/(inh-d) DILUTION dilution factor 10 [Default]			1.5	µg/L	≥ 0.01 threshold: Y
Phase II - Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**	**Value**	**Unit**	**Remarks**
Adsorption-Desorption Soil 1 = *Loam (CA-Hanford)* Soil 2 = *Loam (Iowa-Fayette)* Soil 3 = *Sandy loam (RMN-SL-PF)* Sludge 1 = *New Bedford* Sludge 2 = *Wareham*	OECD 106			L/kg_{oc}	Below the criterion of 10,000 L/kg
Aerobic transformation study	OECD 308	[^{14}C] glecaprevir was present in sediments after 14 days	>10%		Triggered the Tier B sediment-water chironomid toxicity test

Phase IIa effect studies : aquatic, functioning and sediment toxicity AF=10					
Study type	**Test protocol**	**Result**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Raphidocelis subcapitata*	OECD 201	NOEC Growth NOEC Yield	40.6 16.9	mg/L mg/L	PEC/PNEC <1
Daphnia magna, Reproduction Test	OECD 211	NOEC	4.91	mg/L	*Biological parameters: Survival; Reproduction (Total Living Offspring per Surviving Female); Total Body Length* *Reproduction endpoints: Total Living Offspring; Total Living Offspring/Surviving Female; Total Living Offspring/Female* $PEC_{SW}/PNEC_{W}$ = 0.0031<1 $PEC_{GW}/PNEC_{W}$= 0.000764<1
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	10.2	mg/L	Biological parameters: Hatching Success; Live, Normal Larve at Hatch; Survival; Total Body Length; Wet Weight PEC/PNEC<1
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000 (EC50 >1000 mg/L)	mg/L	$PEC_{SW}/PNEC_{MICROORG}$= 0.000015
Tier B					
Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC	813	mg/kg	$PEC_{SEDIMENT}$ = 0.052 mg/kg $PNEC_{SEDIMENT}$ = 29.04 mg/kg

					PEC/PNEC ratio=0.0083 <1

Table 2. Summary of main study results of pibrentasvir (ABT-530)

Substance (INN/Invented Name): pibrentasvir Established name: pibrentasvir Other name: Maviret					
CAS-number (if available): CAS No. 1353900-92-1					
PBT screening not required	**Test protocol**		**Result**	**Conclusion**	
Bioaccumulation potential- log K_{ow}	OECD 107		7.47	>4.5: Potential PBT: Y, PBT/vPvB study trigger >3: Secondary poisoning study trigger	
Phase I					
Calculation			**Value**	**Unit**	**Conclusion**
$PEC_{SURFACEWATER}$ = (DOSEai * Fpen)/(WASTEWinhab * DILUTION) **DOSEai** maximum daily dose consumed per inhabitant 120 mg/(inh-d) **Fpen** market penetration 0.01 [Default] **WASTEWinhab** amount of wastewater per inhabitant per day 200 L/(inh-d) **DILUTION** dilution factor 10 [Default]			0.6	µg/L	≥ 0.01 threshold: Y
Phase II - Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**	**Value**	**Unit**	**Remarks**
Water solubility	OECD 105				Low water solubility
Adsorption-Desorption Soil 1 = *Loam (CA-Hanford)* Soil 2 = *Loam (Iowa-Fayette)* Soil 3 = *Sandy loam (RMN-SL-PF)*	OECD 106	Koc sludge values for pibrentasvir of	13990 and 48040	L/kg_{oc}	Greater than the criterion of 10,000 L/kg

Sludge 1 = *New Bedford* Sludge 2 = *Wareham*					
Aerobic transformation study	OECD 308	[^{14}C] glecaprevir was present in sediments after 14 days	>10%		Triggered the Tier B sediment-water chironomid toxicity test
Phase IIa effect studies: aquatic, functioning and sediment toxicity					
Study type	**Test protocol**	**Result**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Raphidocelis subcapitata*	OECD 201	NOEC	0.0044	mg/L	No effects at highest attainable concentrations
Daphnia magna, Reproduction Test	OECD 211	NOEC	0.0057	mg/L	$PEC_{GROUNDWATER}$ = 0.00015 mg/L $PNEC_{GROUNDWATER}$ = 0.00057 mg/L PEC/PNEC= 0.26 < Action limit of 1 ABT-530 is unlikely to represent a risk to the groundwater environment PECSURFACEWATER = 0.6µg/L PEC/PNEC ratio for surface water was slightly greater than 1 (1.05)
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	0.0030	mg/L	No effects at highest attainable concentrations
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000	mg/L	$PEC_{SW}/PNEC_{MICROORG}$< 0.1
Terrestrial plants	OECD 208	NOEC	1000	mg/kg	No effects were observed on seedling emergence or survival for any of the six terrestrial plant species tested at 1000 mg/kg , and there were no visual effects on plant growth or health

Earthworm Acute Toxicity	OECD 207	NOEC	1000	mg/kg	No effects were observed to the earthworm, *Eisenia fetida*, at concentrations up to 1000 mg/kg
Collembolan Reproduction Test in Soil	OECD 232	NOEC	1000	mg/kg	No effects were observed, including on survival and reproduction, on the Collembolan (springtail) Folsomia candida at 1000 mg/kg dry soil
Tier B					
Nitrogen Transformation	OECD 216	NOEC	12.5	mg/kg	No effects were observed on nitrogen transformation in soil at the highest test concentration of 100 times the estimated PECSOIL value of 0.125 mg/kg.
Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC	1000	mg/kg	No effects were observed, including on emergence, development rate, or sex ratio of emerging adult chironomids
PBT / vPvB assessment					
Persistence Aerobic and Anaerobic Transformation in Soil	OECD 307				The aerobic transformation in soil study (OECD 307) yielded up to 21 components (metabolites) in addition to ABT-530. In general, extractable ABT-530 decreased through the study while detection of degradation products increased. The components initially assigned as Met E (up to a mean of 13.5% applied radioactivity) and Met F (up to a mean of 28.3% applied

					radioactivity) were analyzed further by LC-MS and were shown to be comprised of multiple different components, each representing an individual degradation product (metabolite) that could potentially exist as a mixture of positional isomers.
Bioaccumulation Dietary Biomagnification Study with Bluegill, *Lepomis macrochirus*	OECD 305	Biomagnification factor (BMF)	≤ 1		ABT-530 is not likely to biomagnify in the environment. Also, the results of this study do not trigger a secondary poisoning assessment. Pibrentasvir is unlikely to represent a risk to the environment, and that no further testing is necessary.

2.2.2. Discussion on non-clinical aspects

The updated ERA report was prepared in accordance with the EMA Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 Rev.1 - Corr). The MAH conducted a series of tests, and these were acceptable.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of glecaprevir and pibrentasvir.

Considering the above data, glecaprevir and pibrentasvir are not expected to pose a risk to the environment.

No further testing is considered necessary.

2.3. Clinical aspects

2.3.1. 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.

Table 3. Tabular overview of clinical studies

Study number	Title	Country	Study completion date
M20-350	A Multicenter, Single-Arm Prospective Study to Evaluate Safety and Efficacy of GLE/PIB 8-Week Treatment in Adults and Adolescents with Acute Hepatitis C Virus (HCV) Infection'	US, Austria, Australia, Canada, France, Germany, Italy, and Spain	17 Sep 2024

2.3.2. Pharmacokinetics

Introduction

The DAA treatment regimen of glecaprevir/pibrentasvir (GLE/PIB) is a fixed-dose combination product that contains GLE, a potent inhibitor of the protease encoded by the NS3 and NS4A (the cofactor) genes of HCV, and PIB, an NS5A inhibitor. In chronic hepatitis C for adults, adolescents aged 12 and older, and children weighing at least 45 kg, Maviret is available as tablets that contain 100 mg glecaprevir and 40 mg pibrentasvir. The recommended dose is three tablets once a day. For children between 3- and 12-years old weighing between 12 and 45 kg, Maviret is available in sachets of granules that contain 50 mg glecaprevir and 20 mg pibrentasvir, with the recommended dose dependent on weight. Both tablets and granules should be taken with food, and treatment lasts 8, 12 or 16 weeks.

The pharmacokinetic properties of glecaprevir and pibrentasvir in chronic HCV have been well established and characterized and are described in section 5.2 of the SmPC.

Pharmacokinetics in target population

No pharmacokinetic data were derived from the study M20-350 in support of this variation (see clinical part), a multicentre, Single-Arm Prospective Study planned to evaluate Safety and Efficacy of GLE/PIB 8-Week Treatment in Adults and Adolescents subjects ≥ 12 years of age (finally only adults were enrolled) with acute HCV infection. The primary objective was to demonstrate the efficacy of 8-week treatment with glecaprevir/pibrentasvir (GLE/PIB) in adults and adolescents with confirmed acute HCV infection by comparing the sustained virologic response at 12 weeks post treatment (SVR12) rate from this study to the historical SVR12 rate in subjects with chronic HCV infection who were treated with GLE/PIB. From a pharmacokinetic perspective, the rationale was to simulate exposure in the adults with acute HCV based on the legacy population PK from the adults with chronic HCV infection and to extrapolate exposure / efficacy from the chronic populations to the acute populations as explained in the following section.

2.3.3. Pharmacodynamics

Maviret is a fixed-dose combination of two pan-genotypic, direct acting antiviral agents, glecapevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor), targeting multiple steps in the HCV viral lifecycle.

Glecaprevir is a pan-genotypic inhibitor of the HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. Pibrentasvir is a pan-genotypic inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action

of pibrentasvir has been characterised based on cell culture antiviral activity and drug resistance mapping studies.

2.3.4. PK/PD modelling

The MAH submitted a multicenter, Single-Arm Prospective Study to evaluate Safety and Efficacy of GLE/PIB 8-Week Treatment in Adults and Adolescents subjects ≥ 12 years of age with acute HCV infection. Although the study design included adolescents, none were enrolled.

The formulation (bilayer tablet) and the dosage administered in this study were the same as for the treatment of chronic HCV, corresponding to three 100 mg/40 mg tablets QD taken orally.

From a pharmacokinetic standpoint, GLE/PIB steady-state exposures in the Study M20-350 population were determined through extrapolation of exposures from adults with chronic HCV infection to adults with acute HCV infection. To enable such extrapolation, the legacy GLE and PIB popPK models that had been developed in adult subjects with chronic HCV infection (R&D/16/0234) were used in combination with statistical matching to predict individual exposures post-treatment period. However, as above underlined, it is important to note that during this study, no PK sampling was performed and therefore no concentration data were included.

The analyses were performed in stepwise manner:

(1) Comparison of baseline characteristics between adults with acute HCV infection and adults with chronic HCV infection.

(2) Application of statistical nearest neighbour (one-to-one) matching to define, for each subject in Study M20-350, the "closest" eligible subject with chronic HCV infection in the legacy population based on 15 individual covariates, including demographics, baseline hepatic parameters, and comorbidities. Pairs of acute and chronic HCV-infected subjects (1:1) were formed by minimizing the propensity score difference.

The analysis used in statistical matching and PK simulations includes data from subjects enrolled in Study M20-350 who received at least one dose of GLE/PIB, and data collected from adults with chronic HCV infection who received GLE/PIB in Studies M13-583,M13-590, M13-594, M14-172, M14-867, M14-868, M15-410, M15-462, and M15-464 (excluding subjects receiving only GLE or PIB monotherapy in Study M13-595 [N = 2664]).

(3) Prediction of GLE/PIB steady-state exposures (AUC24ss) for adult subjects participating in Study M20-350 based on the legacy population PK models for adults with chronic HCV infection, on the individual baseline characteristics, and on individual variability parameters transferred from matched chronic subjects to each of the subjects with acute HCV infection. In addition to the main analyses mentioned above, the time courses of hepatic parameters (AST, ALT, bilirubin) were explored graphically.

Model-predicted steady-state GLE and PIB AUC24ss were calculated as:

$$AUC24ss\ [ng * h/mL] = Dose\ [\mathrm{mg}] * F * dosing\ interval\ [\mathrm{QD} = 24\ h]/(CL/F)[L/day]$$

where, CL/F is the apparent clearance, and F is the relative oral bioavailability, respectively. For all subjects with chronic HCV infection in the legacy populations, steady-state exposures are calculated with the above formula, with Bayesian parameter estimates as of the PK legacy report (R&D/16/0234) and assuming the GLE/PIB 300/120 mg QD (co-formulated tablets, Phase 3 formulation) dosing regimen. For each subject participating in Study M20-350, CL/F and F are calculated according to the correspondent formulas in the GLE/PIB population PK legacy models, using:

1. Subject specific covariates (age, sex, Asian race, comedications at first dose, renal impairment, cirrhotic status), as of Study M20-350 data,

2. Population parameters (THETAs) from the HCV chronic legacy population, as estimated in the population PK legacy report (R&D/16/0234),

3. Individual variability (ETAs) for model parameters, using the post-hoc estimates from matched HCV chronic subjects as estimated in the population PK legacy modelling report (R&D/16/0234).

The GLE and PIB AUC24,ss were considered as acceptable exposure metrics for assessing PK comparability between acute and chronic HCV infections, based on the main assumption that GLE/PIB likely follows similar absorption, distribution, metabolism, and excretion (ADME) pathways regardless of HCV infection type (acute or chronic), and AUC24,ss had been used as exposure metrics in exposure-response analysis for patients with chronic HCV infection.

The results for the exposure metrics across populations are the following:

Table 4. Model-Predicted GLE/PIB AUC24ss Across different populations based on matching model

Compound	Acute HCV (N = 286)	Chronic HCV Matched (N = 286)	Chronic HCV Legacy Population (N = 2664)
GLE AUC_{24ss} (ng•h/mL) Geometric Mean (%CV) [Min, Max]	4469 (111) [562, 93889]	4587 (114) [514, 170338]	5475 (126) [123, 297091]
PIB AUC_{24ss} (ng•h/mL) Geometric Mean (%CV) [Min, Max]	1222 (54.0) [149, 8482]	1288 (55.9) [149, 7075]	1489 (56.5) [149, 14280]

Extrapolation to Paediatric Populations:

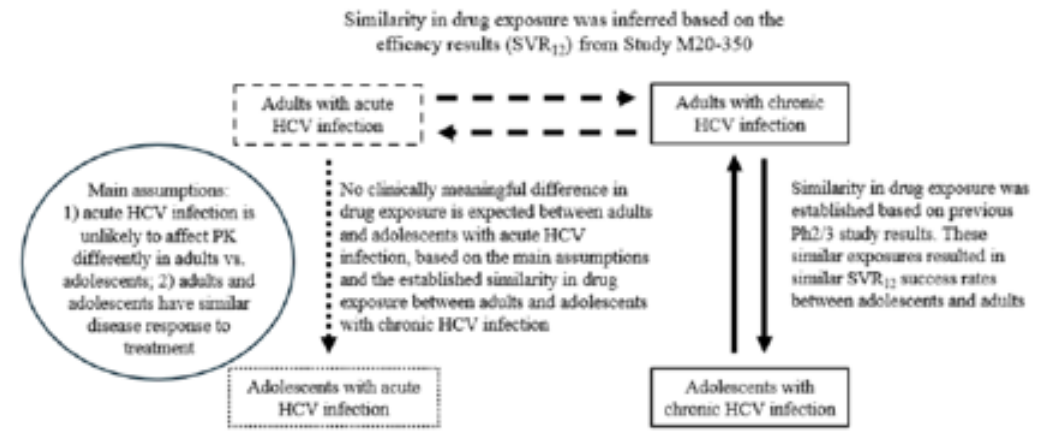
Study M16-123 (DORA Part 1 [adolescents] and Part 2 [children]) established that treatment with GLE/PIB in paediatric patients with chronic HCV infection is safe and effective, and response to treatment was similar to that in the adult population with chronic HCV infection.

Due to no adolescents enrolled in Study M20-350, data from adults with acute HCV infection are meant to be extrapolated to adolescents with acute HCV infection in the same manner as for children.

1) Adolescents:

The popPK analysis was previously conducted for Study M16-123 in adolescents with chronic HCV infection indicated that steady-state exposures of GLE and PIB in adolescents with chronic HCV infection were similar to the exposures in adults with chronic HCV infection. Specifically, following administration of the GLE/PIB 300 mg/120 mg QD regimen, there was ⩽ 9% difference in the model-predicted AUC24,ss between adolescents and adults with chronic HCV infection.

The MAH based the rationale for extrapolation mainly on these previous data from the legacy popPK data of adults and adolescents with chronic HCV and on the efficacy / exposure results of the Study M20-350 in adults with acute hepatitis. The main hypothesis being that acute HCV infection is unlikely to affect PK differently in adults versus adolescents as depicted in the following Figure 1.

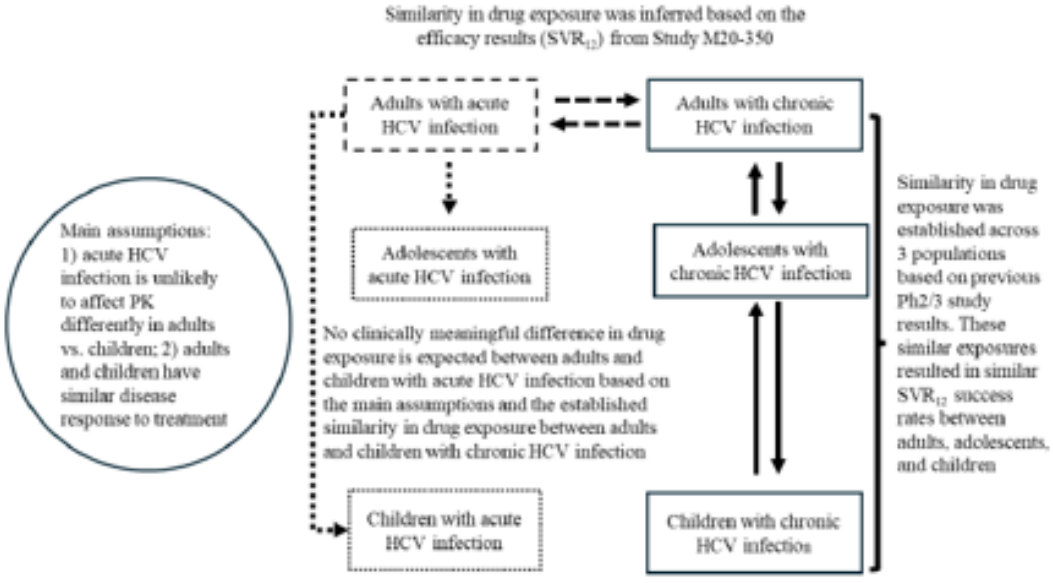


Note: Solid line rectangles indicate populations where both efficacy and exposure data are available; dashed line rectangle indicates a population where efficacy data are available but without exposure data; dotted line rectangle indicates a population where no data are available. Solid arrows show that similarity of exposure has been established; dashed arrows show that similarity of exposure has been inferred based on similar efficacy; dotted arrow shows extrapolation of exposure and efficacy.

Figure 1 Flowchart of rationale to demonstrate no clinically meaningful difference in exposure between adults and adolescents with acute HCV infection, supporting efficacy extrapolation

2) Children from 3 to 12 years of age:

An extrapolation approach is also considered for children from 3 years of age, as depicted in Figure 2. The rationale is based on the fact that the antiviral response of GLE/PIB were similar in paediatric and adult patients with chronic HCV infection, and the assumption that acute HCV infection is unlikely to affect PK differently in adults versus children.



Note: Solid line rectangles indicate populations where both efficacy and exposure data are available; dashed line rectangle indicates a population where efficacy data are available but without exposure data; dotted line rectangles indicate populations where no data are available. Solid arrows show that similarity of exposures has been established; dashed arrows show that similarity of exposures has been inferred based on similar efficacy; dotted arrows show extrapolation of exposure and efficacy.

Figure 2 Flowchart of rationale to demonstrate no clinically meaningful difference in exposure is expected between adults and children with acute HCV infection, supporting extrapolation of efficacy

2.3.5. Discussion on clinical pharmacology

The CHMP considered that the MAH did not plan for PK sampling in the pivotal study to corroborate the assumption that acute HCV infection is unlikely to affect PK differently than in chronic infection. Nevertheless, the CHMP acknowledged that the high level of treatment response in adults, as discussed under Clinical Efficacy, supports the acceptability of using the same dose in adults as in chronic hepatitis C.

The proposed pharmacokinetic rationale for the extension of indication from chronic to acute HCV patients was based on two main steps as described the previous section:

The first step is to demonstrate that systemic exposure is similar in adult patients with chronic and acute HCV infection. For this purpose, simulation of exposure in the adults with acute HCV was conducted using the legacy popPK model developed for the chronic population after statistical subject matching. The main assumption here was that the previous legacy PopPK model developed in chronic patients could adequately describe exposure in adult patients with acute HCV.

Therefore, the outcome of the simulations needed to be confirmed.

To gain further insight on Maviret steady state exposure in adults with acute HCV, re-access to stored samples would have been useful for this purpose. However, due to feasibility issues and challenges to obtain accurate pk sampling for this purpose, this issue was not further pursued.

The second step was then to extrapolate exposure and efficacy from adults with acute HCV to adolescents and children from three years of age with acute HCV and to adapt dosing regimens accordingly. No PK, exposure or efficacy/safety data was included to support such a claim.

Even though inclusion of adolescent patients was planned, none were enrolled. It was also established that GLE is mainly metabolized by CYP3A4. The extrapolation in the paediatric population was solely based on the established similarity in drug exposure between adults and children with chronic HCV. The MAH proposed to extend further this level of reasoning in the acute HCV context, from adults to children (same dose is likely to be required as in CHC) as young as 3 years of age.

In support of this reasoning, the MAH in response to CHMP addressed the expected changes in the metabolism of GLE and PIB in the target paediatric population from 3 years of age, taking into account all the determinants of Maviret PK (maturation/function of CYP3A hepatic enzymes, intestinal and hepatic P-gp,BCRP, and OATP1B1/3, as well as hepatic blood flow).

It is acknowledged that PIB is not metabolized which limits the influence of enzyme maturation on its PK profile. In addition, for GLE, given the hepatic maturation achieved in children from 3 years of age (levels functionally comparable to adults), the metabolic differences are not considered to have a clinically meaningful impact on GLE pharmacokinteics in children.

2.3.6. Conclusions on clinical pharmacology

The CHMP concluded that that the clinical pharmacology data support the use of Maviret in the treatment of acute hepatitis C virus infection in adults and children aged 3 years and older.

2.4. Clinical efficacy

2.4.1. Introduction

Maviret is currently indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults and children aged 3 years and older.

The MAH proposes to update the Maviret (GLE/PIB) label to extend its indication to acute hepatitis C virus infection based on data from the Phase III M20-350 study. This extended indication addresses an unmet need in people with acute hepatitis C, supporting the "treat to prevent" approach that aims to improve the management of hepatitis C.

Acute hepatitis C refers to the initial phase of infection with the hepatitis C virus (HCV), typically occurring within the first six months after exposure. Acute HCV is often asymptomatic, and thus, it is difficult in clinical practice to identify patients with acute infection to provide them with proper monitoring and treatment.

In 2022, in 29 EU/European Economic Area (EEA) Member States, among the 23,249 reported cases of hepatitis C virus (HCV) infection including acute, chronic, and unspecified forms, only 1 308 cases (5.6%) were identified as acute hepatitis C, a figure that is likely underestimated due to the difficulties of early diagnosis and the frequent absence of symptoms. The majority of cases (57%) remain unspecified in terms of their stage, which limits the accuracy of epidemiological analyses. Among cases where the route of transmission is known, injection drug use is the main mode of infection, accounting for 40% of cases across all categories and up to 53% of acute hepatitis C cases. Furthermore, only 4% of infections involve people under the age of 25. These data highlight the importance of strengthening targeted screening, particularly among drug users, as well as the need to improve case characterization in order to refine public health strategies.

European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD recommend treatment of acute HCV infection to prevent progression to chronic HCV and the attendant hepatic complications and risks associated with the disease, patient loss to follow-up and care. Furthermore, this could reduce large-scale community transmission.

2.4.2. Main study - Study M20-350

Study M20-350 - A Multicenter, Single-Arm Prospective Study to Evaluate Safety and Efficacy of GLE/PIB 8-Week Treatment in Adults and Adolescents with Acute Hepatitis C Virus (HCV) Infection

Methods

Table 5. Study M20-350 protocol synopsis

Title	A Multicenter, Single-Arm Prospective Study to Evaluate Safety and Efficacy of GLE/PIB 8-Week Treatment in Adults and Adolescents with Acute Hepatitis C Virus (HCV) Infection
Study participants	- Adult or adolescent, age 12 years and older with Acute Hepatitis C Virus (HCV) Infection: • Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening OR

	• Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 11-month period prior to Screening; AND risk behaviour for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen; OR • Clinical signs and symptoms compatible with acute hepatitis (ALT > 5 × ULN and/or jaundice) in the absence of a history of chronic liver disease or other cause of acute hepatitis and positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening; AND risk behaviour for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen; OR • Negative anti-HCV antibody with a positive HCV RNA or HCV core antigen within a 5-month period prior to Screening. - Negative test result for hepatitis B surface antigen (HBsAg). - Subject with HCV/human immunodeficiency virus 1 (HIV-1) co-infection must also meet the following criteria: • Naïve to HIV treatment or • On a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to Screening
Treatments	Glecaprevir/Pibrentasvir (GLE/PIB) 100 mg/40 mg tablets: three 100 mg/40 mg tablets
Objectives	The primary objective of this study is to demonstrate the efficacy of 8-week treatment with GLE/PIB in adults and adolescents with confirmed acute HCV infection by comparing the SVR12 rate from this study to the historical SVR12 rate in subjects with chronic HCV infection who were treated with GLE/PIB. The primary efficacy objective will be assessed based on the ITT population which is defined as all enrolled subjects who received at least 1 dose of study drug. The key secondary objective of this study is the same as the primary objective of this study except that the key secondary objective will be assessed in the modified ITT – virologic failure (mITT-VF) population. The mITT-VF population is defined as all enrolled subjects who received at least one dose of study drug, excluding those who did not achieve SVR12 for reasons other than virologic failure (i.e., those with HCV reinfection, those who did not achieve SVR12 due to early premature discontinuation of study drug, and those who were missing HCV RNA data in the SVR12 window after backward imputation).
Study design	This study will be conducted as a Phase 3b, multicenter, single-arm, prospective study to evaluate the safety and efficacy of GLE/PIB 8-week treatment in adult and adolescent subjects with acute HCV infection.

	 GLE = glecaprevir; PIB = pibrentasvir; PTW = post-treatment week
Outcomes/ endpoints	**Efficacy**: The primary endpoint is the achievement of SVR12 (defined as HCV RNA < the lower limit of quantification [LLOQ] 12 weeks after the last actual dose of study drug) for each subject in the ITT population. Serum HCV RNA values were measured during the clinical study using either the Roche COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) or the Roche Cobas 6800 test, both of which have a LLOQ of 15 IU/mL. The key secondary endpoint is achievement of SVR12 for each subject in the mITT-VF population. Supportive Secondary Endpoints: On-treatment virologic failure (defined as confirmed increase of > 1 log10 IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the EOT with at least 6 weeks of treatment)) for each subject in the ITT population Post-treatment relapse (Relapse12: defined as confirmed HCV RNA ≥ LLOQ between EOT and 12 weeks after the last dose of study drug [up to and including the SVR12 assessment time point], excluding cases of reinfection) for each subject in the ITT population who completed treatment as planned (defined as study drug duration ≥ 52 days) with HCV RNA < LLOQ at the EOT and with at least 1 post-treatment HCV RNA value. Post-treatment reinfection with HCV (defined as confirmed HCV RNA ≥ LLOQ in the PT period along with the PT detection of a different HCV genotype, subtype, or clade compared with baseline) for each subject in the ITT population. **Safety**: • Alanine aminotransferase elevations of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade 1, 2, 3 or 4 with ALT grade increased from baseline for each subject in the Safety Analysis Set. • Post-nadir ALT elevation > 3 × upper limit of normal (ULN) with total bilirubin > 2 × ULN for each subject in the Safety Analysis Set. • Treatment-emergent hepatic decompensation/hepatic failure events for each subject in the Safety Analysis Set. • Treatment-emergent AEs leading to discontinuation of study drug for each subject in the Safety Analysis Set • Treatment-emergent SAEs for each subject in the Safety Analysis Set

Sample size	Assuming this Phase 3 open-label study enrols 283 subjects, with efficacy thresholds derived from a weighted average of the SVR12 rates in the PWID and non-PWID chronically infected populations of subjects who received GLE/PIB in Phase 2 and 3 trials for ITT and mITT-VF populations and a 6% margin Efficacy success requires the lower 95% CI limit to exceed the efficacy threshold. The study has 80% power to show superiority in PWID (88.7% vs. 82.7%) and >95% in non-PWID (97.8% vs. 91.8%) in the ITT population. For mITT-VF population, 255 subjects will provide > 95% power in the case that all subjects are PWID (98.2% vs. 92.2%) and if all subjects are non-PWID (98.8% vs. 92.8%). Additionally, the sample size ensures >94% probability of detecting toxicities with ≥1% incidence.
Statistical methods	**Definition of success and efficacy threshold** Superiority is concluded if the lower limit (LL) of the two-sided 95% confidence interval (CI) for the observed SVR12 rate exceeds a predefined weighted efficacy threshold. The weighted efficacy threshold is defined as: $(pPWID \times 88.7\%) + (pnon\text{-}PWID \times 97.8\%) - 6\%$ where: • pPWID is the proportion of subjects categorised as current/recent people who inject drugs (PWID), • pnon-PWID is the proportion of subjects categorised as former/non-PWID, based on PWID categorisation 1 in the respective analysis population (ITT or mITT-VF). **Statistical Analysis** The SVR12 rate is estimated together with a two-sided 95% confidence interval calculated using Wilson's score method. The primary analysis tests superiority of the SVR12 rate in the ITT population against the weighted efficacy threshold. The study does not include interim analyses. A fixed-sequence testing procedure controls the overall type I error rate: • The primary analysis assesses superiority in the ITT population. • If superiority is demonstrated in the ITT population, the key secondary analysis assesses superiority in the mITT-VF population. • If superiority is not demonstrated in the ITT population, the key secondary analysis is not performed. **Handling of missing data** Subjects who discontinue the trial with unknown SVR12 status, after application of backward imputation as specified in the SAP, are counted as treatment failures. Backward Imputation For analyses of SVR, backward imputation is applied, where possible, to subjects with missing HCV RNA values within the SVR window: • If the nearest HCV RNA value after the SVR window is unquantifiable or undetectable, this value is used to impute the missing value within the SVR window.

	• If HCV RNA remains missing within the SVR window after backward imputation, a local laboratory HCV RNA value is used, if available. • If no such value is available, the HCV RNA value remains missing. Subjects with missing HCV RNA data in the SVR window after application of the above imputations are considered non-responders (failure imputation). **Sensitivity and Supportive Analyses** Sensitivity and supportive analyses include: • An efficacy threshold based on PWID classifications 2 or 3. • An analysis of the ITT population excluding subjects with baseline HCV RNA < LLOQ, as pre-specified in the SAP. • Pre-specified subgroup analyses, as detailed in the SAP.

Results

Participant flow

Table 6. Subject disposition – all enrolled subjects

	Number of Subjects
Enrolled/treated	286
Study treatment disposition	
Completed study treatment	278
Discontinued study treatment	8
Study disposition	
Completed study	278
Discontinued study	8

Table 7. Discontinuation of study treatment – safety analysis set

	Number (%) of Subjects (N = 286)
Discontinuation for any reason	8 (2.8)
Primary reason for discontinuation	
Adverse event	1 (0.3)[a]
Lost to follow-up	3 (1.0)
Lack of efficacy	0
Withdrawal from treatment by subject	1 (0.3)
Non-compliance with study treatment	3 (1.0)
Other	0

a. Event was considered to have no reasonable possibility of relationship to study treatment per the investigator

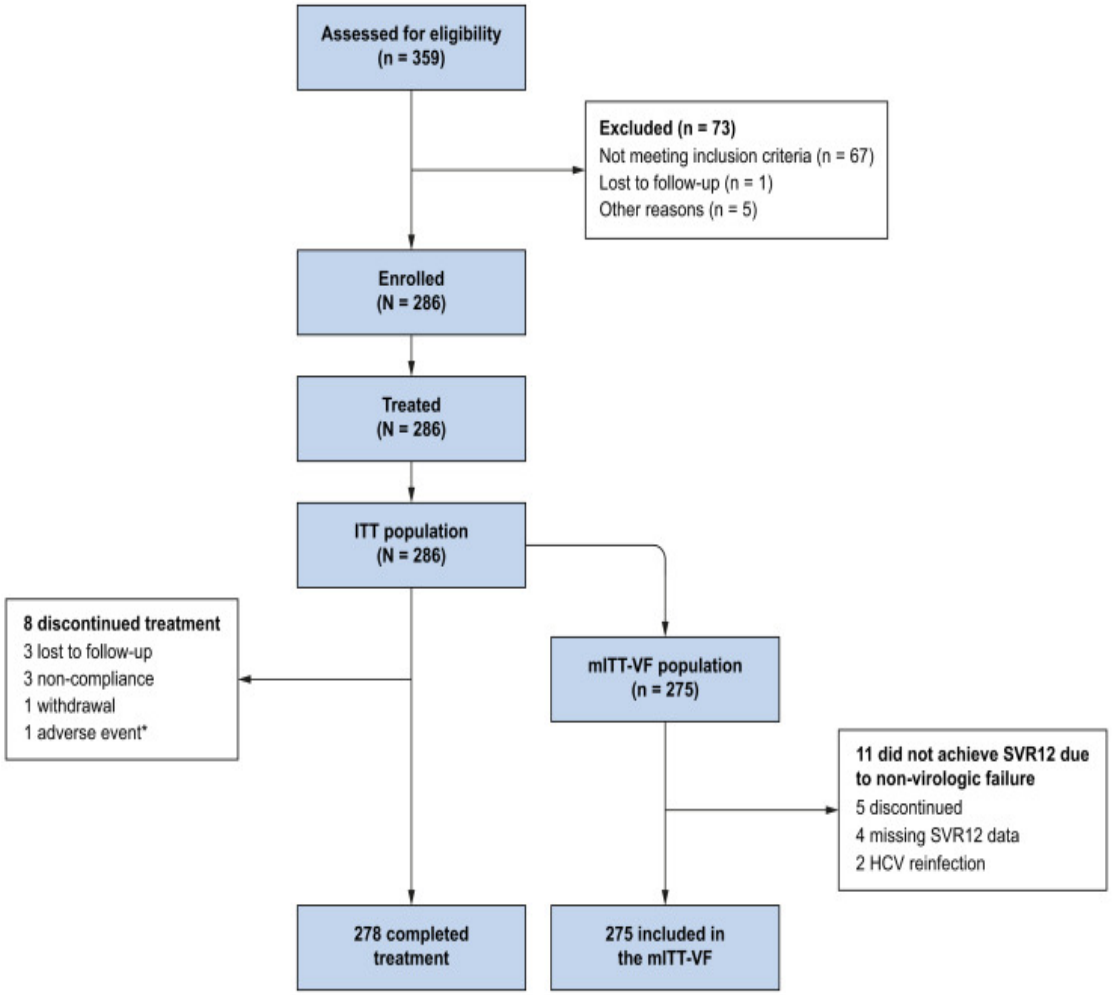


Figure 3. Patient disposition

Overall, the percentage of participants who prematurely discontinued study treatment / withdrew from study was low (8 [2.8%] participants). The most common primary reasons for premature discontinuation of study treatment were due to loss of follow-up (3 [1%] participants) and non-compliance with study treatment (3 [1%] participants).

The significant protocol deviations were related to eligibility criteria not met and use of prohibited concomitant medications.

Recruitment

First Subject First Visit: 24 August 2021

Last Subject Last Visit: 17 September 2024

Study Sites: 70 sites in 8 countries (the United States, Austria, Australia, Canada, France, Germany, Italy, and Spain)

Baseline data

Table 8. Baseline characteristics

Characteristic	Population ITT (N = 286)	Population mITT-VF (N = 275)
Sex, n (%)		
Male	255 (89.2)	247 (89.8)
Female	31 (10.8)	28 (10.2)
Race, n (%)		
White	246 (86.0)	235 (85.5)
Black or African American	30 (10.5)	30 (10.9)
Asian	7 (2.4)	7 (2.5)
Multiple	3 (1.0)	3 (1.1)
Ethnicity, n (%)		
Hispanic or Latino	76 (26.6)	73 (26.5)
Not Hispanic or Latino	210 (73.4)	202 (73.5)
Age (years), n (%)		
18 to < 40	109 (38.1)	103 (37.5)
40 to < 65	161 (56.3)	156 (56.7)
65 to < 75	15 (5.2)	15 (5.5)
≥ 75	1 (0.3)	1 (0.4)
Age (years)		
Mean (SD)	43.7 (11.71)	44.0 (11.78)
Median (min, max)	43.0 (20, 78)	43.0 (20, 78)

Characteristic	Population ITT (N = 286)	Population mITT-VF (N = 275)
HCV genotype,[a] n (%)		
1	165 (64.2)	159 (64.1)
2	11 (4.3)	11 (4.4)
3	33 (12.8)	31 (12.5)
4	48 (18.7)	47 (19.0)
5	0	0
6	0	0
Missing	29	27
HCV RNA (log_{10} IU/mL)		
Mean (SD)	5.00 (1.640)	5.03 (1.632)
Median (min, max)	5.37 (1.2, 7.6)	5.38 (1.2, 7.6)
HCV RNA (IU/mL), n (%)		
< LLOQ	12 (4.2)	12 (4.4)
≥ LLOQ	274 (95.8)	263 (95.6)
< 800,000	191 (66.8)	184 (66.9)
≥ 800,000	95 (33.2)	91 (33.1)
< 1,000,000	198 (69.2)	191 (69.5)
≥ 1,000,000	88 (30.8)	84 (30.5)

Characteristic	Population	
	ITT (N = 286)	mITT-VF (N = 275)
ALT (U/L)		
Mean (SD)	228.2 (287.76)	224.1 (272.90)
Median (min, max)	136.5 (9, 2002)	138.0 (9, 2002)
ALT, n (%)		
≤ ULN	63 (22.0)	62 (22.5)
> ULN to ≤ 3 × ULN	83 (29.0)	77 (28.0)
> 3 × ULN to ≤ 5 × ULN	57 (19.9)	56 (20.4)
> 5 × ULN to ≤ 10 × ULN	47 (16.4)	46 (16.7)
> 10 × ULN	36 (12.6)	34 (12.4)
Total bilirubin (µmol/L)		
Mean (SD)	13.4 (13.32)	13.2 (12.83)
Median (min, max)	10.1 (3, 172)	10.3 (3, 172)
Total bilirubin (µmol/L),[b] n (%)		
< 34.2	274 (95.8)	265 (96.4)
≥ 34.2	12 (4.2)	10 (3.6)
Cirrhosis status, n (%)		
Cirrhotic	5 (1.7)	5 (1.8)
Non-cirrhotic	278 (97.2)	267 (97.1)
Unknown – test results indeterminate	3 (1.0)	3 (1.1)
Fibrosis stage, n (%)		
F0 to F1	238 (85.6)	227 (85.0)
F2	15 (5.4)	15 (5.6)
F3	20 (7.2)	20 (7.5)
F4	5 (1.8)	5 (1.9)
Missing	8	8
Baseline FIB-4, n (%)		
< 1.45	178 (67.9)	169 (67.1)
≥ 1.45 to ≤ 3.25	62 (23.7)	62 (24.6)
> 3.25	22 (8.4)	21 (8.3)
Missing	24	23

Characteristic	Population ITT (N = 286)	Population mITT-VF (N = 275)
HCV/HIV-1 co-infection, n (%)		
HCV mono-infected	144 (50.3)	137 (49.8)
HCV/HIV-1 co-infected	142 (49.7)	138 (50.2)
Prior HCV infection, n (%)		
Yes	52 (18.2)	51 (18.5)
No	234 (81.8)	224 (81.5)
History of non-prescribed illicit drug use, n (%)		
Yes, ongoing as of the end of study participation	34 (11.9)	31 (11.3)
Yes, last dose after last dose of study treatment	3 (1.0)	2 (0.7)
Yes, last dose during study treatment period	12 (4.2)	11 (4.0)
Yes, last dose less than 6 months prior to start of study treatment	73 (25.5)	70 (25.5)
Yes, last dose 6 to 12 months prior to start of study treatment	15 (5.2)	14 (5.1)
Yes, last dose more than 12 months prior to start of study treatment	20 (7.0)	20 (7.3)
Yes, timing of last dose unknown	3 (1.0)	3 (1.1)
No	126 (44.1)	124 (45.1)
History of non-prescribed illicit injection drug use, n (%)		
Yes, ongoing as of the end of study participation	11 (3.8)	10 (3.6)
Yes, last dose after last dose of study treatment	2 (0.7)	1 (0.4)
Yes, last dose during study treatment period	1 (0.3)	1 (0.4)
Yes, last dose less than 6 months prior to start of study treatment	20 (7.0)	18 (6.5)
Yes, last dose 6 to 12 months prior to start of study treatment	7 (2.4)	6 (2.2)
Yes, last dose more than 12 months prior to start of study treatment	7 (2.4)	7 (2.5)
Yes, timing of last dose unknown	0	0
No	238 (83.2)	232 (84.4)

Characteristic	Population	
	ITT (N = 286)	mITT-VF (N = 275)
PWID Classification 1,[c] n (%)		
Current/recent PWID	41 (14.3)	36 (13.1)
Current PWID	14 (4.9)	12 (4.4)
Recent PWID	27 (9.4)	24 (8.7)
Former/non-PWID	245 (85.7)	239 (86.9)
Former PWID	7 (2.4)	7 (2.5)
Non-PWID	238 (83.2)	232 (84.4)
PWID Classification 2,[d] n (%)		
Current/recent PWID	43 (15.0)	37 (13.5)
Current PWID	18 (6.3)	15 (5.5)
Recent PWID	25 (8.7)	22 (8.0)
Former/non-PWID	243 (85.0)	238 (86.5)
Former PWID	6 (2.1)	6 (2.2)
Non-PWID	237 (82.9)	232 (84.4)
PWID Classification 3,[e] n (%)		
Current/recent PWID	45 (15.7)	39 (14.2)
Current PWID	21 (7.3)	18 (6.5)
Recent PWID	24 (8.4)	21 (7.6)
Former/non-PWID	241 (84.3)	236 (85.8)
Former PWID	6 (2.1)	6 (2.2)
Non-PWID	235 (82.2)	230 (83.6)
Acute HCV infection criteria met,[f] n (%)		
Criterion a: yes, negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening	83 (29.0)	80 (29.1)
Criterion b: yes, negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 11-month period prior to Screening; AND risk behavior within 6 months prior to positive HCV RNA or HCV core antigen	90 (31.5)	87 (31.6)

Characteristic	Population	
	ITT (N = 286)	mITT-VF (N = 275)
Criterion c: yes, clinical signs and symptoms compatible with acute hepatitis (ALT > 5 × ULN and/or jaundice) in the absence of a history of chronic liver disease or other cause of acute hepatitis and positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening; AND risk behavior within 6 months prior to positive HCV RNA or HCV core antigen	239 (83.6)	228 (82.9)
Criterion d: yes, negative anti-HCV antibody with a positive HCV RNA or HCV core antigen within a 5-month period prior to Screening	43 (15.0)	40 (14.5)
No criteria met	6 (2.1)	6 (2.2)
Estimated duration of acute HCV infection[g] (days)		
n	280	269
Mean (SD)	105.37 (49.225)	106.43 (49.727)
Median (min, max)	85.00 (51.5, 299.0)	86.00 (51.5, 299.0)
Estimated duration of acute HCV infection,[g] n (%)		
< 3 months	158 (56.4)	149 (55.4)
≥ 3 months to < 6 months	101 (36.1)	99 (36.8)
≥ 6 months	21 (7.5)	21 (7.8)
Missing	6	6
Time since diagnosis of acute HCV infection (days)		
Mean (SD)	59.2 (50.07)	59.5 (50.32)
Median (min, max)	39.0 (10, 257)	39.0 (10, 257)
Time since diagnosis of acute HCV infection, n (%)		
< 3 months	228 (79.7)	219 (79.6)
≥ 3 months	58 (20.3)	56 (20.4)
History of opiate substitution therapy use		
Yes, ongoing at start of study treatment	21 (7.5)	16 (5.9)
Yes, less than 6 months prior to start of study treatment	3 (1.1)	2 (0.7)
Yes, 6 to 12 months prior to start of study treatment	1 (0.4)	1 (0.4)
Yes, more than 12 months prior to start of study treatment	3 (1.1)	3 (1.1)

Characteristic	Population	
	ITT (N = 286)	mITT-VF (N = 275)
Yes, timing of last dose unknown	0	0
No	252 (90.0)	248 (91.9)
Unknown	6	5
Risk behavior for acute HCV infection,[h] n (%)		
Shared drug-injection equipment	54 (18.9)	47 (17.1)
Shared non-injection drug use equipment	53 (18.5)	50 (18.2)
Unprotected sexual activity with multiple partners	172 (60.1)	166 (60.4)
Unprotected sexual activity with other male(s)	190 (66.4)	188 (68.4)
Risky tattoos or body piercings	11 (3.8)	9 (3.3)
Shared personal items possibly contaminated with blood	20 (7.0)	14 (5.1)
Healthcare worker with occupational exposure	6 (2.1)	6 (2.2)
Other behavior	25 (8.7)	24 (8.7)

a. Final available GT from phylogenetic analysis or central laboratory if phylogenetic result was not available.

b. 34.2 µmol/L = 2 mg/dL; the upper limit of normal for total bilirubin is approximately 1.2 mg/dL.

c. PWID Classification 1 defined with respect to study treatment start.

d. PWID Classification 2 defined with respect to study treatment period.

e. PWID Classification 3 defined with respect to study participation.

f. Subjects may have been counted under each acute criterion; therefore, the sum of the counts given for the acute criteria may be greater than the overall number of subjects.

g. Estimated acute HCV infection duration (days) was calculated as (study treatment start date – estimated infection start date) + 1 day. Estimated infection start date is defined as follows, using the HCV test(s) that defined the acute diagnosis criteria: criteria (a) and criteria (b), the midpoint between the HCV negative test and the HCV positive test; criteria (c) and criteria (d), 42 days prior to the date of the positive HCV test. Since a subject could have qualified under multiple acute criteria, the following prioritization was used to estimate the infection start date: (d), (a), (b), (c).

h. Subjects may be counted under each risk behavior for acute HCV infection; therefore, the sum of the counts given for the risk behavior for acute HCV infection may be greater than the overall number of subjects.

Note: Percentages calculated on non-missing and non-unknown values.

Numbers analysed

286 participants were enrolled and treated at 70 sites across 8 countries (United States, Austria, Australia, Canada, France, Germany, Italy, and Spain). Approximately 70% of participants were enrolled in European countries. The study population is therefore considered broadly representative of the EU population.

The proportion of participants who prematurely discontinue study treatment or withdraw from the study is low (8 participants; 2.8%). The most common primary reasons for premature discontinuation are loss to follow-up (3 participants; 1%) and non-compliance with study treatment (3 participants; 1%).

Significant protocol deviations mainly relate to eligibility criteria not met and the use of prohibited concomitant medication. These deviations are not considered to impact the interpretability of the trial results. No adverse events are reported by the sponsor as resulting from these protocol deviations.

The majority of subjects (89%) are male, not Hispanic or latino (73%). The median age was 43 years (range: 20 to 78).

While Study M20-350 was intended to enrol both adults and adolescents, no adolescents were ultimately included. As a result, data from adults had to be extrapolated to adolescents for the treatment of acute HCV infection. Similarly, this extrapolation approach must also be applied to children, as there are no available data on acute HCV infection in paediatric populations.

The diagnosis of acute HCV infection during screening was based on the physician's diagnosis, HCV RNA quantification, and one or more of the following: negative HCV antibodies, recent conversion from negative to positive HCV antibodies, HCV RNA or HCV core antigen screening test, signs of liver disease associated with acute HCV infection, and recent risk behaviours for HCV infection. At baseline, only 2.1% had not met these criteria. 96% of subjects had quantifiable HCV RNA. 97.2% of subjects had non cirrhotic status, no fibrosis (85.6%). 50% had HIV co-infection.

The main risk behaviour for acute HCV infection was unprotected sexual activity with multiple partners or with other male(s).

The majority of participants are former/non-PWID, and this distribution is consistent across the three PWID classifications.

Genotype 1 is predominantly (64%) consistent with the geographical origin of the recruited population (North America, Europe, South America, Asia, and Australia).

8% of patients have an acute HCV infection of duration exceeding 6 months. It is nevertheless acknowledged that more globally, recently acquired de novo HCV infection as defined by the presence of anti-HCV antibodies, HCV RNA and/or HCV core antigen that were not detectable in previous samples up to 12 months better covers the notion of acute infection in line with EASL.

Outcomes and estimation

Table 9. Main analysis of virologic response at post-treatment week 12 (SVR12): ITT population

	ITT Population
SVR_{12}, n/N (%)	275/286 (96.2)
95% CI[a]	(93.2, 97.8)
Threshold (%)[b]	90.5
Nonresponders, n/N (%)	11/286 (3.8)
Reason for nonresponse, n/N (%)	
Virologic failure	0/286
On-treatment virologic failure	0/286
Breakthrough	0/286
End-of-treatment failure	0/286
$Relapse_{12}$	0/278
Non-virologic failure	11/286 (3.8)
Premature study treatment discontinuation	5/286 (1.7)
HCV reinfection	2/286 (0.7)
Missing SVR_{12} data	4/286 (1.4)
Other	0/286

a. Calculated using Wilson's score method.

b. Threshold calculated as (0.143 × 88.7%) + (0.857 × 97.8%) – 6%, where 0.143 is the proportion of current/recent PWID and 0.857 is the proportion of former/non-PWID in the ITT population, calculated using PWID Classification 1 (with respect to study treatment start).

For the primary efficacy endpoint, the SVR12 (defined as HCV RNA < the lower limit of quantification [LLOQ] 12 weeks after the last actual dose of study treatment) rate was 96.2% (275/286).

High response rate was also observed in patients co-infected with HIV: the SVR12 rate was 97.2% (138/142) for subjects with HCV/HIV-1 co-infection and 95.1% (137/144) for subjects with HCV mono-infection.

No subject failed to achieve SVR12 because of virologic failure.

2/286 (0.7%) subjects experienced reinfection; both of these subjects reported continued significant risk factors for HCV infection.

Table 10. Main analysis of virologic response at post-treatment week 12(SVR12): mITT-VF population

	mITT-VF Population
SVR_{12}, n/N (%)	275/275 (100)
95% CI[a]	(98.6, 100.0)
Threshold (%)[b]	92.7
Nonresponders, n/N (%)	0/275
Reason for nonresponse, n/N (%)	
Virologic failure	0/275
On-treatment virologic failure	0/275
Breakthrough	0/275
End-of-treatment failure	0/275
$Relapse_{12}$	0/273

a. Calculated using Wilson's score method.

b. Threshold calculated as (0.131 × 98.2%) + (0.869 × 98.8%) – 6%, where 0.131 is the proportion of current/recent PWID and 0.869 is the proportion of former/non-PWID in mITT-VF population, calculated using PWID Classification 1 (with respect to study treatment start).

A lower SVR12 is observed in recent/current PWID (87.8%) vs. former/non-PWID (97.6%) and in patients undergoing opioid substitution therapy (OST) (76,2%) vs. those not on OST (98,1%).

The effectiveness is similar in the other subgroups such as HCV genotype, baseline HCV/HIV-1 coinfection status, baseline HCV RNA or prior HCV infection history.

For the key secondary efficacy endpoint, the SVR12 rate of 100% (275/275, 95% CI:98.6%, 100.0%) in the mITT-VF population was superior to the efficacy threshold of 92.7%, as the lower bound of the 95% CI was above the threshold. Therefore, the key secondary objective was achieved.

The mITT SVR12 was not affected by genotype, baseline HCV/HIV-1 coinfection status, baseline HCV RNA, PWID status, OST use, or history of prior HCV infection.

Supportive Secondary Endpoints:

- No patients in the ITT population experienced on-treatment virologic failure (0/286, 0%; 95% CI 0.0%–1.3%) or post-treatment relapse (0/278, 0%; 95% CI 0.0%–1.4%).
- Post-treatment reinfection was experienced by 2/286 (0.7%, 95% CI; 0.2%– 2.5%) patients. Both of these subjects reported continued significant risk factors for HCV infection.
- Baseline polymorphisms in NS3 and/or NS5A had no impact on treatment outcome.

Efficacy relative to the chronic HCV phase 2/3 analysis set

The efficacy results from study M20-350 were compared with the results for the ITT and mITT-VF populations within the chronic HCV Phase 2/3 analysis set.

Participants were adults and adolescents included in any of the 14 GLE/PIB studies received 8-week at least one dose GLE/PIB treatment.

Table 11. Select Demographic Characteristics in Study M20-350 and in the Chronic HCV Phase 2/3 Analysis Set: ITT and mITT-VF Populations

	ITT Population				mITT-VF Population			
	Study M20-350	Chronic HCV Phase 2/3 Analysis Set			Study M20-350	Chronic HCV Phase 2/3 Analysis Set		
Characteristic	(N = 286)	Adolescent (N = 44)	Adult (N = 2534)	Overall (N = 2578)	(N = 275)	Adolescent (N = 44)	Adult (N = 2498)	Overall (N = 2542)
Sex, n (%)								
Male	255 (89.2)	20 (45.5)	1354 (53.4)	1374 (53.3)	247 (89.8)	20 (45.5)	1333 (53.4)	1353 (53.2)
Female	31 (10.8)	24 (54.5)	1180 (46.6)	1204 (46.7)	28 (10.2)	24 (54.5)	1165 (46.6)	1189 (46.8)
Race, n (%)								
White	246 (86.0)	32 (72.7)	1412 (55.7)	1444 (56.0)	235 (85.5)	32 (72.7)	1390 (55.6)	1422 (55.9)
Black or African American	30 (10.5)	4 (9.1)	140 (5.5)	144 (5.6)	30 (10.9)	4 (9.1)	133 (5.3)	137 (5.4)
Asian	7 (2.4)	6 (13.6)	955 (37.7)	961 (37.3)	7 (2.5)	6 (13.6)	948 (38.0)	954 (37.5)
American Indian or Alaska native	0	0	6 (0.2)	6 (0.2)	0	0	6 (0.2)	6 (0.2)
Native Hawaiian or other Pacific Islander	0	0	8 (0.3)	8 (0.3)	0	0	8 (0.3)	8 (0.3)
Multiple	3 (1.0)	2 (4.5)	13 (0.5)	15 (0.6)	3 (1.1)	2 (4.5)	13 (0.5)	15 (0.6)
Ethnicity, n (%)								
Hispanic or Latino	76 (26.6)	5 (11.4)	248 (9.8)	253 (9.8)	73 (26.5)	5 (11.4)	245 (9.8)	250 (9.8)
Not Hispanic or Latino	210 (73.4)	39 (88.6)	2286 (90.2)	2325 (90.2)	202 (73.5)	39 (88.6)	2253 (90.2)	2292 (90.2)
Age (years), n (%)								
< 18	0	44 (100)	N/A	44 (1.7)	0	44 (100)	N/A	44 (1.7)
18 to < 40	109 (38.1)	N/A	472 (18.6)	472 (18.3)	103 (37.5)	N/A	462 (18.5)	462 (18.2)
40 to < 65	161 (56.3)	N/A	1637 (64.6)	1637 (63.5)	156 (56.7)	N/A	1620 (64.9)	1620 (63.7)
65 to < 75	15 (5.2)	N/A	328 (12.9)	328 (12.7)	15 (5.5)	N/A	321 (12.9)	321 (12.6)
≥ 75	1 (0.3)	N/A	97 (3.8)	97 (3.8)	1 (0.4)	N/A	95 (3.8)	95 (3.7)
Age (years)								
Mean (SD)	43.7 (11.71)	14.2 (1.55)	52.2 (12.97)	51.5 (13.77)	44.0 (11.78)	14.2 (1.55)	52.2 (12.95)	51.5 (13.76)
Median (minimum, maximum)	43.0 (20, 78)	14.0 (12.0, 17.0)	53.0 (19.0, 88.0)	53.0 (12.0, 88.0)	43.0 (20, 78)	14.0 (12.0, 17.0)	53.0 (19.0, 88.0)	53.0 (12.0, 88.0)
Geographic region, n (%)								
Europe	203 (71.0)	18 (40.9)	733 (28.9)	751 (29.1)	195 (70.9)	18 (40.9)	722 (28.9)	740 (29.1)
North America	81 (28.3)	22 (50.0)	700 (27.6)	722 (28.0)	78 (28.4)	22 (50.0)	686 (27.5)	708 (27.9)
Rest of World	2 (0.7)	4 (9.1)	1101 (43.4)	1105 (42.9)	2 (0.7)	4 (9.1)	1090 (43.6)	1094 (43.0)
HCV genotype,[a] n (%)								
1	165 (64.2)	37 (84.1)	1346 (53.1)	1383 (53.6)	159 (64.1)	37 (84.1)	1327 (53.1)	1364 (53.7)
2	11 (4.3)	3 (6.8)	601 (23.7)	604 (23.4)	11 (4.4)	3 (6.8)	596 (23.9)	599 (23.6)
3	33 (12.8)	1 (2.3)	367 (14.5)	368 (14.3)	31 (12.5)	1 (2.3)	359 (14.4)	360 (14.2)
4	48 (18.7)	3 (6.8)	88 (3.5)	91 (3.5)	47 (19.0)	3 (6.8)	85 (3.4)	88 (3.5)
5	0	0	23 (0.9)	23 (0.9)	0	0	23 (0.9)	23 (0.9)
6	0	0	109 (4.3)	109 (4.2)	0	0	108 (4.3)	108 (4.2)
Missing	29	0	0	0	27	0	0	0

The percentage of male subjects was higher in Study M20-350 than in the chronic HCV Phase 2/3 analysis set, and the percentage of white subjects in Study M20-350 was higher than in the chronic HCV Phase

2/3 analysis set. Subjects were younger and current alcohol use was greater in Study M20-350 than in the chronic HCV Phase 2/3 analysis set.

Other demographic characteristics for both the ITT and mITT-VF populations in Study M20-350 were generally similar to those of the chronic HCV Phase 2/3 analysis set.

As previously specified, no adolescents were included in Study M20-350.

Table 12. Virologic Response at Post-Treatment Week 12 (SVR12) in Study M20-350 and in the Chronic HCV Phase 2/3 Analysis Set: ITT and mITT-VF Populations

	ITT Population		mITT-VF Population	
	Study M20-350	Chronic HCV Phase 2/3 Analysis Set	Study M20-350	Chronic HCV Phase 2/3 Analysis Set
SVR_{12}, n/N (%)	275/286 (96.2)	2520/2578 (97.8)	275/275 (100)	2520/2542 (99.1)
95% CI[a]	(93.2, 97.8)	(97.1, 98.3)	(98.6, 100.0)	(98.7, 99.4)
Nonresponders, n/N (%)	11/286 (3.8)	58/2578 (2.2)	0/275	22/2542 (0.9)
Reason for nonresponse, n/N (%)				
Virologic failure	0/286	22/2578 (0.9)	0/275	22/2542 (0.9)
On-treatment virologic failure	0/286	3/2578 (0.1)	0/275	3/2542 (0.1)
Breakthrough	0/286	3/2578 (0.1)	0/275	3/2542 (0.1)
End-of-treatment failure	0/286	0/2578	0/275	0/2542
$Relapse_{12}$	0/278	19/2546 (0.7)	0/273	19/2529 (0.8)
Non-virologic failure	11/286 (3.8)	36/2578 (1.4)	N/A	N/A
Premature study treatment discontinuation	5/286 (1.7)	13/2578 (0.5)	N/A	N/A
HCV reinfection	2/286 (0.7)	0/2578	N/A	N/A
Missing SVR_{12} data	4/286 (1.4)	23/2578 (0.9)	N/A	N/A
Other	0/286	0/2578	N/A	N/A

a. Calculated using Wilson's score method.

The high SVR12 rates in the ITT and mITT-VF populations of Study M20-350 (96.2% and 100% respectively) were similar to those of the chronic HCV Phase 2/3 analysis set (97.8% and 99.1%, respectively). Relapse12 (0%), and post-treatment reinfection (0.7%) in the ITT population in Study M20-350 were similar to those in the chronic HCV Phase 2/3 analysis set (0.1%, 0.7%, and 0%, respectively).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is supported by Study M20-350 and an extrapolation in the paediatric population from 3 years of age (discussed under Clinical Pharmacology).

Study M20-350 was a Phase 3b, multicenter, single-arm, prospective clinical trial to evaluate safety and efficacy of GLE/PIB 8-Week treatment in adults and adolescents with acute hepatitis C virus (HCV)

infection. The CHMP considered that the existing EU and US therapeutic guidelines recommending treatment of acute hepatitis C preclude equipoise for considering a placebo-controlled study.

The recommended dosage and administration of Maviret in the study M20-350 were the same as for patients with chronic HCV indication, which is agreed.

The diagnosis of acute HCV was based on 4 clinical/biological criteria, combining recent seroconversion, symptoms, and risk behaviour reflecting real-world clinical scenarios.

The subjects enrolled were adults with acute HCV, treatment-naive, including people who inject drugs (PWID) and those with HIV co-infection. Despite being targeted in the study, there was a complete absence of adolescent participants, even though they were eligible, which can be explained by the low incidence of acute hepatitis C in this age group and the lack of systematic screening in paediatric settings.

The choice of SVR12 as primary endpoint is appropriate and in line with regulatory guidance. The 6% subtraction applied in the weighted efficacy threshold was requested to be justified in the pre-submission meeting with the MAH. The MAH stated that a 6% margin for comparison to a historical control (or active control in Study M13-594) has been used since early in the GLE/PIB development program as indicated by the following GLE/PIB chronic HCV registrational studies that were submitted in CHC. Moreover, the calculation of the efficacy threshold, using a weighted average of the SVR12 rates from the PWID and non-PWID subjects in the GLE/PIB Phase 2/3 chronic HCV studies along with a 6% margin, was discussed with and agreed to by the U.S. FDA. A similar approach (i.e., weighted average of chronic HCV SVR12 rates and 6% margin) was used for the calculation of the efficacy threshold in the prospective acute HCV Study M20-350. This approach, although somewhat arbitrary, can be acknowledged.

The original protocol was amended 4 times and had 2 administrative changes. None of these changes affected the study objectives, endpoints (choice or timing), entry criteria, or any aspect of study conduct that could impact the interpretation of results. The SAP was amended 3 times, with all changes summarized and justified in the latest version (v4). No modifications were made to the analyses of primary or key secondary endpoints.

Efficacy data and additional analyses

In the ITT population, 96.2% (275/286) of participants achieved SVR12 (95% CI: 93.2%–97.8%). The predefined efficacy threshold of 90.5%, based on historical data from chronic HCV patients, was exceeded.

In modified ITT population excluding Non-Virological Failures (mITT-VF; n = 275), 100% (275/275) of participants achieved SVR12 (95% CI: 98.6%–100%). This analysis excluded participants who did not achieve SVR12 due to reinfection (n = 2), premature discontinuation (n = 5), or missing data (n = 4). The efficacy threshold of 92.7% was surpassed.

The presence of NS3 and/or NS5A polymorphisms did not significantly reduce SVR12 rates.

The CHMP considered that primary and key secondary efficacy objectives were met. Treatment efficacy was unaffected by HCV genotype, baseline HCV/HIV-1 coinfection status, baseline HCV RNA or prior HCV infection history.

However, two subgroups showed lower SVR12 rates: Current/Recent People Who Inject Drugs (PWID) with 87.8% (36/41) achieved SVR12, compared to 97.6% (239/245) in former/non-PWID and Participants on Opioid Substitution Therapy (OST) with 76.2% (16/21) achieved SVR12, compared to 98.1% (254/259) in those not on OST.

There is a relatively low proportion of people who have recently or currently injected drugs (PWID), which could limit the generalizability of the results regarding dropout rates, reinfections, or adverse events unrelated to treatment. Finally, the study population was characterized by a majority of white patients, followed in high-volume centres and receiving regular medical follow-up, which may influence the conclusions drawn.

Comparing the results between population in Study M20-350 and in the chronic HCV infection 2/3 analysis set showed a similarity of SVR12.

Post-treatment reinfections were observed in 0.7% of the ITT population and therefore, the CHMP discussed whether a new course of treatment might be possible. Of note, the toxicology profile of GLE/ PIB was considered to support the safety of potential punctual re-treatments for episodes of re-infection. Furthermore, data on patients with a history of HCV reinfection were available from the M20-350 study. Specifically, 52 (18.2%) of the 286 participants enrolled in M20-350 reported 1 or more prior infections that were successfully treated prior to their M20-350 qualifying acute HCV infection. Of those reinfection cases, 13 (25%) were previously treated with GLE/PIB. The percentage of participants achieving SVR12 based on reinfection status (i.e., at least 1 or more prior infection versus no prior infection), as well as the safety profile for AE's related to GLE/PIB, did not appear to differ based on prior infection status. Among the 52 participants in the ITT population who had prior HCV infection, 51 (98.1%; 95% CI, 89.9–99.7) achieved SVR12 in Study M20-350. One participant (1.9%) did not achieve SVR12 due to premature discontinuation of GLE/PIB. Overall, the CHMP considered that there is sufficient evidence to support potential re-treatment for episodes of re-infection.

2.4.4. Conclusions on the clinical efficacy

The CHMP concluded that that the efficacy data support the use of Maviret in the treatment of acute hepatitis C virus infection in adults and children aged 3 years and older.

2.5. Clinical safety

Patient exposure

A total of 286 subjects were enrolled/treated at 70 sites in 8 countries: the US, Austria, Australia, Canada, France, Germany, Italy, and Spain. Subject disposition for all enrolled subjects is presented in Table 13.

Table 13. Subject Disposition: All Enrolled Subjects

	Number of Subjects
Enrolled/treated	286
Study treatment disposition	
Completed study treatment	278
Discontinued study treatment	8
Study disposition	
Completed study	278
Discontinued study	8

Of the 8 patients who discontinued the study treatment, 1 was due to an adverse event, which however was considered not related to study treatment by the investigator.

Adverse events

Table 14. Overview of adverse events: Safety analysis set

	Number (%) of Subjects (N = 286)
Any AE	171 (59.8)
AEs related to study treatment	45 (15.7)
AEs Grade 3 or higher	16 (5.6)
SAEs	10 (3.5)
SAEs related to treatment	0
AEs that led to discontinuation of study treatment	1 (0.3)
Related AEs that led to discontinuation of study treatment	0
Related AEs of Grade 3 or higher	0
SAEs that led to discontinuation of study treatment	0
AEs that led to interruption of study treatment	3 (1.0)
AEs that led to death	0
Deaths[a]	0

a. Includes death that were not treatment-emergent

Unless stated otherwise, all AEs presented in this overview were treatment-emergent, defined as those that began after the first dose of study treatment and no more than 30 days after the last dose of study treatment.

A total of 171 subjects (59.8%) in Study M20-350 (safety was analysed in comparison with the chronic HCV Phase 2/3 dataset, similar to the efficacy section) had at least 1 AE and 1436 subjects (55.7%) overall (adolescents and adults combined) in the safety chronic HCV Phase 2/3 analysis set had at least 1 AE. The 3 most frequently reported AEs in Study M20-350 were diarrhea (6.3%), fatigue (6.3%), and nasopharyngitis (4.9%), and the 3 most frequently reported AEs overall in the safety chronic HCV Phase 2/3 analysis set were headache (10.0%), fatigue (7.8%), and nausea (5.5%). No AEs occurred in ≥ 10% of subjects in Study M20-350; headache was the only AE that occurred in ≥ 10% of subjects in the safety chronic HCV Phase 2/3 analysis set overall. In both Study M20-350 and the safety chronic HCV Phase 2/3 analysis set, most subjects who had AEs had events with a maximum severity of Grade 1 or Grade 2.

Forty-five subjects (15.7%) in Study M20-350 and 660 subjects overall (25.6%) in the safety chronic HCV Phase 2/3 analysis set had at least 1 AE that was related to study treatment. Most AEs that were

related to study treatment occurred in < 1% of subjects in both analysis sets. AEs related to study treatment that occurred in ≥ 1% of subjects in Study M20-350 were fatigue (3.5%), asthenia (2.4%), headache (2.4%), diarrhea (1.7%), and nausea (1.4%). In the safety chronic HCV Phase 2/3 analysis set overall, these AEs were headache (6.8%), fatigue (6.2%), nausea (4.0%), pruritus (3.6%), diarrhea (1.6%), dizziness (1.5%), asthenia (1.2%), and insomnia (1.1%) overall.

Low percentages of subjects had AEs ≥ Grade 3 in severity in both Study M20-350 and the safety chronic HCV Phase 2/3 analysis set. A total of 5.6% of subjects in Study M20-350 had AEs ≥ Grade 3 in severity; these events occurred in 1 subject (0.3%) each, except for abscess limb, which occurred in 2 subjects (0.7%). No subject in Study M20-350 had an AE ≥ Grade 3 in severity that was related to study treatment. A total of 3.1% of subjects overall in the safety chronic HCV Phase 2/3 analysis set had AEs ≥ Grade 3 in severity; the ≥ Grade 3 events that occurred in more than 0.1% of subjects were hypertension (0.3%) and bronchitis (0.2%).

Six subjects (0.2%) overall in the safety chronic HCV Phase 2/3 analysis set had AEs ≥ Grade 3 in severity that were related to study treatment.

Overall, safety results from Study M20-350 were consistent with the known safety profile of Maviret and the safety chronic HCV Phase 2/3 analysis set and no new safety issue was identified.

Serious adverse event/deaths/other significant events

No subject died in Study M20-350. One adult subject in the safety chronic HCV Phase 2/3 analysis set had an AE of adenocarcinoma that led to death. This AE was not related to study treatment.

In study M20-350 ten subjects (3.5%) had ≥ 1 SAE (safety objective), none of which was related to study treatment or led to study treatment discontinuation (Table 15 below). Each SAE (except for abscess limb, which occurred in 2 subjects), occurred in 1 subject each.

Table 15. Number and Percentage of subjects with treatment-emergent serious adverse events by primary MedDRA system organ class and preferred term (safety analysis set)

MedDRA 27.0 system organ class preferred term	**Glecaprevir/Pibrentasvir (N = 286) n (%)**
Any adverse event	10 (3.5)
Gastrointestinal disorders	**2 (0.7)**
Enterocolitis	1 (0.3)
Rectal perforation	1 (0.3)
Infections and infestations	**3 (1.0)**
Abscess limb	2 (0.7)
Bacteraemia	1 (0.3)
Periorbital cellulitis	1 (0.3)
Septic embolus	1 (0.3)
Staphylococcal infection	1 (0.3)

Injury, poisoning and procedural complications	**4 (1.4)**
Alcohol poisoning	1 (0.3)
Ankle fracture	1 (0.3)
Overdose	1 (0.3)
Rib fracture	1 (0.3)
Road traffic accident	1 (0.3)
Toxicity to various agents	1 (0.3)
Metabolism and nutrition disorders	**1 (0.3)**
Hypoglycaemia	1 (0.3)
Psychiatric disorders	**2 (0.7)**
Drug abuse	1 (0.3)
Substance-induced psychotic disorder	1 (0.3)
Reproductive system and breast disorders	**1 (0.3)**
Pelvic pain	1 (0.3)

Glecaprevir/Pibrentasvir 300 mg/120 mg QD for 8 weeks.

Note: subjects are counted once in each row, regardless of the number of events they may have had.

Adverse events considered by the investigator to be AIDS-associated opportunistic infections are not included.

In the safety chronic HCV Phase 2/3 analysis set fifty-four subjects (2.1%) overall had SAEs; 4 of these subjects had SAEs (ileus [1 subject], adenocarcinoma [1 subject], and angioedema [2 subjects]) that led to discontinuation of study treatment; only the SAEs of angioedema (listed) were related to study treatment.

In study M20-350 the following AEs were to be considered as adverse events of special interest (AESI) for GLE/PIB:

- Treatment-emergent hepatic decompensation/hepatic failure events (safety objective), identified using the AbbVie PMQ for hepatic decompensation and hepatic failure.
- Postbaseline treatment-emergent and non-treatment-emergent events of HCC identified with the MedDRA PTs of hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, hepatic cancer metastatic, and hepatic cancer recurrent.

No subject had an AESI of hepatic decompensation or hepatic failure (safety objective) and no subject had an AESI of hepatocellular carcinoma (HCC).

In the safety chronic HCV Phase 2/3 analysis set, one subject had an AESI of hepatic decompensation/hepatic failure (ascites).

Laboratory findings

In study M20-350, Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 hematology or chemistry values that worsened from Baseline during the Treatment Period (Table 16) were isolated and

not clinically significant; no subject had haematology or chemistry values that worsened to Grade 4 during the Treatment Period.

Table 16. CTCAE Grade 3 Laboratories Values during the treatment Period that worsened from Baseline: Safety Analysis Set

Variable (unit)	**n/N Observed (%)** **(N = 286)**
Hemoglobin (g/L)	0/282
Platelets (109 /L)	0/280
Leukocytes (109 /L)	0/282
Neutrophils (109 /L)	5/282 (1.8)
Lymphocytes (109 /L)	0/282
Prothrombin INR (ratio)	0/280
ALT (U/L)	0/282
AST (U/L)	2/282 (0.7)
GGT (U/L)	0/281
ALP (U/L)	0/282
Total bilirubin (µmol/L)	1/282 (0.4)
Creatinine (µmol/L)	0/282
Creatinine clearance (mL/min)	0/281
eGFR (mL/min/1.73m2)	0/281
Sodium (mmol/L)-high	0/281
Sodium (mmol/L)-low	0/281
Potassium (mmol/L)-high	0/281
Potassium (mmol/L)-low	0/281
Glucose (mmol/L)-high	0/282
Glucose (mmol/L)-low	0/282
Albumin (g/L)	0/282
Cholesterol (mmol/L)	0/281
Triglycerides (mmol/L)	1/281 (0.4)
Magnesium (mmol/L)-high	0/280
Magnesium (mmol/L)-low	0/280

Note: Grades based on NCI CTCAE Version 4.03. Grade must have been more extreme than baseline grade. Subject must have had a baseline and at least 1 postbaseline value during treatment for the respective parameter to be included in the summary

As expected, subjects with acute HCV infection had higher mean baseline ALT (228.2 U/L in the ITT population of Study M20-350 versus 63.2 U/L in the overall ITT population of the chronic HCV Phase 2/3 analysis set) and higher mean baseline total bilirubin levels (13.4 µmol/L versus 10.4 µmol/L) than subjects with chronic HCV infection.

No subject in Study M20-350 worsened from the baseline grade to an ALT Grade 2 or higher during the Treatment Period (safety objective); 1 subject (0.4%) had Grade 3 total bilirubin during the Treatment Period that worsened from the baseline grade (Grade 2); 14 subjects (5.0%) had Grade 2 total bilirubin during the Treatment Period that worsened from the baseline grade. Six subjects (0.2%) overall in the safety chronic HCV Phase 2/3 analysis set worsened from the baseline grade to an ALT Grade 2, and 2 subjects (< 0.1%) worsened from the baseline grade to an ALT Grade 3 during the Treatment Period. Seven subjects (0.3%) overall in the safety chronic HCV Phase 2/3 analysis set had Grade 3 total bilirubin during the Treatment Period that worsened from the baseline grade, and 77 subjects (3.0%) had Grade 2 total bilirubin during the Treatment Period that worsened from the baseline grade.

For ALT and total bilirubin in Study M20-350, shifts from Baseline to Week 4, the final treatment visit, and the maximum grade during treatment were summarized for subjects who had a baseline value and a value at the respective time point; therefore, the number of subjects with a baseline value could differ between Week 4 and final treatment visit summaries.

All subjects who had baseline ALT elevations of Grade 2, 3, or 4 improved from Baseline to a lesser grade at Week 4 (55, 73, and 6 subjects, respectively) and at the final treatment visit (57, 75, and 8 subjects, respectively). No subject in Study M20-350 with an ALT elevation of Grade 1, 2, or 3 at Baseline worsened to a higher-grade during treatment.

Of the subjects who had baseline total bilirubin elevations of Grade 2, 9 subjects (75.0%) and 8 subjects (66.7%) improved from Baseline to a lesser grade at Week 4 and at the final treatment visit, respectively. Of the subjects who had baseline total bilirubin elevations of Grade 3, all improved from Baseline at Week 4 (2 subjects) and at the final treatment visit (3 subjects). No subject had a baseline total bilirubin elevation of Grade 4. Of those subjects with a total bilirubin of Grade 1, 2, or 3 at Baseline, 6 subjects (31.6%), 1 subject (8.3%), and 0 subjects, respectively, worsened to a higher-grade during treatment. Overall, a mild increase in total bilirubin postbaseline in Study M20-350 is consistent with what was seen in the safety chronic HCV Phase 2/3 analysis set. No subject in Study M20-350 discontinued or interrupted study treatment because of elevations in total bilirubin. No subject in Study M20-350 had ALT or total bilirubin values that met the criteria listed below:

- Post-nadir ALT > 5 × ULN
- Post-nadir ALT > 3 × ULN with total bilirubin > 2 × ULN (safety objective)
- Post-nadir ALT > 3 × ULN and total bilirubin ≤ 2 × ULN
- Confirmed (2 consecutive values) post-nadir ALT > 5 × ULN
- Post-nadir ALT > 3 × ULN and a concurrent total bilirubin > 2 × ULN with a direct bilirubin: total bilirubin ratio > 0.4

One subject (< 0.1%) in the safety chronic HCV Phase 2/3 analysis set, who was not a PWID and who did not have HIV-1 co-infection, had post-nadir ALT > 3 × ULN with total bilirubin > 2 × ULN.

Six of 282 subjects in Study M20-350 with on-treatment values (2.1%) met the criterion of total bilirubin ≥ 2 × ULN and > Baseline. None of these subjects had post-nadir AST > 3 × ULN during the Treatment Period. These bilirubin elevations did not require study treatment discontinuation or interruption.

No subject in Study M20-350 had suspected drug-induced liver injury.

No clinically meaningful differences in laboratory values were observed between subgroups in Study M20-350 based on the intrinsic and extrinsic factors and no clinically meaningful differences were observed between the subgroups in Study M20-350 and those in the safety chronic HCV Phase 2/3 analysis set.

No clinically important trends in vital signs were observed in Study M20-350. Any significant physical examination findings after the first dose of study drug in Study M20-350 were recorded as AEs. No pregnancies were reported in Study M20-350.

Safety in special populations

Since no adolescent were enrolled in the study M20-350, the MAH's compared data for the paediatric population based on study M16-123 in paediatric patients with chronic HCV infection (subjects aged ≥3 to <18 years).

The results of this study demonstrated that the safety profile in both children and adolescents was consistent with that in adults.

Safety related to drug-drug interactions and other interactions

No analyses were performed to evaluate drug-drug interactions.

Discontinuation due to adverse events

In study M20-350

One subject had an adverse event that led to discontinuation of study treatment; this was a Grade 2 AE of abdominal pain upper; the AE was not serious and was not related to study treatment.

Three subjects had at least 1 AE that led to interruption of study treatment:

1 subject reported Grade 1 AEs of diarrhoea, nausea, and regurgitation that were considered to have a reasonable possibility of being related to study treatment. Diarrhoea and nausea are listed in Maviret SmPC. The other 2 subjects experienced abscess limb and overdose, which were not related to study treatment.

In the safety chronic HCV Phase 2/3 analysis set

Six subjects (0.2%) had AEs that led to discontinuation of study treatment. Of them, the nonserious events of nausea, vomiting, and pruritus and SAEs of angioedema were related to study treatment. Angioedema is a listed adverse drug reaction (rare) in all GLE/PIB Reference Safety Information.

No new safety concerns were identified.

Post marketing experience

As reported in the Periodic Safety Update Report for the reporting interval from 26 July 2022 through 25 July 2025, the worldwide post-marketing patient exposure to GLE/PIB was estimated to be 1,277,774 patient treatment courses (PTC) cumulatively, since 26 July 2017, with an estimated patient exposure

of 419,349 PTC for the reporting interval. PTC was estimated based on a treatment duration of 8 weeks or 56 days. The adverse events evaluated during the reporting interval were consistent with the established safety profile of GLE/PIB, as described in the product label for treatment of chronic HCV infection.

Data concerning study M16-123 in the paediatric population were submitted by the MAH in the latest Periodic Safety Update Report, and no new safety concerns were identified.

2.5.1. Discussion on clinical safety

Safety assessment is based on data from study M20-350 and the safety chronic HCV Phase 2/3 analysis set.

Study M20-350 was a multicentre, single-arm prospective study evaluating the safety and efficacy of 8-week treatment with glecaprevir/pibrentasvir in adults and adolescents with confirmed acute HCV infection by comparing the sustained virologic response at 12 weeks post treatment (SVR12) rate from this study to the historical SVR12 rate in subjects with chronic HCV infection who were treated with GLE/PIB.

286 participants in the study M20-350 were enrolled, all of whom were adults, although the study was designed to enrol both adults and adolescents.

The most common adverse events related to the study treatment were fatigue, asthenia, headache, diarrhoea and nausea. All of these are listed in Maviret SmPC.

Most adverse events were grade 1 and grade 2 intensity; a total of 5.6% of subjects had AEs ≥ Grade 3 in severity, of which none was related to study treatment.

One subject had an adverse event that led to discontinuation of study treatment; however, the adverse event was not serious and was not related to study treatment.

Ten subjects had ≥1 SAE, none of which was related to study treatment or led to study treatment discontinuation.

No subject died or had an adverse reaction of special interest (AESI).

The review of laboratory findings and other safety parameters did not raise new significant safety concern.

Parameters regarding ALT grade and elevation of total bilirubin were consistent with data from the safety chronic HCV Phase 2/3 analysis set.

In the safety chronic HCV Phase 2/3 analysis set, 2578 subjects were enrolled, of which 44 adolescents and 2534 adults. The most common AEs related to the study treatment were headache (6.8%), fatigue (6.2%), nausea (4.0%), pruritus (3.6%), diarrhea (1.6%), dizziness (1.5%), asthenia (1.2%), and insomnia (1.1%). Fifty-four subjects (2.1%) had SAEs, of which one, angioedema, was related to study treatment.

Six subjects (0.2%) had AEs that led to discontinuation of study treatment. Of them, the non-serious events of nausea, vomiting, and pruritus and SAEs of angioedema were related to study treatment.
There was one fatal case of adenocarcinoma; however, this AE was not related to study treatment.
One subject had an AESI of hepatic decompensation/hepatic failure (ascites).

In view of these data, the CHMP considered that the safety profile of Maviret in acute hepatitis C virus infection is consistent with the known safety profile in chronic hepatitis C virus infection. No new significant safety issues were identified.

2.5.2. Conclusions on clinical safety

The CHMP concluded that that the safety data support the use of Maviret in the treatment of acute hepatitis C virus infection in adults and children aged 3 years and older.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 10.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 10.0 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	Safety in patients with moderate hepatic impairment (Child-Pugh B)

Pharmacovigilance plan

Safety Concern	**Routine Risk Minimization Activities**
Missing information: Safety in patients with moderate hepatic impairment (Child-Pugh B)	Routine risk communication: • 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). Routine risk minimization activities recommending specific clinical measures to address the risk: • 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). Other routine risk minimization measures: • Restricted medical prescription. o Maviret treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.

Risk minimisation measures

Safety Concern	**Risk Minimization Measures**	**Pharmacovigilance Activities**
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). • Restricted medical prescription. o Maviret treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection. Additional risk minimization measures: None.	Pharmacovigilance activities include adverse reaction reporting, signal detection and aggregate safety reporting via PSUR. Additional pharmacovigilance activities: None.

2.7. Update of the Product information

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

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Denmark, Malta and Iceland. The local representative of the United Kingdom has been deleted.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- No updates have been made to section "2. What you need to know before you take Maviret / What you need to know before your child takes Maviret".
- No updates have been made to the posology under section 3 "How much to take". The recommended dose for acute HCV infection patients is the same as that for chronic HCV infection patients: for adults, children aged 12 years and older, or children weighing at least 45 kg: 3 tablets of Maviret 100 mg/40 mg taken together, once a day; for children aged 3 years to less than 12 years old: 3 sachets for children from 12 to less than 20 kg, 4 sachets for children from 20 to less than 30 kg, 5 sachets for children from 30 to lesss than 45 kg.
- No new adverse reactions have been identified under section "4. Possible side effects". No safety changes are proposed in section 2 or 4 at all as a result of the proposed extension to the indication.
- The proposed leaflet content includes updates to section "1. What Maviret is and what it is used for" to include additional text for the acute HCV infection indication in lay terms. The addition of limited acute HCV infection specific information does not change the format or layout of the approved package leaflets.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Approximately 50 million people are infected with hepatitis C virus (HCV) worldwide. There were approximately 1 million new infections worldwide in 2022 and an estimated 67,400 new infections in the United States (US) in 2022,1,2 with acute HCV infections 2 times as high as in 2015. In 2021, 7,535 cases of HCV (acute, chronic, and unspecified combined) were reported from all 13 Canadian provinces and territories at a rate of 19.7 cases per 100,000 people living in Canada. Of these 7,535 cases of HCV, 209 cases were reported as acute infection. In 2022, 23,273 new cases of HCV were reported in 29 EU/European Economic Area (EEA) Member States, a crude rate of 6.2 per 100,000. This rise in acute HCV infection rates is thought to be related to an increase in the prevalence of behaviours that increase the risk of HCV transmission, primarily injection drug use.

Acute HCV infection can be detected following known or suspected exposures and periodically among populations with ongoing exposure. Acute HCV infection is confirmed when a patient has a negative hepatitis C antibody and a detectable HCV viral load or when an individual with a recent exposure seroconverts from a negative to a positive hepatitis C antibody. Acute hepatitis C (HCV) infection is defined as the 6-month time-period following exposure to hepatitis C.

Spontaneous clearing of HCV RNA by the subject may occur with a variable rate, higher in children (25% to 50% of infected infants spontaneously by 4 years of age) than adults (15 to 25%).

However, no reliable predictors of spontaneous clearance have been established for any age group. Furthermore, adult/adolescent patients with acute HCV infection are still at risk of downstream transmission while they await spontaneous clearance of the virus. It is necessary to reduce community transmission in order to achieve HCV elimination. The WHO has set a goal to eliminate HCV as a major public health threat by 2030.

3.1.2. Available therapies and unmet medical need

Current HCV treatment guidelines recommend immediate treatment, as waiting to treat results in loss of patients to care and increases onward community transmission. European (EASL) guidelines recommend treatment without delay for all treatment-naïve and treatment-experienced patients with recently acquired or chronic HCV infection. Similarly, US guidelines (AASLD) also recommend treatment for any patients with confirmed acute HCV infection without awaiting possible spontaneous clearance (i.e., test and treat approach).

Unlike the US, Maviret in the EU is currently only authorized in the treatment of chronic hepatitis C virus infection. With this submission, the MAH has applied for extension of indication to treatment of acute hepatitis C virus infection.

3.1.3. Main clinical studies

The application is supported by a Phase 3b, multicentre, single-arm, prospective Study M20-350 that was designed to evaluate the safety and efficacy of 8 weeks of GLE/PIB treatment in adults and adolescents with physician-diagnosed acute HCV infection, with no prior treatment for the current infection, and with no cirrhosis or with compensated cirrhosis.

Supportive data are based on comparing the M20-350 study results with the results for the ITT and mITT-VF populations within the chronic HCV Phase 2/3 analysis set, which consisted of adults and adolescents with chronic HCV infection who participated in any of 14 GLE/PIB studies.

3.2. Favourable effects

The study M20-350 results demonstrated that the primary efficacy endpoint was met with a sustained virologic response at 12 weeks (SVR_{12}) of 96.2% (275/286) in the intention-to-treat (ITT) population (95% CI: 93.2%–97.8%). In addition, the key secondary endpoint was also met with a SVR_{12} rate of 100% (275/275) in the mITT-VF population (95% CI: 98.6%–100%).

Comparing the results between population in Study M20-350 and in the chronic 2/3 analysis set showed a similar sustained virologic response (SVR_{12}).

This high level of SVR12 largely is considered to supersede the rate of spontaneous clearance in adults and to a lesser extent in children.

3.3. Uncertainties and limitations about favourable effects

The CHMP considered that the MAH has not planned any PK sampling in study M20-350 to corroborate the assumption that acute hepatitis is unlikely to impact the pharmacokinetics of the active substances. In this context, the CHMP acknowledged that the high sustained virologic response rate reported in adults treated with the same dose as authorised in the treatment of chronic hepatitis C indicates that, if differential pharmacokinetics exists, it is unlikely to translate into differences of clinical relevance in

adults. Moreover, the MAH elaborated on the absence of biological plausibility for a different impact on hepatic functionality between adults and subjects from 3 years of age. In particular, the CHMP considered that the MAH thoroughly addressed the expected changes in the metabolism of glecaprevir and pibrentasvir in the target paediatric population with acute hepatitis, taking into account all pharmacokinetic determinants (maturation/function of CYP3A hepatic enzyme, intestinal and hepatic P-gp, BCRP, and OATP1B1/3, as well as hepatic blood flow). It is acknowledged that pibrentasvir it is not metabolized, which limits the influence of enzyme maturation on its pharmacokinetic profile. In addition, for glecaprevir, given the hepatic maturation achieved in children from 3 years of age, the metabolic differences are not anticipated to have a clinically meaningful impact on in its pharmacokinetics in children and can be considered relatively comparable to adults. Overall, the CHMP considered that the dose authorised in the treatment of chronic hepatitis C virus infection can also be used in treatment of acute hepatitis C virus infection.

3.4. Unfavourable effects

The most common adverse events related to the study treatment were fatigue, asthenia and headache, which are all listed in the Product Information. No subject treated with Maviret had a serious adverse reaction and no subject discontinued treatment due to an adverse reaction.

In view of the available data, the CHMP considered that the safety profile of Maviret in acute hepatitis C virus infection is consistent with the known safety profile in chronic hepatitis C virus infection.

No new significant safety issues were identified.

3.5. Uncertainties and limitations about unfavourable effects

Paediatric population was not enrolled in study M20-350, although the study was designed to enrol adults and adolescents. Considering that Maviret is already authorised in treatment of chronic hepatitis C infection with the same posology, this limitation is not considered to pose an additional risk in terms of safety.

3.6. Effects Table

Table 17. Effects Table for Maviret in the treatment of acute hepatitis C virus infection in adults and children aged 3 years and older

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
SVR12 rate in the ITT population	Primary Efficacy Endpoint	%	96.2%		Open label study (275/286, 95% CI: 93.2%, 97.8%)	M20-350
SVR12 rate in the mITT-VF population	Secondary Efficacy Endpoint	%	100%		Open label study (275/275, 95% CI:	M20-350

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					98.6%, 100.0%)	

Unfavourable Effects

With regard to the common adverse events considered related to the study treatment, the qualitative and quantitative safety data are consistent with the safety information currently described in the SmPC of Maviret. No serious adverse event related to the study treatment was reported.

No subject died or had an AESI.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A high SVR12 rate translates into high clinical cure rates, and subsequently low risk for the development of resistance associated substitutions. Clinical cure reduces the risk of HCV progression to end-stage liver disease and its complications, e.g. decompensated cirrhosis, liver transplantation, and hepatocellular carcinoma.

Routine risk minimization activities, i.e. adverse reaction reporting, signal detection and aggregate safety reporting via PSUR, are sufficient to manage the safety of the product.

3.7.2. Balance of benefits and risks

An 8-week short treatment course of Maviret is shown as providing a high response rate, superseding the expected rate of spontaneous clearance, with a safety profile not significantly mitigating such a benefit. Considering the risk of HCV secondary transmission, the benefits can both be regarded as both individual and collective, echoing the WHO 2030 objective of eradicating HCV.

3.8. Conclusions

The overall B/R of Maviret in the treatment of acute hepatitis C in adults and children from 3 years of age is positive.

4. Recommendations

Outcome

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

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

Extension of indication to include treatment of acute HCV infection, based on the final results from study M20-350; this was a multicentre, single-arm prospective study to evaluate safety and efficacy of GLE/PIB 8-week treatment in adults and adolescents with acute hepatitis C virus (HCV) infection. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2, of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.0 of the RMP has also been approved. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

The variation leads to amendments to the annex(es) I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.