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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Maviret

glecaprevir / pibrentasvir

Procedure no: EMEA/H/C/004430/P46/012

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	27 Mar 2023	27 Mar 2023
☐	CHMP Rapporteur Assessment Report	02 May 2023	26 Apr 2023
☐	CHMP members comments	15 May 2023	15 May 2023
☐	Updated CHMP Rapporteur Assessment Report	17 May 2023	N/A
☒	CHMP adoption of conclusions:	25 May 2023	25 May 2023

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1. Introduction

On 27 March 2023, the MAH submitted the final clinical study report for the completed paediatric study M16-123 for Maviret (glecaprevir/pibrentsavir) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study M16-123 (called DORA study) is a Phase 2/3, open-label, multicenter study to evaluate the pharmacokinetics (PK), efficacy, and safety of glecaprevir /pibrentasvir (GLE/PIB) for 8, 12, or 16 weeks in hepatitis C virus (HCV) genotype (GT) 1 - GT6-infected pediatric subjects ≥ 3 to < 18 years of age without cirrhosis or with compensated cirrhosis, with or without human immunodeficiency virus (HIV) co-infection, who were either treatment-naïve (TN), treatment-experienced (TE) with pegylated interferon (pegIFN) with or without ribavirin (RBV), or TE with sofosbuvir (SOF) + RBV with or without pegIFN.

Part 1 of the study evaluated the use of the adult bilayer tablets in adolescents (Cohort 1) and was previously submitted and assessed to support the extension of the indication in paediatric patients from 12 years of age (through type II variation II12). Part 2 of the study evaluated the use of the pediatric coated granules formulation of GLE + PIB in children ≥ 3 to < 12 years of age (Cohorts 2 to 4). The interim efficacy and safety data up to week 12 post-treatment of all children included in the Part 2 were supportive for the extension of indication in paediatric patients aged > 3 years (Line extension X33G).

The MAH is now submitting the final data from this study through 144 weeks post-treatment after completion of the whole study.

A short critical expert overview has also been provided.

No SmPC update for Maviret is proposed by the MAH in relation to this study.

2. Scientific discussion

2.1. Information on the development program

The clinical study report (CSR) (R&D/22/1094) for Study M16-123 contains data through 144 weeks post-treatment and presents the final analysis after completion of the whole study.

2.2. Information on the pharmaceutical formulation used in the study

Each dose of study drug was dispensed in the form of an adult coformulated tablet (GLE/PIB 100 mg/40 mg) or a pediatric formulation (Coated granules in sachets, 50 mg/ 20 mg unit dose) at the visits.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study M16-123, "An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Subjects with Genotypes 1 – 6 Chronic Hepatitis C Virus (HCV) Infection (DORA) " .

2.3.2. Clinical study

Description

Study M16-123 was a Phase 2/3, open-label, multicenter study to evaluate the PK, efficacy, and safety of GLE/PIB for 8, 12, or 16 weeks in HCV GT1 – GT6-infected pediatric subjects ≥ 3 to < 18 years of age, with or without compensated cirrhosis, with or without human immunodeficiency virus (HIV) coinfection, who were either treatment-naïve (TN), treatment-experienced (TE) with pegylated interferon (pegIFN) with or without ribavirin (RBV) or TE with sofosbuvir (SOF) plus RBV with or without pegIFN.

Methods

The study was divided into 2 parts:

- Part 1 of the study allowed for enrollment of approximately 44 HCV GT1 – GT6-infected adolescent subjects into the ≥ 12 to < 18 years old age group who were willing to swallow the adult formulation of GLE/PIB (Cohort 1).
- Part 2 of the study allowed for enrollment of approximately 81 HCV GT1 – GT6 infected pediatric subjects divided into the ≥ 9 to < 12 (Cohort 2), ≥ 6 to < 9 (Cohort 3), and ≥ 3 to < 6 (Cohort 4) years old age groups who received the pediatric formulation of GLE + PIB. In each cohort, subjects were enrolled first into the intensive pharmacokinetic (IPK) portion, followed by the non-IPK safety/efficacy portions.

In Part 2, subjects in each cohort were enrolled in parallel. Each cohort was expected to enrol approximately 12 HCV-infected subjects in the IPK portions to adequately characterize the PK of a particular age group. Subjects in the IPK portion of the study had to be HCV TN and HIV-negative, and the HCV genotype must have been identified. The remainder of subjects were enrolled for the evaluation of safety and efficacy of each age group until the total pediatric study population reached approximately 125 subjects (TN or TE [prior interferon, RBV, or SOF exposure], with or without HIV-1 coinfection, and could have included subjects with mixed or indeterminate HCV genotype). Additional PK assessments were obtained for subjects enrolled in Japan for the purpose of further characterization within Japanese subjects (this was not included within the aforementioned 12 subjects). Safety and efficacy were assessed throughout the study.

In the Post-Treatment (PT) **Period, all subjects administered at least 1 dose of study drug were to be followed though PT Week 144 to monitor for safety, viral response, emergence and/or persistence of resistance-associated viral substitutions, and growth and development.**

The planned total duration of the study (excluding screening) was up to 160 weeks for all subjects.

Study participants

Approximately 125 subjects overall in Part 1 and Part 2 of the study, divided into 4 age groups, ≥ 3 to < 6, ≥ 6 to < 9, ≥ 9 to < 12, and ≥ 12 to < 18 years of age.

Approximately 12 subjects were to be enrolled into the IPK portion of the study for each age group.

Main Inclusion Criteria:

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

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

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

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

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

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

Main Exclusion Criteria:

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

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

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

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

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

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

- Confirmed presence of hepatocellular carcinoma (HCC).

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

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

Treatments

Subjects in Part 1 were dosed with GLE/PIB 300 mg/120 mg QD, and subjects in Part 2 were dosed based on body weight/age.

The final proposed 50 mg/20 mg dose ratio of GLE/PIB was administered to a total of 30 subjects across all 3 age cohorts in the IPK portion of Part 2. Treatment duration was 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, prior treatment experience, and geographical location in accordance with the use of GLE/PIB in adults.

Objective(s)

The primary objectives of this study were to:

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

• Evaluate the safety and tolerability of GLE/PIB by age group, cirrhosis status, and across all subjects;

• Evaluate the percentage of subjects with sustained virologic response for 12 weeks post-treatment (SVR12) in HCV genotype (GT)1 – GT6 infected pediatric subjects (US Food and Drug Administration [FDA] only, otherwise secondary).

The secondary objectives of this study were to assess:

• Maximum observed plasma concentration (Cmax) and clearance of GLE and PIB;

• The percentage of subjects with on-treatment HCV virologic failure (i.e., breakthrough or failure to suppress at the end of treatment) summarized for each age group and overall;

• The percentage of subjects with post-treatment HCV relapse summarized for each age group and overall;

• The percentage of subjects with new HCV infection (or reinfection) summarized for each age group and overall;

• Pharmacokinetics and emergence/persistence of viral variants in subjects with available samples;

• Palatability/acceptability of pediatric formulation by age group and overall.

Outcomes/endpoints

The primary PK endpoints in Part 1 and Part 2 were steady state AUC values for GLE and PIB estimated by non-compartmental analysis or population PK analysis including AUC at Week 2 in subjects with IPK samples and AUC in all subjects with or without IPK samples.

The primary (for US FDA) efficacy endpoint in Part 1 and Part 2 was SVR12.

The secondary endpoints in Part 1 and Part 2 were:
• Cmax and clearance of GLE and PIB at Week 2;
• The percentage of subjects with on-treatment virologic failure (i.e., breakthrough or failure to suppress at EOT) by age group and overall;
• The percentage of subjects with PT relapse by age group and overall;
• The percentage of subjects with new HCV infection (i.e., reinfection) at any time up to the last study visit by age group and overall;
• Assessment of palatability/acceptability of the pediatric formulation by age group and overall.

Sample size

It was planned to enroll a total of approximately 125 subjects into this study. The primary PK endpoint was steady state AUC of GLE and PIB. Practical considerations included the expected larger number of adolescents within this population, in comparison to the younger age cohorts.

The proposed sample size of 48 subjects (approximately 12 subjects for each age cohort) for IPK sampling (separate from sampling performed in subjects in Japan) was expected to adequately characterize the PK of GLE and PIB to enable dose selection in pediatric subjects. Approximately 10

subjects underwent additional PK sampling to support characterization of GLE and PIB exposures in children from Japan. Additional subjects were enrolled to reach the proposed total of 125 subjects to provide safety and efficacy information.

Randomisation and blinding (masking) This was an open-label study.

Statistical Methods

ITT Population

The ITT population included all enrolled subjects who received at least 1 dose of study drug (Cohort 1 [Part 1, adolescents], N = 47; Cohorts 2 – 4 [Part 2, pediatric], N = 80) and was used to summarize demographics and baseline characteristics; medical history; previous, concomitant, and PT medications; treatment exposure and compliance; and efficacy.

mITT-VF Population

Sensitivity analyses of SVR12, when applicable, were performed on the ITT population modified to exclude subjects who did not achieve SVR12 for reasons other than virologic failure (mITT-VF [Cohort 1 [Part 1, adolescents] N = 47; Cohorts 2 – 4 [Part 2, pediatric] N = 78]). For Part 1, the mITT-VF population was the same as the ITT population as all subjects achieved SVR12. In Part 2, two subjects who prematurely discontinued were excluded from the mITT-VF population; 1 subject from Cohort 2 who prematurely discontinued on Treatment Day 4 and 1 subject from Cohort 4 who prematurely discontinued on Treatment Day 1.

Results

Baseline Disease data

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

A total of 70 female (70/127, 55.1%) and 57 male (57/127, 44.9%) patients were included in the ITT population.

Of the 127 treated patients, 47 (37.0%) were enrolled in Cohort 1 (≥ 12 to < 18 years old), 29 (22.8%) in Cohort 2 (≥ 9 to < 12 years old), 27 (21.3%) (in Cohort 3 (≥ 6 to < 9 years old) and 24 (18.9%) in Cohort 4 (≥ 3 to < 6 years old).

All subjects were noncirrhotic, and the majority of subjects were HCV GT1-infected (74.8%). Two subjects from Cohort 1 (adolescents) and 1 subject from Cohort 3 (pediatric) were HCV/HIV-1 coinfected. There were no substantial differences in Japanese subjects compared to the non-Japanese and the overall subjects.

Number analysed

A total of 48 subjects were enrolled in Part 1 of the study (≥ 12 to < 18 year-old age group) and 47 subjects received at least 1 dose of the study drug. A total of 81 subjects were enrolled in Part 2 of the study (≥ 3 to < 12 year-old age group) and 80 subjects received at least 1 dose of the study drug.

Efficacy results

For Cohort 1 (adolescent), an SVR12 rate of 100% (47/47) with a 2-sided 95% CI of (92.4%, 100.0%) was achieved.

No subjects experienced on-treatment virologic failure (breakthrough or end-of-treatment failure), relapse, or had a new HCV infection (reinfection) at any time up to the last study visit. Overall, with an SVR12 rate of 100% among all subjects, there was no evidence that the SVR12 rate was affected by any demographic or baseline characteristic, including baseline HCV RNA levels, HCV/HIV-1coinfection, or other relevant comorbidities.

No adolescent subjects experienced relapse after achieving SVR12, and all 47 subjects achieved sustained virologic response 24 weeks post-treatment (SVR24).

For Cohorts 2 – 4 (pediatric), an SVR12 rate of 96.3% (77/80 subjects) with a 2-sided 95% CI of (89.5%, 98.7%) was achieved.

Three subjects were considered SVR12 non responders:

- One subject due to virologic failure : a TN male, from Cohort 2, with HCV GT3b, experienced relapse by PT Week 4. The subject was administered GLE 200 mg + PIB 75 mg (Initial Dose) once daily (QD) for 8 weeks and had HCV RNA < 15 IU/mL at Treatment Day 26 with no HCV RNA detected at Treatment Day 56. At PT Day 29, HCV RNA was detected. Study drug was completed and there were no reports of non-compliance.
- Two subjects due to non-virologic reasons (premature discontinuation of study drug due to rash erythematous and refusal to swallow entire dose, respectively)

Results of sensitivity analyses were consistent with those of the primary analyses for SVR12. Sustained virologic response 12 weeks post-treatment was achieved by 98.7% (77/78) of subjects in Cohorts 2 – 4 (pediatric subjects) in the mITT-VF population.

No other subject experienced on-treatment virologic failure (breakthrough or end-of-treatment failure). No subject had a new HCV infection (reinfection) at any time up to the last available study visit.

None of the subjects on the GLE + PIB final 50 mg/20 mg dose ratio experienced virologic failure.

No pediatric subjects between ≥ 3 to < 12 years of age experienced relapse after achieving SVR12.

As only 1 subject exhibited virologic failure, no negative baseline predictors/trends could be identified, including demographics, baseline HCV RNA level, genotype, presence of baseline polymorphisms, or common comorbidities.

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***Rapporteur's comment**:*

No new relevant efficacy data is identified in these final study results. Most of important efficacy results have already been discussed within the type II variation II12 (extension of indication in adolescents) and in the line extension X33G (extension of indication in paediatric patients aged ≥ 3years to < 12 years). Except the case of relapse in cohort 2 already discussed as part of the X33G dossier, no other paediatric subjects experienced on–treatment virological failure, relapse, or had a new HCV infection during the entire duration of the study.

Pharmacokinetic

PK parameters summary of GLE and PIB at Week 2 for adolescent subjects aged ≥ 12 to < 18 years (cohort 1) and children aged ≥ 3 to < 12 years (cohorts 2, 3 and 4) are presented in Table 1 and Table 2 respectively.

Table 1: Geometric mean (mean CV%) PK parameters of GLE and PIB (week 2 IPK) from Part 1

		GLE/PIB 300 mg/120 mg QD Adult Formulation Week 2 (N = 14)[a]	
PK Parameters	(Units)	GLE	PIB
		Adolescent Subjects ≥ 12 to < 18 Years of Age	
C_{max}	(ng/mL)	1040 (1310, 66)	174 (183, 28)
T_{max}[b]	(h)	4.0 (2.0 – 6.0)	4.0 (4.0 – 6.0)
AUC_{24}	(ng•h/mL)	4790 (5790, 67)	1380 (1460, 31)
C_{trough}	(ng/mL)	3.79 (4.57, 61)	15.0 (16.9, 44)
CL/F	(L/h)	62.6 (76.0, 68)	86.9 (94.3, 50)

Table 2: Geometric mean (mean CV%) PK parameters of GLE and PIB (week 2 IPK) following the final proposed dosing regimens (Part 2)

		GLE + PIB QD Pediatric Formulation Week 2	
PK Parameters	(Units)	GLE	PIB
		Cohort 2 (N = 13)	
C_{max}	(ng/mL)	1370 (2960, 177)	225 (266, 55)
T_{max}[a]	(h)	4.0 (2.0 – 6.0)	4.0 (2.0 – 6.0)
AUC_{24}	(ng•h/mL)	7870 (21800, 215)	2200 (2930, 78)
C_{trough}	(ng/mL)	12.4 (220, 329)	36.5 (69.7, 141)
CL/F	(L/h)	31.8 (55.7, 104)	45.4 (62.8, 88)
		Cohort 3 (N = 13)[b]	
C_{max}	(ng/mL)	1600 (2960, 155)	197 (217, 42)
T_{max}[a]	(h)	3.0 (2.0 – 6.0)	4.0 (2.0 – 6.0)
AUC_{24}	(ng•h/mL)	6860 (12700, 162)	1640 (1870, 47)
C_{trough}	(ng/mL)	7.44 (41.7, 264)	19.4 (27.0, 88)
CL/F	(L/h)	29.1 (45.8, 112)	48.7 (58.3, 74)
		Cohort 4 (N = 12)	
C_{max}	(ng/mL)	1530 (3450, 120)	233 (255, 42)
T_{max}[a]	(h)	4.0 (1.7 – 6.0)	4.0 (2.0 – 6.0)
AUC_{24}	(ng•h/mL)	7520 (14400, 112)	1790 (2020, 49)
C_{trough}	(ng/mL)	6.58 (24.1, 190)	17.9 (25.5, 87)
CL/F	(L/h)	19.9 (38.8, 111)	33.6 (38.6, 58)

The steady-state exposures of GLE and PIB in HCV-infected adolescent subjects (≥ 12 to < 18 years of age) were similar to the exposures observed in HCV-infected adult subjects following administration of GLE/PIB 300 mg/120 mg. No significant relationship between weight and exposures or between age and exposures was observed.

The observed steady-state exposure ranges of GLE and PIB in HCV-infected pediatric subjects (≥ 3 to < 12 years of age) following administration of GLE + PIB granules at the final proposed doses, according to age group/body weight, were within the exposure ranges of GLE and PIB observed in HCV-infected noncirrhotic adult subjects.

***Rapporteur's comment**:*

Compared to the initial submission (please refer to EMEA/H/C/004430/X/0033/G), additional PK data of 3, 4 and 2 subjects were added to cohort 2, 3 and 4 respectively.

PK results remain similar to those initially submitted, and the applicant statement that the observed PK exposure in children (based on AUC24) for GLE and PIB are within the exposure range of GLE and PIB observed in adults is acceptable.

Japanese subjects

Similarly in Japanese subjects, PK parameters summary of GLE and PIB at Week 2 for adolescent subjects aged 12 to 18 years (cohort 1) and children aged 3 to 12 years (cohorts 2, 3 and 4) are presented in Table 3 and Table 4 respectively.

Table 3: Geometric mean (mean CV%) PK parameters of GLE and PIB (week 2 IPK) from Part 1 (Japanese subjects)

		GLE/PIB 300 mg/120 mg QD Adult Formulation Week 2 (N = 4)	
PK Parameters	**(Units)**	**GLE**	**PIB**
		Adolescent Subjects ≥ 12 to < 18 Years Of Age	
C_{max}	(ng/mL)	1170 (1430, 54)	176 (196, 42)
T_{max}[a]	(h)	4.0 (2.0 – 4.0)	4.0 (4.0 – 4.0)
AUC_{24}	(ng•h/mL)	4780 (5690, 59)	1390 (1580, 45)
C_{trough}	(ng/mL)	4.95 (5.33, 42)	17.6 (19.4, 46)
CL/F	(L/h)	62.7 (78.6, 84)	86.1 (103, 79)

Table 4: Geometric mean (mean CV%) PK parameters of GLE and PIB (week 2 IPK) following the final proposed dosing regimens (Part 2) of Japanese subjects

		GLE + PIB QD Pediatric Formulation Week 2	
PK Parameters	**(Units)**	**GLE**	**PIB**
		Cohort 2 (N = 3)	
C_{max}	(ng/mL)	1170 (1270, 48)	247 (265, 47)
T_{max}[a]	(h)	4.0 (4.0 – 4.0)	4.0 (4.0 – 4.0)
AUC_{24}	(ng•h/mL)	5780 (6580, 60)	1920 (2110, 56)
C_{trough}	(ng/mL)	4.29 (5.05, 70)	25.2 (29.9, 69)
CL/F	(L/h)	43.2 (49.3, 61)	52.1 (56.5, 44)
		Cohort 3 (N = 4)[b]	
C_{max}	(ng/mL)	2450 (2640, 43)	244 (260, 37)
T_{max}[a]	(h)	2.0 (2.0 – 4.0)	4.0 (4.0 – 4.0)
AUC_{24}	(ng•h/mL)	9550 (11000, 58)	2000 (2120, 38)
C_{trough}	(ng/mL)	6.05 (10.1, 111)	18.2 (21.8, 60)
CL/F	(L/h)	20.9 (24.1, 61)	40.0 (42.5, 41)
		Cohort 4 (N = 2)	
C_{max}[c]	(ng/mL)	3700 (3870)	388 (392)
T_{max}[a]	(h)	4.0 (4.0 – 4.0)	4.0 (4.0 – 4.0)
AUC_{24}[c]	(ng•h/mL)	13200 (13400)	2710 (2740)
C_{trough}[c]	(ng/mL)	5.03 (6.26)	20.3 (20.4)
CL/F[c]	(L/h)	11.4 (11.6)	22.1 (22.4)

The exposures for all Japanese subjects were contained within the exposure range of non- Japanese pediatric subjects. Their exposures were also falling within the efficacious range observed in Japanese adult subjects.

***Rapporteur's comment**:*

Compared to the initial submission, the applicant provide in Table 4 *[New PK data] the observed PK exposures in Japanese from cohort 2 to 4, PK data from cohort 1 has been submitted as part of EMEA/H/C/004430/X/0033/G.*

*For a reminder observed PK data from adolescent Japanese subjects (n=4) were similar to those observed in adolescent non-Japanese subjects (n=12) in terms of Cmax and AUC24h for both compounds (GLE and PIB) [*Table 1 *vs* Table 3*]*

For subjects from cohort 2 to 4, even if the number of subjects are very small per each cohort, for both compounds (GLE and PIB) and particularly for GLE, a relationship between weight/age and PK exposure metrics (Cmax and AUC24) cannot be ruled out. Such trend is not observed for non-Japanese subjects. Nevertheless, no strong safety signals were observed particularly in Japanese subjects.

Safety results

Patient exposure

The safety population included all subjects who received at least 1 dose of study drug (Cohort 1 [Part 1, adolescents] N = 47; Cohorts 2 – 4 [Part 2, pediatric] N = 80).

All subjects administered at least 1 dose of study drug were to be followed through post-treatment week 144.

All subjects in Cohort 1 and all but 2 subjects in Cohorts 2 – 4 completed the assigned study treatment duration: one subject (Cohort 4) refused to swallow the study drug granule formulation and one subject (Cohort 2) experienced a study drug related adverse event (AE) of rash erythematous.

Adverse events

Overwiew of adverse events

	Cohort 1 ≥ 12 to < 18 years old (N = 47) n (%)	Cohort 2 ≥ 9 to < 12 years old (N = 29) n (%)	Cohort 3 ≥ 6 to < 9 years old (N = 27) n (%)	Cohort 4 ≥ 3 to < 6 years old (N = 24) n (%)	Cohorts 2 – 4 ≥ 3 to < 12 years old (N = 80) n (%)	Total (N = 127) n (%)
Subjects with:						
Any adverse event (AE)	41 (87.2)	20 (69.0)	16 (59.3)	21 (87.5)	57 (71.3)	98 (77.2)
Any AE with a reasonable possibility of being related to DAAs (glecaprevir/pibrentasvir)[a]	9 (19.1)	7 (24.1)	9 (33.3)	8 (33.3)	24 (30.0)	33 (26.0)
Any AE with a Grade 3 or higher	1 (2.1)	1 (3.4)	0	0	1 (1.3)	2 (1.6)
Any DAA related AE with a Grade 3 or higher	0	1 (3.4)	0	0	1 (1.3)	1 (0.8)
Any serious AE	0	0	0	0	0	0
Any DAA related serious AE	0	0	0	0	0	0
Any AE leading to discontinuation of study drug	0	1 (3.4)	0	0	1 (1.3)	1 (0.8)
Any DAA related AE leading to discontinuation of study drug	0	1 (3.4)	0	0	1 (1.3)	1 (0.8)
Any serious AE leading to discontinuation of study drug	0	0	0	0	0	0
Any AE leading to interruption of study drug	0	1 (3.4)	0	0	1 (1.3)	1 (0.8)
Any fatal AE	0	0	0	0	0	0
Deaths[b]	0	0	0	0	0	0

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

a. As assessed by investigator.

b. Includes non treatment-emergent deaths.

Most frequently reported (≥ 5% of subjects) AEs

Cohort 1 Adolescent Subjects ⩾ 12 to < 18 years of age

The most frequently reported (⩾ 10%) AEs for adolescent subjects were nasopharyngitis, upper respiratory tract infection, headache, fatigue, oropharyngeal pain, pyrexia, and vomiting. All events of nasopharyngitis and upper respiratory tract infection were assessed as not study drug-related and likely due to expected seasonal medical conditions common in the paediatric population.

The majority of adolescent subjects who experienced AEs (61.0%; 25/41) had AEs with a maximum severity of Grade 1 (mild). One subject in Cohort 1 with a history of depression experienced a Grade 3 AE of depression during the study.

Rapporteur's comment:

The case of Grade 3 AE of depression reported in a 12-year old male subject with a history of depression was already presented in the application file for extension of indication in adolescents (Type II variation II12). The event was assessed as not related to study drug by the investigator.

Cohorts 2 – 4 Pediatric Subjects ≥ 3 to < 12 years of age

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

The majority of paediatric subjects who experienced AEs (73.7%; 42/57) had AEs with a maximum severity of Grade 1 (mild). One female subject, from Cohort 2, prematurely discontinued study drug on Treatment Day 4 due to a non-serious Grade 3 erythematous rash, which was considered study drug-related by the investigator.

Rapporteur's comment:

No new significant information is raised from these data, whom the majority was already assessed as part of the application for extension of indication in paediatric subjects ≥ 3 years of age. The Grade 3 erythematous rash leading to study drug discontinuation was already presented and discussed as part of the X33G extension line dossier.

Cohort 1 Adolescent Subjects ≥ 12 to < 18 years of age

Overall, 9 (19.1%) adolescent subjects experienced study drug-related AEs. The most frequently reported study drug-related AE (≥5 % subjects overall) was fatigue.

Cohorts 2-4 Pediatric Subjects ≥ 3 to < 12 years of age

Overall, 24 (30.0%) paediatric subjects experienced study drug-related AEs with the most frequently reported (≥ 5% subjects overall) being fatigue, vomiting and headache (7.5% each).

Rapporteur's comment:

No new safety data identified

Serious adverse event/deaths/other significant events

No subjects experienced a treatment-emergent SAE during the study. In the post-treatment period, more than 30 days after the last dose of study drug, the following SAE was reported:

- 1 SAE of osteomyelitis of the hip/pelvic bone was reported for a female subject in Cohort 4 on post-treatment Day 171, which was considered as a spontaneous infection by the investigator.
- 1 SAE of attempted suicide was reported for a pediatric subject in Cohort 2 on post-treatment Day 809. The event was considered related to undelying anxiety and depression secondary to COVID isolation.
- 1 SAE of arteriovenous malformation was reported for a male adolescent in Cohort 1. On post-treatment Day 1064, the patient reported having tics in the form of blinking, sudden movements and picking movements. As part of the diagnostic work-up, the patient underwent an MRI of the brain which demonstrated a large left occipital arteriovenous malformation which was diagnosed as congenital by the investigator.

Rapporteur's comment:

Three SAEs were reported in the post-treatment period. All of these were assessed as not study-drug related by the investigator.

No new safety data identified

No subject experienced treatment-emergent hepatic decompensation/hepatic failure events or postbaseline hepatocellular carcinoma events.

No clinically significant laboratory abnormalities were observed. There were no liver-related toxicities and no cases consistent with drug-induced liver injury.

Laboratory findings

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

No subjects had hepatic laboratory values of specific interest.

Growth outcomes

No clinically important trends in growth results ((BMI, height and weight Z-scores) were observed.

Safety in special populations

No pregnancies were reported during the study

Discontinuation due to adverse events

One pediatric subject (Cohort 2) experienced a study drug-related AE of rash erythematous and discontinued study drug.

Discussion and conclusion on clinical safety

No new significant safety data is identified from these final results for the DORA paediatric study including a patients' follow-up to post-treatment week 144. The high majority of data regarding treatment-emergent AEs and laboratory abnormalities had been already submitted and discussed within the type II 12 variation pertaining to the extension of indication in adolescents (data from Cohort 1) or within the Line extension X33G for the extension of indication in paediatric patients $\geq$ 3 years of age (data from Cohorts 2 to 4).

The only new safety data shown in this submission pertains to the reporting of three post-treatment SAEs, for all of which a drug causality can be definitely ruled out.

No relevant impact on growth outcomes was observed.

In total, no safety signal was identified. On the basis of these data, there is no need to update the SmPC or the PIL.

2.3.3. Discussion on clinical aspects

In the post-treatment (PT) Period, all subjects administered at least 1 dose of study drug were to be followed through PT Week 144 to monitor for safety, viral response, emergence and/or persistence of resistance-associated viral substitutions, and growth and development.

No new relevant efficacy data is identified in these final study results. Except the case of relapse in cohort 2 already discussed as part of the X33G dossier, no other paediatric subjects experienced on–treatment virological failure, relapse, or had a new HCV infection during the entire duration of the study.

From a PK perspective, with the additional PK data from Japanese and non-Japanese subjects it is agreed with the applicant that the observed steady-state exposure ranges of GLE and PIB in HCV-infected pediatric subjects (≥ 3 to < 12 years of age) following administration of GLE + PIB granules at the final proposed doses, according to age group/body weight, were within the exposure ranges of GLE and PIB observed in HCV-infected non cirrhotic adult subjects for both populations.

There is no new safety signal identified for the paediatric population.

To conclude, the benefit/risk balance of Marivet is unchanged and no SmPC update is necessary.

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.