16 September 2021
EMA/564993/2021
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Zepatier

International non-proprietary name: elbasvir / grazoprevir

Procedure No. EMEA/H/C/004126/II/0029

Marketing authorisation holder (MAH): Merck Sharp & Dohme B.V.

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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ASaT	All Subjects as Treated
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC0-24	Area under the concentration-time curve through 24 hours post-dose
BLOQ	Below the level of quantification
BMI	Body mass index
C24	Concentration at 24 hours post-dose, used here as synonym for Ctrough
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent clearance
Cmax	Maximum concentration
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CRF	Case report form
CSR	Clinical Study Report
Ctrough	Drug concentration immediately pre-dose, used here as synonym for C24
DAA	Direct acting antiviral
EBR	Elbasvir
ECG	Electrocardiograms
ECIs	Events of Clinical Interest
ERC	Ethics Review Committee
FAS	Full Analysis Set
FDC	Fixed-dose combination
FW	Follow-up Week
GCP	Good Clinical Practice
GMR	Geometric mean ratio
GT	Genotype
GZR	Grazoprevir
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IRB	Institutional Review Board
IU	International Units
LLOQ	Lower limit of quantification
LPLV	Last participant last visit
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MRL	Merck Research Laboratories
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
NCA	Noncompartmental analysis
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PP	Per Protocol
QA	Quality Assurance
QC	Quality Control
QD	Once daily
RAS	Resistance associated substitution
RCF	Relative Centrifugal Field
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOP	Standard Operating Procedure
SVR12	Sustained virologic response 12 weeks after the end of all study intervention

SVR24	Sustained virologic response 24 weeks after the end of all study intervention
TD(u)	Target detected but unquantifiable
TE	Treatment-experienced
TEAE	Treatment-emergent adverse event
Tmax	Time of maximum concentration
TN	Treatment-naïve
TND	Target not detected
TW	Treatment Week
ULN	Upper limit of normal
VF	Virologic failure
WOCBP	Women of childbearing potential

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 10 March 2021 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of chronic hepatitis C (CHC) in paediatric patients 12 years of age and older who weigh at least 30 kg for Zepatier; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) 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 P/0255/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0255/2017 was completed.

The PDCO issued an opinion on compliance for the PIP P/0255/2017.

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: Johann Lodewijk Hillege

Timetable	Actual dates
Submission date	10 March 2021
Start of procedure:	27 March 2021
CHMP Co-Rapporteur Assessment Report	21 May 2021
CHMP Rapporteur Assessment Report	21 May 2021
PRAC Rapporteur Assessment Report	28 May 2021
PRAC members comments	2 June 2021
Updated PRAC Rapporteur Assessment Report	4 June 2021
PRAC Outcome	10 June 2021
CHMP members comments	14 June 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 June 2021
Request for supplementary information (RSI)	24 June 2021
Re- start of procedure:	18 August 2021
PRAC Rapporteur Assessment Report	23 August 2021
PRAC members comments	25 August 2021
Updated PRAC Rapporteur Assessment Report	26 August 2021
CHMP Rapporteur Assessment Report	01 September 2021
PRAC Outcome	02 September 2021
CHMP members comments	06 September 2021
Updated CHMP Rapporteur Assessment Report	09 September 2021
Opinion	16 September 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Zepatier is a fixed dose combination (FDC) consisting of Elbasvir and Grazoprevir (EBR/GZR), indicated for the treatment of chronic hepatitis C infection (CHC) in adults. The currently approved posology is one tablet, consisting of 50 mg elbasvir and 100 mg grazoprevir, once daily.

Disease or condition

Hepatitis C virus causes both acute and chronic infection. New HCV infections are usually asymptomatic. Around 30% (15–45%) of infected persons spontaneously clear the virus within 6 months of infection without any treatment. The remaining 70% (55–85%) of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of liver cirrhosis ranges between 15% and 30% within 20 years (WHO).

CHC has similar clinical features and risks for complications (progression to advanced liver fibrosis, cirrhosis, end-stage liver disease, hepatocellular carcinoma) in both adults and adolescents. It is estimated that between 40% and 60% of HCV-antibody-positive adolescents are chronically infected and viremic. Perinatal (vertical) transmission is the most common source of CHC in paediatrics. However, in adolescents, the incidence of CHC increases due to high-risk behaviours such as intra-venous (IV) drug use and shared tattoo equipment. In particular, the opioid epidemic has resulted in an increasing incidence of CHC among adolescents. Therefore, within the paediatric population, adolescents are the group in greatest need of treatment options.

State the claimed the therapeutic indication

The MAH hereby applies for an extension of the indication: "for the treatment of CHC infection in paediatric patients (12 to <18 years of age) who weigh at least 30 kg."

Management

The goal of treatment of chronic HCV is the eradication of the virus as measured by sustained virologic response with a halt in the progression of liver damage.

The current standard of care for the treatment of CHC in adolescents is the use of all-oral combination direct-acting antiviral (DAA) regimens (e.g., sofosbuvir/velpatasvir or glecaprevir/pibrentasvir). Treatment with DAAs is usually very effective, and treatment duration is short (usually 12 to 24 weeks), depending on the absence or presence of cirrhosis.

2.1.2. About the product

EBR/GZR is an FDC of 2 DAAs with distinct mechanisms of action and non-overlapping resistance profiles targeting HCV at multiple steps in the viral lifecycle (see section 2.3.3)

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

The PK, efficacy, and safety profiles of EBR/GZR have been demonstrated in a comprehensive clinical development program. The original marketing application supported the clinical efficacy and safety of QD administration of EBR/GZR 50 mg/100 mg FDC tablet in adults with CHC GT1 or GT4 infection.

The paediatric clinical program included a single study, MK-5172-079 (P079), which evaluated EBR/GZR in paediatric participants (3 to <18 years of age) and was part of an agreed PIP (P/0255/2017 , EMEA-C-001604-PIP01-13-M03).

This study has been evaluated in two previous art. 46 procedures (EMEA/H/C/004126/P46/013 and EMEA/H/C/004126/P46/014).

No dedicated scientific advice was received for the paediatric study.

2.1.4. General comments on compliance with GCP

The MAH claims that all clinical studies were conducted in compliance with GCP.

Quality aspects

The Zepatier FDC tablet is appropriate for adolescents 12 years of age and older based on the palatability and acceptance data, and the ability of all participants to complete dosing. In accordance with EMA Guideline on Pharmaceutical Development of Medicines for Paediatric Use (EMA/CHMP/QWP/805880/2012 Rev. 2), acceptance of Zepatier FDC tablets was measured using a palatability and acceptability questionnaire during the study. These data (*Table 1*) are consistent with papers published on the topic. As noted in a workshop on the topic of drug development for children, "most children 12 years and older can swallow a tablet or capsule of reasonable size".

The tablet in this study is the same size as other oblong/oval shaped medications approved for other adolescent populations 12 years of age and older. In Protocol 079, palatability and acceptance of study medication were evaluated at two timepoints, treatment weeks 4 and 8. The results of the questionnaire used can be found in *Table 1*. Results for 22 participants in Age Cohort 1 (age 12 years to <18 years) were obtained at treatment week 4 and results from 21 participants were obtained at treatment week 8. Participants in Age Cohort 1 were only offered the tablet and switching formulation was not permitted, therefore the results in the table below pertain to participants receiving only tablets.

The portion of the questionnaire categorized as "problems taking dose" as listed in *Table 1*, provides Protocol 079 data regarding swallowability of the Zepatier FDC tablet. Every participant was counted a single time for each applicable row. One participant experienced both refusing medication and spitting out medication at treatment week 4 and spitting out medication at treatment week 8. That participant missed a total of 2 doses of study medication during the 84 days of dosing. This participant achieved SVR. One participant reported gagging from study medication at treatment week 8. This participant missed no doses during 84 days of dosing and achieved SVR (*Table 1*). The data show that fewer than 10% of participants provided any negative response categorized as "problems taking dose" and no complaint was associated with an inability to complete therapy. All participants in this study completed the course of study medication.

Table 1: *Summary of Responses for Patient Reported Palatability and Acceptance Measure for Participants who Received Adult Tablet Full Analysis Set Population*

Table 1-1
Summary of Responses for Patient Reported Palatability and Acceptance Measure for Participants who Received Adult Tablet
Full Analysis Set Population

Age Cohort 1 (12 to <18 years): Mini and Expanded

	Treatment Week 4 n (%)	Treatment Week 8 n (%)
Number Of Subjects Completing Palatability Questionnaire	22	21
Person Completing The Palatability Questionnaire		
The Patient	16 (72.7)	14 (66.7)
The Patient/Primary Caregiver	2 (9.1)	3 (14.3)
The Patient And Parent/Primary Caregiver	4 (18.2)	4 (19)
Taste		
Very Good	1 (4.5)	1 (4.8)
Good	4 (18.2)	3 (14.3)
Neither Good Nor Bad	14 (63.6)	13 (61.9)
Bad	1 (4.5)	4 (19)
Very Bad	2 (9.1)	0 (0)
Problems Taking Dose		
Any Problem	1 (4.5)	2 (9.5)
Refusing Medication	1 (4.5)	0 (0)
Spitting Out Medication	1 (4.5)	1 (4.8)
Gagging From Medication	0 (0)	1 (4.8)
Percentages are based on number of subjects completing palatability questionnaire at Treatment Week 4 and Treatment Week 8.		

Source: [P079V01MK5172: adam-adsl; adppam]

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 has provided the completed an updated ERA.

Conclusions of the Environmental Risk Assessment for Grazoprevir

The results of the assessment showed grazoprevir is unlikely to pose a risk to the environment. The estimated PEC/PNEC ratios were all well below levels of concern. Based on measured BCF values, grazoprevir is not expected to bioaccumulate and is not considered to be a PBT compound. Therefore, no further action is necessary in this case and no special precautionary or safety measures need to be taken for the storage, labelling, administration, and disposal of grazoprevir.

Conclusions of the Environmental Risk Assessment for Elbasvir

The Phase I screening for persistence, bioaccumulation and toxicity (PBT) indicates that further evaluation of elbasvir was warranted due to a log Pow > 4.5.

Based on the outcome of the Phase I environmental assessment, the predicted environmental concentration in surface water (PECSW) for the active ingredient, elbasvir, exceeded the action limit of 0.01 µg/L, initially indicating that elbasvir may represent a risk to the environment following its prescribed usage in patients. Therefore, a Phase II Tier A environmental effect assessment and concomitant risk assessment was required.

The outcome of the Phase II Tier A assessment comparing the Predicted No Effect Concentration (PNEC) and PEC ratios conclude that elbasvir does not present a risk to ground water, sediment or micro-organisms. Risk to surface water was slightly greater than 1, indicating the need for further refinement in a Phase II Tier B assessment. Also, because the sludge Koc values are greater 10,000 L/kg, a Phase II Tier B environmental effect assessment was conducted.

The outcome of the Phase II Tier B assessment evaluating the fate and effects of elbasvir in surface water and the terrestrial environment concludes that elbasvir does not present a risk to any ecosystem.

Additionally, elbasvir will not bioconcentrate and thus does not meet the criterion to be defined as a persistent, bioaccumulative and toxic (PBT) compound. Elbasvir is not expected to pose a significant risk to the environment due to normal patient use. Thus, no further action is necessary in this case and no special precautionary or safety measures need to be taken for the storage, labeling, administration, and disposal of elbasvir.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data were provided.

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

Considering the above data, elbasvir and grazoprevir are not expected to pose a risk to the environment.

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.

Tabular overview of clinical studies:

Table 2: Overview of the EBR/GZR Pediatric Study P079

Study Number (Status) [CTD Location] ***Number of Study Sites (Regions)***	***Design (Indication)***	***Number of Participants by Intervention Group***	***Study Population (N)***	***Primary Endpoint(s)***
P079 Completed 14 sites (3 countries) allocated participants in the study	Multicentre, pharmacokinetics, safety, efficacy, single arm, multiple cohort, open-label, unblinded intervention Duration: approximately 12 weeks of treatment and 24 weeks of follow-up	Age Cohort 1 (12 to <18 years) Mini and Expanded Groups combined: 22 participants treated with the EBR/GZR (50 mg/100 mg) FDC tablet. Age Cohort 2 (7 to <12 years): Mini and Expanded Groups combined: 17 participants were treated with EBR/GZR (30 mg/60 mg) paediatric granules Age Cohort 3 (3 to <7 years): Mini Cohort: 7 participants were treated with EBR/GZR (15 mg/30 mg) paediatric granules Age Cohort 3 (3 to <7 years): Expanded: 11 participants were treated with EBR/GZR (25 mg/50 mg) paediatric granules	57 treated subjects overall: 28 males (49.1%) 29 females (50.9%) Median age 9.0 years (range, 3 to 17 years)	Primary Endpoints PK Endpoints: Week 4 AUC0-24, Cmax, Ctrough, and CL/F. Secondary Endpoints Safety Endpoints: adverse events, adverse events leading to discontinuation of study drug. Efficacy Endpoint: SVR_{12}.
Abbreviations: AUC0-24 = area under the concentration-time curve from zero to 24 hours; Cmax = maximum concentration; CL/F = Apparent clearance; CTD = Common Technical Document; Ctrough = concentration immediately pre-dose; EBR = elbasvir; FDC = fixed dose combination; GZR= grazoprevir; SVR_{12} = sustained virologic response 12 weeks after the end of all study intervention.				

2.3.2. Pharmacokinetics

The pharmacokinetics of elbasvir and grazoprevir were previously characterised in an adult population. The ADME properties, the clinical comparability bounds, and the influence of intrinsic factors and DDIs were investigated *in vivo* and *in vitro*. The pharmacokinetic properties of elbasvir and grazoprevir in adults are summarised below.

Elbasvir

Following single- or multiple-dose administration, elbasvir was rapidly absorbed, with t_{max} ranging from 2 to 4 hours. Elbasvir PK was dose-proportional over a dose range of 10 to 100 mg and was time-independent. Steady-state occurred within 2-3 days. The accumulation ratios for AUC_{0-24} ranged from 0.981 at 100 mg/day to 2.05 at 10 mg/day in healthy volunteers and 1.5- to 1.9-fold in patients.

Elbasvir is extensively (>99.9%) bound to human plasma proteins, and the blood-to-plasma ratio was 0.62. The apparent volume of distribution (Vd/F) is 680 L. Elbasvir has low solubility and low permeability.

Elbasvir is metabolised by CYP3A. Elbasvir is a substrate of P-glycoprotein, but not of OATP1B1 and 1B3.

Elbasvir and metabolites are excreted via faeces (<1% via urine). The elimination half-life was 20 to 24 hours.

Elbasvir showed clinically relevant decreases in exposure with moderate and strong CYP3A inducers, but no clinically relevant increases in exposure with CYP3A inhibitors. P-glycoprotein and BCRP inhibitors did not have a significant effect on the absorption of elbasvir. Elbasvir is an inhibitor of intestinal BCRP and intestinal P-glycoprotein.

Grazoprevir

Following single- or multiple-dose administration, grazoprevir was rapidly absorbed, with t_{max} ranging from 2 to 4 hours. The absolute bioavailability was estimated to be in the range ~10% to 40% at doses from 25 to 200 mg. Plasma exposure is ~2-fold higher in patients than in healthy subjects. Grazoprevir increased in a greater than dose-proportional manner over the range tested and was time-dependent. Steady state is reached in ~5 days. The accumulation ratio is 2-4-fold for the AUC_{0-24}.

The plasma protein binding is 98.3-98.8% and the blood-to-plasma ratio was 0.7. The volume of distribution at steady-state was estimated to be ~3600 L following a single dose of 25 mg and ~1400 L following single and once-daily doses of 200 mg. Grazoprevir has low solubility and high permeability

Grazoprevir is metabolised by CYP3A. No metabolites were observed in plasma. Grazoprevir is a substrate of the transporters P-glycoprotein, OATP1B1 and OATP1B3.

Grazoprevir and metabolites are excreted via faeces (<1% via urine). The elimination of grazoprevir is biphasic with a $t_{½}$ of ~25 to 45 h.

Grazoprevir is a weak inhibitor of CYP3A, an intestinal BCRP inhibitor, but not an inhibitor of OATP1B. Grazoprevir showed clinically relevant decreases in exposure with moderate and strong CYP3A inducers, but no clinically relevant increases in exposure with CYP3A inhibitors. Furthermore, grazoprevir exposure increases to a clinically relevant extent with OATP1B inhibitors. Overall this indicates that hepatic uptake is the rate limiting step in the elimination of grazoprevir. P-glycoprotein and BCRP inhibition did not significantly affect the absorption of grazoprevir.

No dose adjustments are recommended for grazoprevir for the intrinsic factors: age, gender, body weight/BMI, renal impairment, and mild hepatic impairment. No dosage adjustment of grazoprevir is required for patients who are on dialysis. However, grazoprevir is contraindicated for patients with moderate (Child Pugh-B) or severe (Child Pugh-C) hepatic impairment, due to expected significantly increased

grazoprevir plasma concentration. Grazoprevir AUC was 50% higher for Asians compared to Caucasian, and the AUC was comparable between Caucasians and Blacks. No dose adjustment is recommended based on race/ethnicity.

The current variation of elbasvir and grazoprevir fixed dose combination is for the treatment of paediatric patients aged 12 to <18 years and weighing ≥30 kg with chronic Hepatitis C genotypes 1 to 4. Two clinical studies were submitted:

- **P082**: a clinical study in healthy adult participants to evaluate the bioavailability of two paediatric formulations (coated and uncoated oral paediatric granule formulation) compared to the adult fixed-dose combination tablet.
- **P079**: a Phase IIb clinical study to assess the pharmacokinetics, safety, and efficacy of elbasvir and grazoprevir in participants aged 3 to less than 18 years with chronic Hepatitis C infection.

Study **P082** is an open-label, single-dose, randomised, 3-period, incomplete block, cross-over study under fasted conditions in 24 healthy male and female adults (18 to 55 years of age). The comparative bioavailability of the paediatric oral granule formulations and the fixed-dose combination tablet were investigated. Study P082 PK data for the paediatric oral granule formulation was used to inform modelling and simulation in support of the adolescent dose. The study was performed at Novum Pharmaceutical Research Services (Las Vegas, Nevada, USA) in the period January 2017 to April 2017. Subjects were treated with a single dose of 50 mg elbasvir and 100 mg grazoprevir:

- Treatment A (n=12): elbasvir oral paediatric coated oral granules (0.5 mg/oral granule) and grazoprevir oral paediatric uncoated oral granules (1 mg/oral granule)
- Treatment B (n=11): elbasvir oral paediatric uncoated oral granules (0.5 mg/oral granule) and grazoprevir oral paediatric coated oral granules (1 mg/oral granule)
- Treatment C (n=11): elbasvir oral paediatric uncoated oral granules (0.5 mg/oral granule) and grazoprevir oral paediatric uncoated oral granules (1 mg/oral granule)
- Treatment D (n=12): elbasvir oral paediatric coated oral granules (0.5 mg/oral granule) and grazoprevir oral paediatric coated oral granules (1 mg/oral granule)
- Treatment E (n=22): Zepatier® fixed dose combination adult formulation tablet

After an overnight fast of at least 10 hours, subjects were treated with the uncoated or coated granules in 15 mL of applesauce (followed by 240 mL of water) or the fixed dose combination tablet with 240 mL of water according to the randomisation scheme in *Table 3.* The interval between doses was 10 days.

Table 3: *Randomisation scheme study P082*

sequence	Period I	Period II	Period III
1	A	B	E
2	B	E	A
3	E	A	B
4	A	E	B
5	B	A	E
6	E	B	A
7	C	D	E

8	D	E	C
9	E	C	D
10	C	E	D
11	D	C	E
12	E	D	C

Blood samples were collected prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, and 120 hours post-dose. Whole blood samples were collected K_2EDTA tubes and centrifuged at 1000 to 1300 RCF between 4°C to 10°C for 10 minutes. Plasma samples were stored at -20°C and transferred to InVentiv Health Clinique (Quebec, Canada) for analysis. Elbasvir and grazoprevir were analysed using a validated LC-MS/MS method (SOP ANI11058-03). A total of 5 re-assayed analyses (0.49%) corresponding to 4 re-analysed study samples were performed out of the 1017 study samples for elbasvir. A total of 1 re-assayed analysis (0.10%) corresponding to 1 reanalysed study sample was performed out of the 1017 study samples for grazoprevir. A total of 104 study samples were analysed for the incurred sample reproducibility analysis. For elbasvir all study samples (100.00%) met the acceptance criteria. For grazoprevir, a total of 103 out of 104 study samples (99.04%) met acceptance criteria. Samples were analysed within 43 days after collection, which was shorter than the demonstrated long term stability of 117 days.

A total of 24 subjects were entered into this study and completed Period I. Twenty-two subjects completed Period II and Period III. One subject did not return for Period III check-in and is considered to have voluntarily withdrawn from the study and discontinued. In addition, one subject was discontinued the day of Period III check-in for a positive substance abuse screen. One subject was not dosed in Period II because of clinically significantly abnormal laboratory results at check-in. One subject was not dosed in Period II because of clinically significantly abnormal protein urinalysis results at check-in. The demographics are summarised in *Table 4*.

Table 4: *Summary of demographics study P082*

parameter	value
age (years)	37.4 ± 9.9 (20-54)
weight (kg)	83 ± 14.5 (50.0-113.9)
BMI (kg/m^2)	27.9 ± 3.2 (21.0-32.0)
gender	71% male 29% female
race	42% Caucasian 25% Black 0% Asian 33% other

The pharmacokinetics of elbasvir and grazoprevir of the different formulations are summarised in *Table 5* and *Table 6,* respectively. The plasma concentration time curves are shown in *Figure 1* and

Figure 2 for elbasvir and grazoprevir, respectively.

Table 5: *Pharmacokinetic parameters and statistical comparison of elbasvir (non-transformed values; arithmetic mean ± SD, t_{max} median, range) following a single oral dose of 50 mg elbasvir (study P082)*

treatment	C_{max} (µM)	C_{24h} (nM)	$AUC_{0\text{-last}}$ (µM × h)	$AUC_{0\text{-}\infty}$ (µM × h)	t_{max} (h)

uncoated granules (n=22)	0.164	50.5	3.21	3.26	3 (2-4)
Zepatier® (n=22)	0.126	39.8	2.49	2.53	4 (2-6)
ratio (90% CI)	1.3 (1.23-1.38)	1.27 (1.19-1.35)	1.29 (1.21-1.37)	1.29 (1.21-1.37)	-
coated granules (n=24)	0.148	46.4	2.96	3.02	3.49 (2-6)
Zepatier® (n=22)	0.126	39.8	2.49	2.53	4 (2-6)
ratio (90% CI)	1.18 (1.09-1.28)	1.17 (1.09-1.24)	1.19 (1.11-1.27)	1.19 (1.11-1.27)	-

Table 6: *Pharmacokinetic parameters and statistical comparison of grazoprevir (non-transformed values; arithmetic mean ± SD, t_{max} median, range) following a single oral dose of 100 mg grazoprevir (study P082)*

treatment	**C_{max} (µM)**	**C_{24h} (µM)**	**$AUC_{0\text{-last}}$ (nM × h)**	**$AUC_{0\text{-}\infty}$ (nM × h)**	**t_{max} (h)**
uncoated granules (n=23)	0.029.4	5.57	434	531	3 (0.5-12)
Zepatier® (n=22)	0.027.5	4.38	358	480	3 (1-8)
ratio (90% CI)	1.07 (0.93-1.22)	1.27 (1.12-1.44)	1.21 (1.10-1.34)	1.11 (1.01-1.21)	-
coated granules (n=23)	0.023.6	3.76	282	476	3 (1.5-16)
Zepatier® (n=22)	0.027.5	4.38	358	480	3 (1-8)
ratio (90% CI)	0.86 (0.67-1.10)	0.86 (0.76-0.97)	0.79 (0.64-0.97)	0.99 (0.80-1.22)	-

Figure 1: *Arithmetic mean concentration versus time plot of elbasvir following single dose administration of 50 mg elbasvir + 100 mg grazoprevir administered in the uncoated paediatric granules formulation, coated paediatric granules formulation, and fixed dose combination tablet (Zepatier®) to healthy subjects (study P082)*

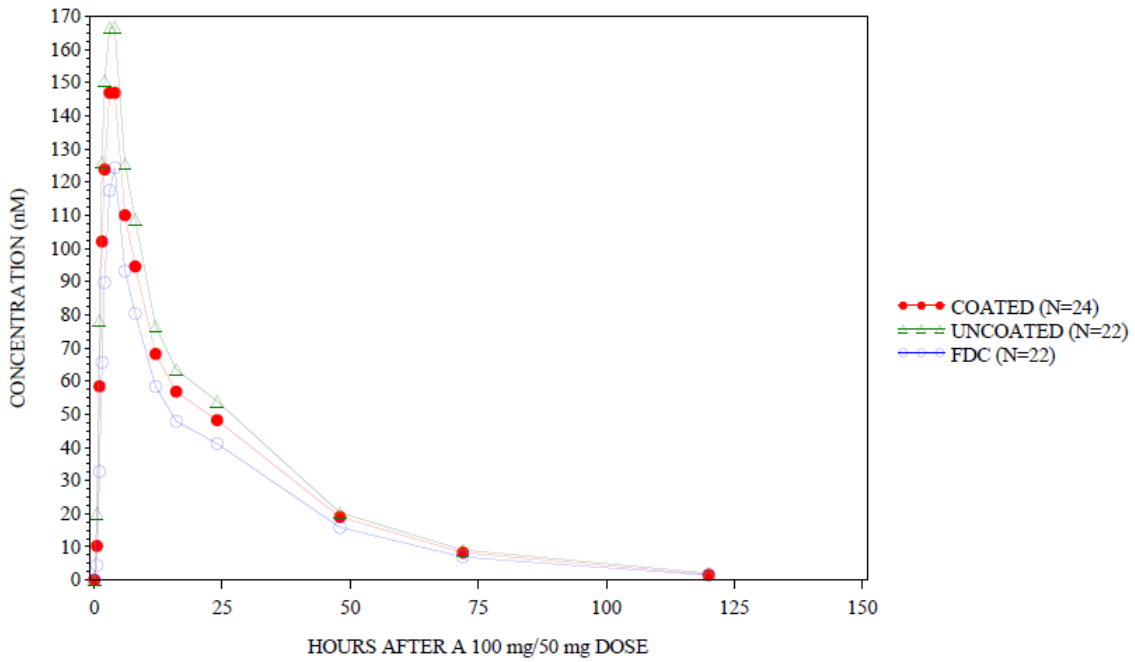
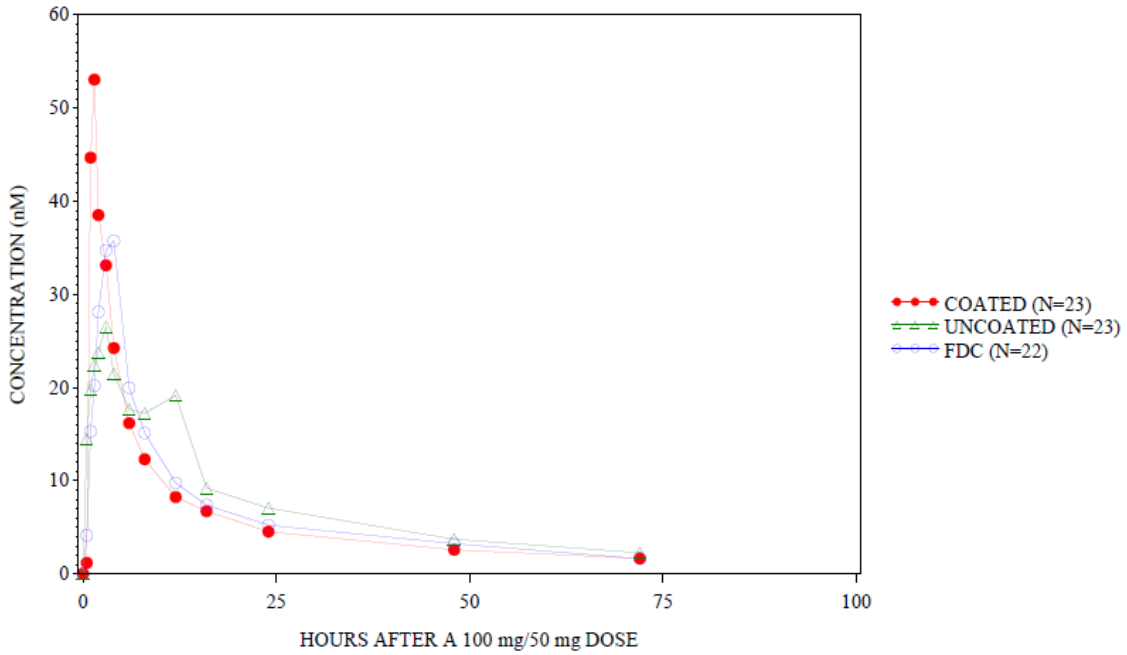


Figure 2: *Arithmetic mean concentration versus time plot of grazoprevir following single dose administration of 50 mg elbasvir + 100 mg grazoprevir administered in the uncoated paediatric granules formulation, coated paediatric granules formulation, and fixed dose combination tablet (Zepatier®) to healthy subjects (study P082)*



Statistical comparisons showed that the elbasvir AUC, C_{max} and C_{24h} parameters of the coated and uncoated formulations were consistently higher than those of the fixed-dose combination tablet. The median t_{max} was 0.5 hours earlier for the coated formulation and 1 hour earlier for the uncoated formulation compared to the fixed-dose combination tablet.

Statistical comparisons showed that the grazoprevir AUC, C_{max} and C_{24h} parameters of the coated formulation were lower, whereas those for the uncoated formulation were higher than those of the fixed-dose combination tablet. The observed median t_{max} values for the 2 formulations and fixed-dose combination tablet were the same (3 h).

The taste questionnaires showed that both the coated and uncoated granules were acceptable from taste, texture, and aftertaste perspectives. Therefore, granule coating for taste masking is not necessary. Uncoated granules were chosen to be used in study P079 for paediatric patients <12 years of age.

Twenty-seven adverse events were reported by 13 of the 24 subjects who participated in this study. All of the reported adverse events were considered "mild". No clinically meaningful relationships were observed for changes in clinical laboratory values, vital signs, or ECG safety parameter values as a function of treatment.

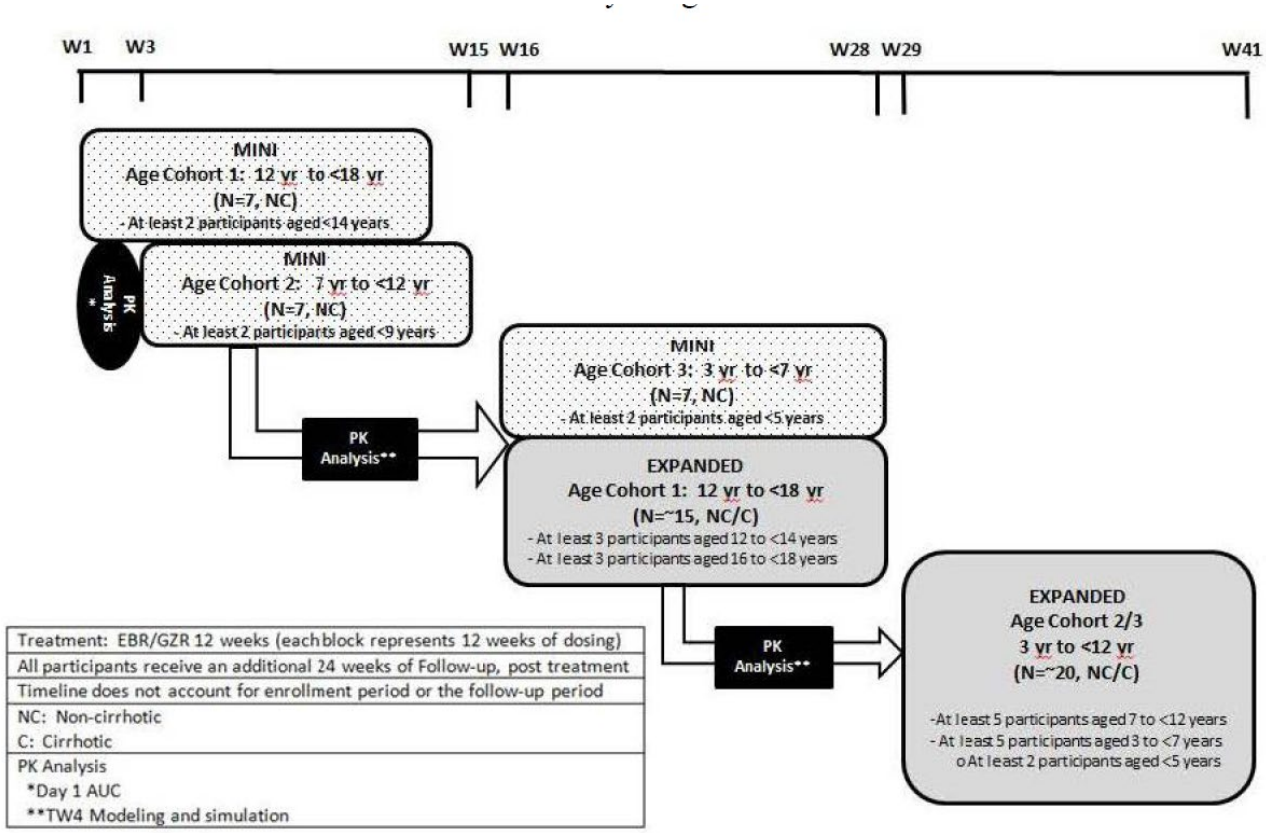
Study **P079** is a non-randomised, single-arm, multiple cohort, multi-site, open-label Phase 2b study to assess the safety, tolerability, PK, and efficacy of elbasvir and grazoprevir in paediatric participants aged 3 to <18 years with chronic Hepatitis C GT1 or GT4. The study evaluated daily oral dosing of elbasvir and grazoprevir in paediatric participants by assessing plasma PK that target a comparable PK to that observed in an adult reference population receiving Zepatier once daily. The study was conducted at 14 centres in 3 countries (Germany, Poland, and United States of America) in the period January 2018 to April 2020.

The study enrolled participants into 3 age cohorts: Cohort 1 (Mini and Expanded) aged 12 years to >18 years receiving the Zepatier tablets (50 mg elbasvir and 100 mg grazoprevir), Cohort 2 (Mini and Expanded)

aged 7 years to <12 years received 30 mg elbasvir and 60 mg grazoprevir as uncoated granules, Cohort 3 Mini aged 3 years to <7 years received 15 mg elbasvir and 30 mg grazoprevir for subjects <20 kg and 15 mg elbasvir and 50 mg grazoprevir for subjects >20 kg as uncoated granules, Cohort 3 Expanded aged 3 years to <7 years received 25 mg elbasvir and 50 mg grazoprevir as uncoated granules. Each Cohort started with a Mini Cohort of 7 participants before enrolling additional participants into the Expanded Cohort. Subjects were treated for 12 weeks according to *Figure 3*.

Only data from Cohort 1 was evaluated in the context of this submission.

Figure 3: *Study diagram study P079*



AUC=area under the concentration-time curve; EBR=elbasvir; GZR=grazoprevir; PK=pharmacokinetic; TW=treatment week; W=week

Blood samples were collected at Day 1 pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10 and 24 post-dose in subjects in Cohort 1 Mini and at pre-dose, 2 and 4 h post-dose for all other Cohorts. In addition, blood samples were collected at Week 4 pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10 and 24 h post-dose in all Cohorts. Furthermore, blood samples were collected at Week 8 pre-dose and 2 h post-dose for all Cohorts. Whole blood samples were collected K_2EDTA tubes and centrifuged at 1000 to 1300 RCF between 4°C to 10°C for 10 minutes. Plasma samples were stored at -20°C and transferred to InVentiv Health Clinique (Quebec, Canada) for analysis. Elbasvir and grazoprevir were analysed using a validated LC-MS/MS method (SOP ANI11058-05). A total of 44 re-assayed analyses (4.85%) corresponding to 44 reanalysed study samples were performed out of the 907 study samples for elbasvir. A total of 20 re-assayed analyses (2.21%) corresponding to 19 re-analysed study samples were performed out of the 907 study samples for grazoprevir. A total of 109 study samples were analysed for the incurred sample reproducibility analysis. For elbasvir, 108 out of 109 study samples (99.08%) met acceptance criteria. For grazoprevir, a total of 107 out of 109 study samples

(98.17%) met acceptance criteria. Samples were analysed within 94 days after collection, which was shorter than the demonstrated long term stability of 117 days.

A total of 57 participants were enrolled (22 in Cohort 1, 17 in Cohort 2, and 18 in Cohort 3). The demographics are summarised in *Table 7*.

Table 7: **Summary of demographics study P079**

parameter	Cohort 1	Cohort 2	Cohort 3 Mini	Cohort 3 Expanded
age (years)	14.1 ± 1.9 (12-17)	8.7 ± 1.2 (7-11)	3.7 ± 0.8 (3-5)	4.8 ± 1.3 (3-6)
BMI (kg/m^2)	20.8 ± 4.1 (16.0-30.8)	19.5 ± 3.8 (14.8-27.9)	15.7 ± 1.2 (13.8-17.4)	17.0 ± 2.6 (13.6-22.1)
gender	50% male 50% female	59% male 41% female	57% male 43% female	27% male 73% female
race	96% Caucasian	100% Caucasian	100% Caucasian	100% Caucasian

NP = not provided

The following PK samples were excluded from all analyses:

- All Day 1 PK samples from 2 participants in Cohort 1 Mini due to mishandling of the samples by the site.
- All Day 56 PK samples from 1 participant in Cohort 2 Expanded. Dosing on Day 56 was uncertain for this participant (due to a missing study diary for this day).
- All Day 1 PK samples from 1 participant in Cohort 3 Mini. The participant mistakenly received double the planned dose of elbasvir and grazoprevir.
- All Day 1 PK samples from 1 participant in Cohort 3 Expanded. The participant vomited a portion of the dose of study intervention.

A protocol deviation was that in one participant in Expanded Age Cohort 1 Day 28 the 24 hour blood sample was collected after participant received the following day's dose.

The pharmacokinetics of elbasvir and grazoprevir at Week 4 are summarised in *Table 8* and *Table 9*, respectively. The plasma AUC_{0-24} at steady state are shown in *Figure 4* for elbasvir and grazoprevir. Steady-state plasma exposures were achieved by Week 4 for both elbasvir and grazoprevir. The pharmacokinetic data in adults were the exposure obtained from the PopPK model at MAA of Zepatier in adults. Daily dosing of the adult fixed dose combination in participants 12 to <18 years of age achieved elbasvir and grazoprevir exposures within the comparability bounds established for adults.

Table 8: *Mean pharmacokinetic parameters of elbasvir at Week 4 (study P079)*

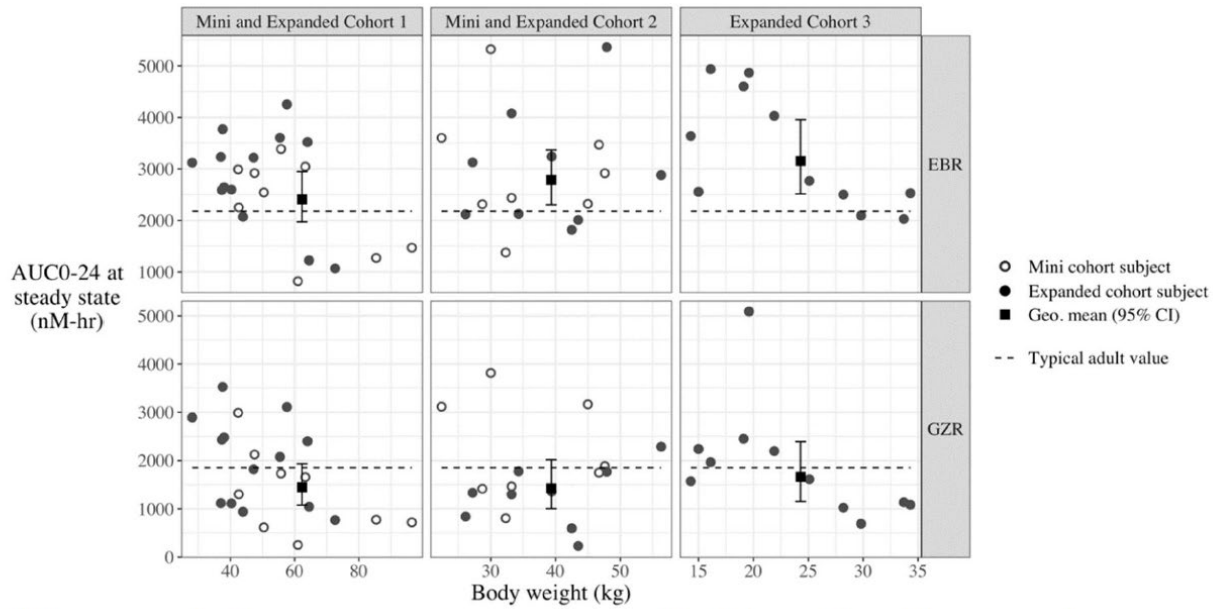
group	dose	C_{max} (µM)	C_{24h} (nM)	AUC_{0-24} (µM × h)
adult	50 mg	0.14 (0.13-0.14)	54.9 (53.6-56.2)	2.18 (2.13-2.22)
Cohort 1	50 mg	0.19 (0.15-0.23)	57.0 (45.5-71.4)	2.41 (1.97-2.94)
Cohort 2	30 mg	0.21 (0.17-0.25)	59.4 (48.7-72.6)	2.79 (2.31-3.37)
Cohort 3 Mini	15 mg	0.14 (0.11-0.19)	34.6 (28.0-42.8)	1.71 (1.36-2.15)
Cohort 3 Expanded	25 mg	0.28 (0.22-0.36)	68.9 (54.3-87.4)	3.15 (2.52-3.96)

Table 9: Mean pharmacokinetic parameters of grazoprevir at Week 4 (study P079)

group	dose	C_{max} (µM)	C_{24h} (nM)	AUC_{0-24} (µM × h)
adult	100 mg	0.22 (0.21-0.23)	23.5 (23.2-25.9)	1.85 (1.83-1.99)
Cohort 1	100 mg	0.25 (0.17-0.35)	15.2 (11.8-19.7)	1.45 (1.08-1.94)
Cohort 2	60 mg	0.19 (0.12-031)	16.3 (12.0-22.1)	1.42 (1.00-2.02)
Cohort 3 Mini	30 or 50 mg*	0.09 (0.05-0.18)	13.8 (9.6-19.9)	0.77 (0.48-1.23)
Cohort 3 Expanded	50 mg	0.29 (0.18-0.47)	16.2 (12.8-20.5)	1.66 (1.16-2.39)

* = 30 mg for subjects <20 kg and 50 mg for subjects >20 kg

Figure 4: Plasma AUC0-24 of elbasvir (EBR) and grazoprevir (GZR) at steady state (Week 4; Day 28) following oral administration to paediatric patients from Cohort 1, Cohort 2 and Expanded Cohort 3 (study P079)



AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; CI=confidence interval; EBR=elbasvir; GZR=grazoprevir.
Adult steady state values referenced in [Table 9-4].
Source: [P079V01MK5172: adam-adpp]

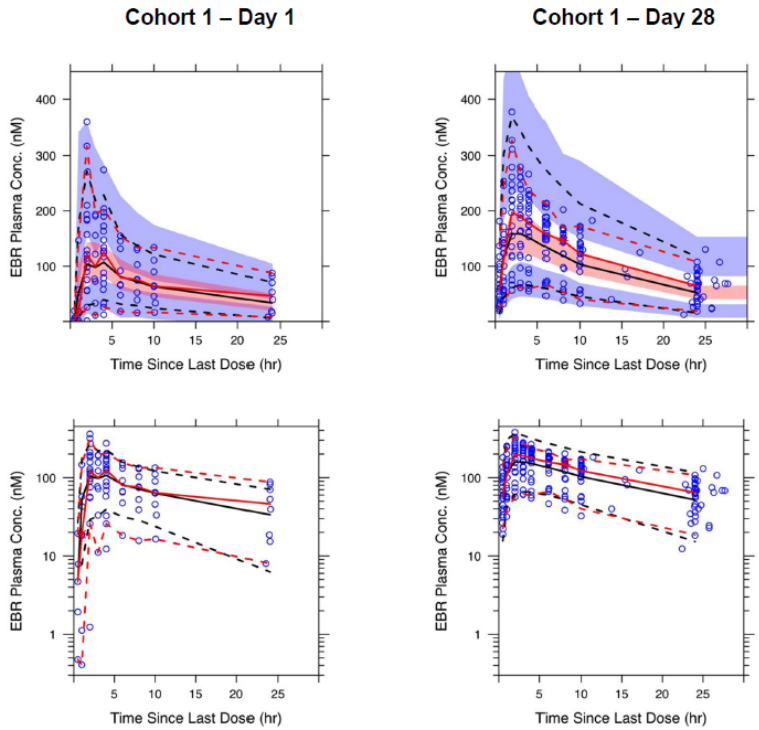
A population approach was used to evaluate the PK of elbasvir and grazoprevir in paediatric patients aged 12 to 17 years with chronic Hepatitis C as a function of body weight, based on data from P079. Separate models were developed for elbasvir and grazoprevir. The PopPK models to characterise adolescent PK of elbasvir and grazoprevir were based on models previously used to characterize adult PK at MAA of Zepatier. Both adolescent models are 2-compartment models with first-order oral absorption and first-order elimination. Weight was included as a covariate in both models. Fed/fasted status was also used as a covariate in the grazoprevir model to characterize absorption. While other covariates used in the adult models were also considered in the analysis, they were not found to improve characterization of adolescent PK in the small cohort.

At Day 1, intensive PK sampling was available for 7 participants in Mini Age Cohort 1 and 1 participant in Expanded Age Cohort 1, while sparse sampling was available for all other participants. At Week 4, intensive PK sampling was available for all participants. At Week 8, sparse sampling was available for all participants.

In total, the adolescent (Age Cohort 1) dataset included 352 measurable elbasvir plasma concentration records and 345 measurable grazoprevir plasma concentration records from 22 participants. The adolescent analysis population was comprised predominantly of White (95%) participants with an overall median (range) age of 13.5 years (12 to 17). Females made up 50% of the subjects. The median (range) weight was 49.0 kg (28.1 to 96.5). In addition, 82% of participants were classified as having normal renal function based upon eGFR, with an overall median (range) eGFR of 106 mL/min/1.73 m^2 (42 to 162). No participants were cirrhotic or co-infected with HIV. While 77% of participants were taking concomitant medications, on review of these medications none were expected to impact the PK objectives of the study.

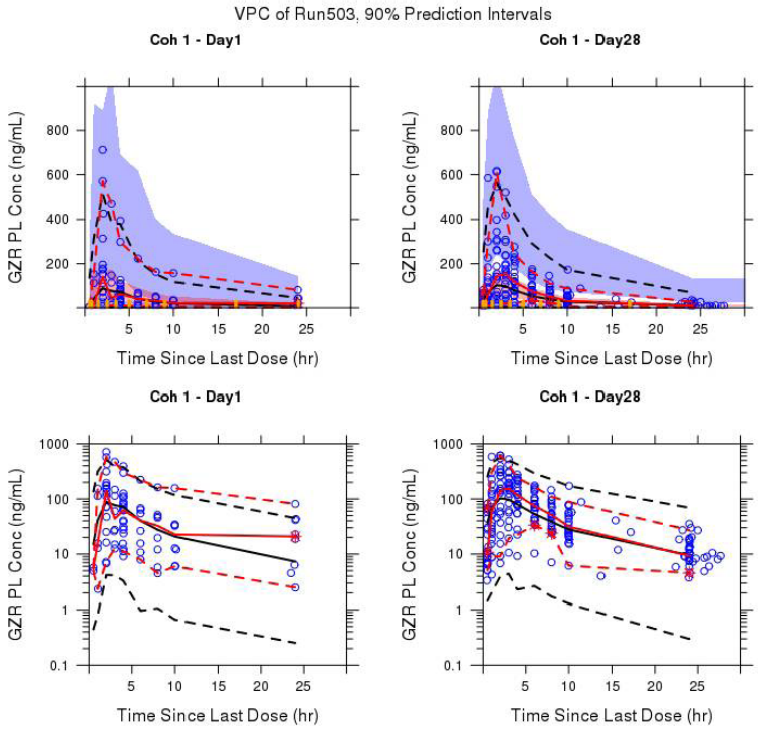
Simulation-based visual predictive checks showed that the models of elbasvir and grazoprevir adolescent PK both accurately characterized the central tendency of the observed data and that an appropriate distribution of the observed data fell with the 5th and 95th percentiles of model-simulated data (see *Figure 5* and *Figure 6*).

Figure 5: *Elbasvir VPC of final model using Cohort 1 data (PopPK report 05KM05)*



Blue circle: observed PK; red solid and dashed lines: median and 5th / 95th percentiles of observed concentrations; black solid and dashed lines: median and 5th / 95th percentiles of predicted concentrations; coral and blue shading: 95% CI of median and of 5th / 95th percentiles of predicted concentrations.

Figure 6: *Grazoprevir VPC of final model using Cohort 1 data (PopPK report 05KM05)*



Blue circle: observed PK; red solid and dashed lines: median and 5th / 95th percentiles of observed concentrations; black solid and dashed lines: median and 5th / 95th percentiles of predicted concentrations; coral and blue shading: 95% CI of median and of 5th / 95th percentiles of predicted concentrations.

Body weight was included as a covariate in the population PK models. Adolescent body weight as low as 30 kg is not expected to cause clinically significant differences in elbasvir and grazoprevir exposures (see *Figure 7* and *Figure 8*). Gender, ethnicity, and renal function (eGFR) were also investigated as potential covariates within the PopPK models for both elbasvir and grazoprevir, but no trends were identified in the paediatric data, consistent with the modest (and not clinically relevant) effects identified in the much larger adult PK dataset.

Figure 7: *Steady-state AUC (90% CI) of elbasvir following oral once daily administration of Zepatier® (50 mg elbasvir/100 mg grazoprevir) tablet to adolescents (12 to <18 years), by weight band, predicted by PopPK simulations, compared to adult reference exposure (horizontal solid line) and clinical comparability bounds (horizontal dashed lines)*

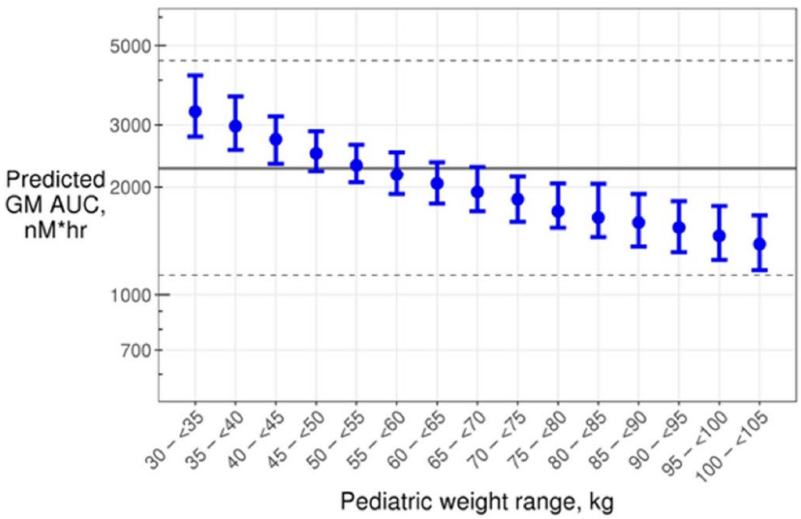
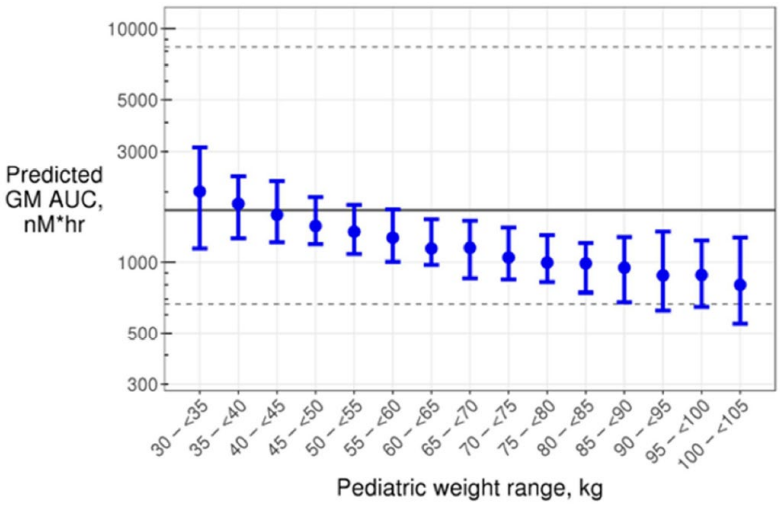


***Figure 8*:** *Steady-state AUC (90% CI) of grazoprevirr following oral once daily administration of Zepatier (50 mg elbasvir/100 mg grazoprevir) tablet to adolescents (12 to <18 years), by weight band, predicted by PopPK simulations, compared to adult reference exposure (horizontal solid line) and clinical comparability bounds (horizontal dashed lines)*



2.3.3. Pharmacodynamics

Mechanism of action

Grazoprevir (GZR; MK-5172) is an 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.

Elbasvir (EBR; MK-8742) is an inhibitor of non-structural protein 5A (NS5A). NS5A is essential for viral RNA replication and virion assembly.

Primary and secondary pharmacology

The primary pharmacology of GZR and EBR has been extensively reviewed at the initial MAA.

Viral resistance results

Baseline NS3 sequence data were available for 97% (30/31), 100% (24/24), 100% (1/1), and 100% (1/1) of participants infected with GT1a, GT1b, GT4a, and GT4d, respectively. Among participants infected with GT1a or GT1b, the prevalence of baseline NS3 RASs in each Age Cohort were in the range of 33% to 75%. Q80K (30%) and A56F (37.5%) were the most prevalent NS3 RASs in participants infected with GT1a and GT1b, respectively. The single participant with GT4a infection from Age Cohort 1 had an NS3 RAS, S122N, at baseline. There was no impact of baseline NS3 RAS on efficacy; all participants achieved SVR12.

Resistance analysis in NS5A was not performed. Participants with baseline NS5A polymorphisms at amino acid positions 28, 30, 31, and/or 93 that are associated with resistance to EBR were excluded from study participation.

No treatment-emergent RASs were evaluated as no participant experienced virologic failure.

2.3.4. PK/PD modelling

Data submitted in the initial dossier showed that in adults;

-GZR AUC0-24 and Ctrough were not associated with SVR12, suggesting that exposures at the 100 mg dose were on the maximal response plateau of the E-R curve for efficacy against GT1 and 4.

-EBR AUC0-24 and EBR Ctrough were both associated with SVR12 in GT1 and 4.

No dedicated PK/PD modelling was conducted within study P079.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

The MAH performed a clinical study investigating the PK of elbasvir and grazoprevir in paediatric patients (3 to 17 years) and compared the observed Cmax, C24h and AUC0-24 to the exposure previously observed in adults treated with Zepatier (50 mg elbasvir and 100 mg grazoprevir). Only the exposure in patients aged 12 to 17 years was assessed. The exposure in the other age categories was not assessed since these age categories are not part of the current Type II variation for Zepatier. Furthermore, study P082 was not assessed since the uncoated granules are not part of the current Type II variation (only patients <12 years of age were treated with granules) and is considered only supportive to this extension of indication.

The pharmacokinetics of Zepatier (fixed-dose combination tablet of 50 mg elbasvir and 100 mg grazoprevir) were sufficiently investigated in paediatric patients aged 12 to 17 years. The exposure (Cmax, C24h and AUC0 24) in paediatric patients was compared to that the exposure in adults (based on exposure data of the original MAA of Zepatier).

In paediatric subjects, 12 years of age and older, the mean steady-state elbasvir AUC0-24 and Cmax were 2.41 μM × h and 0.19 μM, respectively, and the mean steady-state grazoprevir AUC0-24 and Cmax were 1.45 μM × h and 0.25 μM, respectively. Exposure (Cmax and AUC0-24) in patients aged 12 to <18 years with chronic Hepatitis C genotype 1 to 4 was comparable to that in adults following once-daily dosing with 50 mg elbasvir 100 mg grazoprevir using the Zepatier® fixed-dose combination tablet. The C24h of grazoprevir in paediatric patients aged 12 to 17 years was lower than that in adults (15.2 nM versus 23.5 nM). However, this is not of clinical consequence since the C24h is not relevant for the exposure-efficacy relationship (see 5.3.3 Pharmacodynamics and 5.4 Efficacy).

Exposure (AUC0-24) is increased with decreasing body weight (elbasvir exposure was 3.27 μM × h in subjects 30-35 kg and 1.39 μM × h in subjects 100-105 kg; grazoprevir exposure was 2.01 μM × h in subjects 30-35 kg and 0.80 μM × h in subjects 100-105 kg). However, the exposure was still within the clinical comparability bound for elbasvir and grazoprevir in adults. No information on the exposure in subjects aged 12 to 17 years and weighing <30 kg is available. Therefore, the limitation of body weight >30 kg is agreed.

Pharmacodynamics

The primary pharmacology of GZR and EBR has been extensively reviewed in the initial marketing authorization.

Resistance associated substitutions (RASs) in NS3, were determined at baseline. However, no impact on efficacy was found (see also section 2.4.2.).

Since patients with known polymorphisms associated with resistance to EBR (NS5A RASs) were excluded from the study, no baseline resistance was present. No determination of treatment-emergent RASs was deemed necessary given the absence of virologic failure

2.3.6. Conclusions on clinical pharmacology

No clinically relevant difference in exposure was observed in patients aged 12 to 17 years compared to adults following once-daily treatment with Zepatier (fixed-dose combination tablet of 50 mg elbasvir and 100 mg grazoprevir).

There were no indications of treatment-emergent RASs.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

As only one dose was evaluated for paediatric patients, a dose-response relationship was not evaluated. The adolescent posology is based on PK bridging (see section 2.3.2.).

2.4.2. Main study

Study P079

P079 was a nonrandomized, single-arm, multiple cohort, multisite, open-label Phase 2b study of EBR/GZR in non-cirrhotic paediatric participants, 3 to <18 years of age. The study consisted of three age cohorts. Each Age Cohort was initiated with a Mini Age Cohort of 7 participants with at least 6 participants with evaluable PK before enrolling additional participants into the Expanded Age Cohort.

Note: Given the proposed extension of the indication to adolescents, only data from cohort 1 will be assessed in this report. However, data from the other cohorts might appear in tables and figures throughout this report.

Age Cohort	Age Range	Enrollment Requirements	
		Mini Cohort	Expanded Cohort
1	12 to <18 years	• N=7 (to ensure at least 6 participants with evaluable PK) • At least 2 participants aged <14 years	• N=~15 • At least 3 participants aged 12 to <14 years • At least 3 participants aged 16 to <18 years
2	7 to <12 years	• N=7 (to ensure at least 6 participants with evaluable PK) • At least 2 participants aged <9 years	• N=~20 • At least 5 participants aged 7 to <12 years • At least 5 participants aged 3 to <7 years • At least 2 participants aged <5 years

3	3 to <7 years	• N=7 (to ensure at least 6 participants with evaluable PK) • At least 2 participants aged <5 years	

Study participants

The following participants were eligible for enrolment:

- HCV RNA (≥1,000 IU/mL in peripheral blood) at the time of screening.
- Documented chronic HCV GT1 or GT4 infection.
- For participants with GT4, HCV RNA <800,000 IU/mL at the time of screening.
- For participants with GT1a, no evidence of NS5A RASs detected at screening at
- positions 28, 30, 31, and/or 93.
- The participant has liver disease staging assessment as follows; Absence of cirrhosis (F0 to F3) or compensated cirrhosis (F4)

Treatments

All participants in age cohort 1 (mini and expanded) received the EBR/GZR (50 mg/100 mg) FDC tablet once daily for 12 weeks.

Objectives

The primary objective was to evaluate the steady-state EBR and GZR PK in children and adolescents grouped by age.

The secondary safety objective was to evaluate the safety and tolerability of 12 weeks of treatment with EBR/GZR in children and adolescents grouped by age.

The secondary efficacy objective was to evaluate the efficacy of 12 weeks of treatment with EBR/GZR in children and adolescents grouped by age, as assessed by the proportion of participants achieving SVR12.

Outcomes/endpoints

The primary endpoint was

- Week 4 $AUC_{0\text{-}24}$, maximum observed drug concentration (C_{max}), drug concentration immediately pre-dose (C_{trough}), and apparent clearance (CL/F).

The secondary safety endpoint was:

- The number of participants experiencing AEs.
- Number of participants discontinuing study drug due to AEs.

The secondary efficacy endpoint was

- SVR12: defined as HCV RNA <LLOQ (either target detected, but unquantifiable [TD(u)] or target not detected [TND]) 12 weeks after the end of all study therapy.

As exploratory endpoint, the sustained virologic response 24 weeks after the end of all study therapy was assessed, defined as HCV RNA <LLOQ (either TD[u] or TND) 24 weeks after the end of all study therapy.

Sample size

This is an estimation study with no hypotheses. With regard to the PK objective, with 22 participants in an Age Cohort, it is ~80% likely that the lower and upper bounds of the 95% CI for GZR AUC0-24 will lie within 44% of the observed GM.

For the efficacy objective, the expected response rate is ~95% based on previous EBR/GZR clinical trials. Treatment is expected to be similarly active in different Age Cohorts in either TN or TE paediatric participants with or without cirrhosis. With a sample size of 22, the lower bound of the 95% CIs for SVR12 given varying assumptions of the number of successes for 22 participants varies from 59.7 in case 18/22 patients achieve SVR12 to 84.6 in case 22/22 patients achieve SVR12.

Randomisation

This was a single arm study, no randomisation occurred.

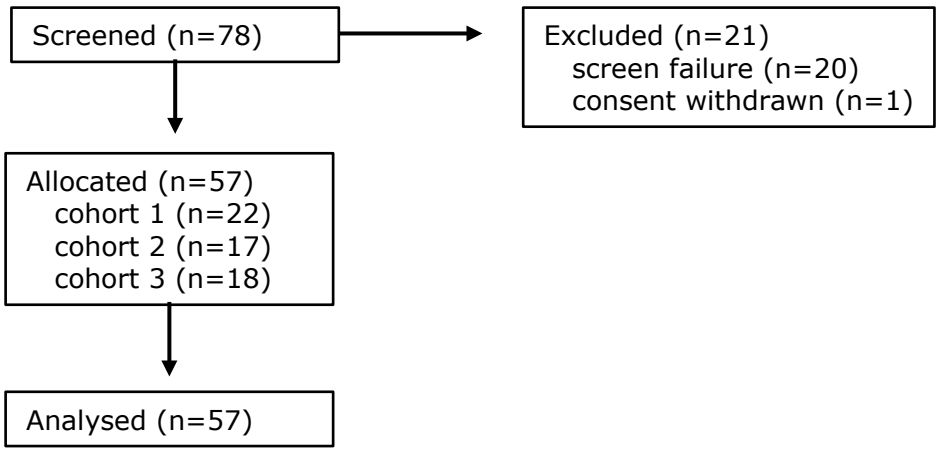
Blinding (masking)

This was an open-label study, hence no blinding occurred.

Statistical methods

This was a descriptive study, no formal analysis were planned.

Participant flow



Recruitment

The first participant was recruited at 25-JAN-2018. The data of the last visit of the last participant was 23-NOV-2020. Patients were recruited from 14 study sites in the US, Germany and Poland.

Conduct of the study

Important protocol deviations were reported for 4 participants in cohort 1. Of these, 2 were considered to be clinically important:

• 1 participant in Age Cohort 1 entered the study without documented child assent. Note: Documented initial consent by the participant's legally acceptable representative was obtained prior to study entry.

• 1 participant in Age Cohort 1 entered the study with a history of gastroduodenal surgery, a condition specified as exclusionary in the protocol.

No participant's data were excluded from analyses due to an important protocol deviation. No important protocol deviations were classified as a serious GCP compliance issue. No protocol deviations due to the pandemic were reported.

The reported protocol deviations are not expected to have influenced the study results and are therefore not of concern.

Baseline data

Table 10: Baseline and demographic data cohort 1.

	Age Cohort 1 (12 to <18 years): Mini and Expanded
	n (%)
Subjects in population	22
Gender	
Male Female	11 (50.0) 11 (50.0)
Age	
3 to <7 years	0 (0.0)
7 to <12 years	0 (0.0)
12 to <18 years	22 (100.0)
Mean	14.1
SD	1.9
Median	13.5
Range	12 to 17
Race	
Multiple Native Hawaiian Or Other Pacific Islander, White White	1 (4.5) 1 (4.5) 21 (95.5)
Hispanic Or Latino Not Hispanic Or Latino Not Reported	3 (13.6) 19 (86.4) 0 (0.0)
HCV Genotype	
1a	16 (72.7)
1b	5 (22.7)
4a	0 (0.0)
4d	1 (4.5)
Prior Treatment History	
Treatment Naïve PR Treatment Experienced	14 (63.6) 8 (36.4)
Baseline HCV RNA (IU/mL)	
Subjects with data	22
Mean	1406305

SD	2080769.6
Median	749334
Range	78579 to 9428091

Of the 22 patients included, 21 patients had HCV genotype 1a/b and 1 patient had genotype 4. Although this limits the conclusions on GT4, the low enrolment of patients infected with GT4 can be expected based on the low prevalence of GT4 (<5%) in the USA and Europe where this study was conducted[1].

Numbers analysed

Efficacy analyses were based on the Full Analysis Set (FAS) population and included all 22 allocated participants who received at least 1 dose of the study intervention. Safety analyses were based on the All subjects as Treated (ASaT) population, which included all 22 allocated participants who received at least 1 dose of study intervention and was the same as the FAS population. Data is presented for Cohort 1.

Outcomes and estimation

Secondary efficacy endpoint

All participants in Cohort 1 achieved SVR12.

Table 11: *Analysis of the Proportion of Subjects with Sustained Virologic Response (HCV RNA < LLoQ) 12 Weeks After End of All Study Therapy (SVR12) (FAS)*

Cohort	N	n (%)	95% Confidence Interval[†]
Age Cohort 1 (12 to <18 years): Mini and Expanded	22	22 (100.0)	(84.6, 100.0)
Age Cohort 2 (7 to <12 years): Mini and Expanded	17	17 (100.0)	(80.5, 100.0)
Age Cohort 3 (3 to <7 years): Mini	7	7 (100.0)	(59.0, 100.0)
Age Cohort 3 (3 to <7 years): Expanded	11	11 (100.0)	(71.5, 100.0)
Total	57	57 (100.0)	(93.7, 100.0)

[†]Based on Clopper-Pearson method.
N = Number of subjects included in the analysis.
n (%) = Number of subjects who achieved undetectable (TND) or unquantifiable (TD(u)) HCV RNA and the percentage calculated as (n/N)*100.
LLoQ is 15 IU/mL.

Source: [P079V01MK5172: adam-adsl; adhcvrna]

Exploratory endpoints

All participants in cohort 1 achieved SVR24.

[1] Guss et al. J Gen Intern Med. 2018 Apr; 33(4): 551–557.

Table 12: *Analysis of the Proportion of Subjects with Sustained Virologic Response (HCV RNA < LLoQ) 24 Weeks After End of All Study Therapy (SVR24)(FAS)*

Cohort	N	n (%)	95% Confidence Interval[†]
Age Cohort 1 (12 to <18 years): Mini and Expanded	22	22 (100.0)	(84.6, 100.0)
Age Cohort 2 (7 to <12 years): Mini and Expanded	17	16 (94.1)	(71.3, 99.9)
Age Cohort 3 (3 to <7 years): Mini	7	7 (100.0)	(59.0, 100.0)
Age Cohort 3 (3 to <7 years): Expanded	11	11 (100.0)	(71.5, 100.0)
Total	57	56 (98.2)	(90.6, 100.0)

[†]Based on Clopper-Pearson method.
N = Number of subjects included in the analysis.
n (%) = Number of subjects who achieved undetectable (TND) or unquantifiable (TD(u)) HCV RNA and the percentage calculated as (n/N)*100.
LLoQ is 15 IU/mL.
One subject in the Age Cohort 2 (7 to <12 years) did not return for their HCV RNA blood draw for follow-up week 24 due to COVID-19 concerns. As a result, per the Missing=Failure approach described in the protocol, this subject is treated as failure in SVR24.

Source: [P079V02MK5172: adam-adsl; adhcvrna]

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy and the benefit-risk assessment (see later sections).

Table 13: *Summary of Efficacy for trial P079*

Title: A Phase IIb Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chronic Hepatitis C Infection.			
Study identifier	P079		
Design	Multicenter, pharmacokinetics, safety, efficacy, single arm, multiple cohort, open-label, unblinded intervention.		
	Duration of treatment phase: Duration of off treatment follow up:		12 weeks 24 weeks
Hypothesis	Not specified		
Treatments groups	Cohort 1: 12-18 years		EBR 50 mg/GZR 100 mg for 12 weeks n=22
Endpoints and definitions	Primary endpoint	PK	AUC_{0-24}, C_{max}, C_{trough}
	Secondary endpoint:	SVR12	Sustained virologic response 12 weeks after end of treatment.
Database lock	20 AUG 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	SVR12 in the FAS (secondary efficacy endpoint).		

Descriptive statistics and estimate variability	Treatment group	Cohort 1
	Number of subjects	22
	SVR12 n/N, %	22/22, 100%
	95% CI	84.6, 100.0
Notes		

2.4.3. Discussion on clinical efficacy

This open-label, single-arm trial in 22 adolescents is not powered to provide comprehensive efficacy data. However, in line with EMA guidance, the use of the adult dose (FDC, 50 mg/100 mg) is based on similar systemic exposure, and efficacy can be extrapolated based on PK bridging.

The main efficacy endpoint was sustained virologic response 12 weeks after the end of treatment. This is in accordance with the guideline on the clinical evaluation of DAA's for hepatitis C (CHMP/EWP/30039/2008) and is suitable to support efficacy in the adolescent population. All patients achieved SVR12.

As an exploratory endpoint, maintenance of virologic response 24 weeks after the end of treatment was assessed, which was achieved by 22/22 patients in cohort 1.

2.4.4. Conclusions on the clinical efficacy

Study data show that 12-week treatment with EBR 50 mg/GZR 100 mg effectively induces sustained virologic response in children aged 12 <18 years of age with a chronic HCV infection (types 1 and 4).

2.5. Clinical safety

Introduction

The knowledge on the safety profile of EBR/GZR comes from 3 placebo-controlled studies and 7 uncontrolled Phase 2 and 3 clinical studies in approximately 2,000 subjects with chronic hepatitis C infection with compensated liver disease (with or without cirrhosis).
In clinical studies, the most commonly reported adverse reactions (greater than 10%) were fatigue and headache. Less than 1 % of subjects treated with EBR/GZR with or without ribavirin had serious adverse reactions (abdominal pain, transient ischaemic attack and anaemia). Less than 1 % of subjects experienced ALT elevations from normal levels to greater than 5 times the ULN, which were typically asymptomatic.

Safety analyses were based on the ASaT population, including all 57 allocated participants who received at least 1 dose of study intervention and was the same as the FAS population. Below, safety data from age cohort 1 is presented.

Patient exposure

All participants in Age Cohort 1 (Mini and Expanded) were treated with the EBR/GZR (50 mg/100 mg) FDC tablet. The majority (95%) of participants in Age Cohort 1 completed 12 weeks of therapy of EBR/GZR.

Adverse events

EBR/GZR was generally well tolerated in non-cirrhotic CHC-infected pediatric participants (3 to <18 years of age). Observed AEs were generally consistent with those expected in a CHC-infected pediatric population and with the known safety profile of EBR/GZR. In cohort 1, 17 patients experienced an adverse event of which 6 were deemed related to the study drug.

Table 14: *Adverse Event Summary Treatment Phase and First 14 Follow-Up Days*

	Age Cohort 1 (12 to <18 years): Mini and Expanded	
	n	(%)
Subjects in population	22	
with one or more adverse events	17	(77.3)
with no adverse event	5	(22.7)
with drug-related[T] adverse events	6	(27.3)
with serious adverse events	1	(4.5)
with serious drug-related adverse events	0	(0.0)
who died	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)

The most common drug-related AEs were headache (3 patients with an event) and nausea (2 patients with an event).

Table 15: *Subjects With Drug-Related Adverse Events (Incidence > 0% in One or More Treatment Groups) in the Treatment Phase and First 14 Follow-Up Days.*

	Age Cohort 1 (12 to <18 years): Mini and Expanded	
	n	(%)
Subjects in population	22	
with one or more drug-related adverse events	6	(27.3)
with no drug-related adverse events	16	(72.7)
Gastrointestinal disorders	**3**	**(13.6)**
Abdominal pain upper	0	(0.0)
Diarrhoea	0	(0.0)
Flatulence	1	(4.5)
Nausea	2	(9.1)
General disorders and administration site conditions	**2**	**(9.1)**
Asthenia	1	(4.5)
Chills	1	(4.5)
Fatigue	1	(4.5)
Investigations	**0**	**(0.0)**
Alanine aminotransferase increased	0	(0.0)
Metabolism and nutrition disorders	**0**	**(0.0)**
Decreased appetite	0	(0.0)
Musculoskeletal and connective tissue disorders	**1**	**(4.5)**
Arthralgia	1	(4.5)
Nervous system disorders	**3**	**(13.6)**
Headache	3	(13.6)
Somnolence	1	(4.5)
Psychiatric disorders	**0**	**(0.0)**
Restlessness	0	(0.0)
Renal and urinary disorders	**0**	**(0.0)**
Proteinuria	0	(0.0)

Every subject is counted a single time for each applicable row and column.

The reported ADR's that occurred in >1 patient were headache (3 patients) and nausea (2 patients). These ADRs are in line with the known safety profile of Zepatier as represented in the SmPC.

All reported ADR's in cohort 1 were mild and resolved without sequelae.

Furthermore, one patient presented with flatulence, which was mild and resolved without further action. Another patient presented with chills and somnolence, which were also mild, of short duration and resolved without further action. It is therefore not considered necessary to include flatulence, chills and somnolence in section 4.8 of the SmPC.

Serious adverse event/deaths/other significant events

One participant experienced an SAE: 1 participant in Age Cohort 1 with hand fracture. This SAE was not considered by the investigator to be related to study intervention.

A participant in Age Cohort 1 experienced an ECI of accidental overdose following inadvertent administration of an extra dose of an EBR/GZR FDC tablet and had no associated AEs.

Laboratory findings

Mean reductions from baseline in ALT and AST and small mean changes in bilirubin were observed throughout the treatment and follow-up periods in each Age Cohort. The changes in these 3 laboratory parameters were not considered to be clinically meaningful.

None of the patients in cohort 1 experienced elevations in ALT and AST that met predetermined criteria.

One patient experienced a grade 1 (1.1 - 1.5 x ULN) increase in bilirubin.

No clinically meaningful changes from baseline in vital signs measurements (diastolic blood pressure, systolic blood pressure, and heart rate) were observed in any Age Cohort.

Safety related to drug-drug interactions and other interactions

DDIs were not evaluated in P079. The potential for DDIs with EBR/GZR has been extensively evaluated in non-clinical studies and in clinical studies in adults (original application CTD Section 2.7.2.3.4). There is no additional information regarding the potential for DDIs that would suggest a change in the safety profile of EBR/GZR for adolescent use.

Discontinuation due to adverse events

There were no discontinuations due to adverse events.

Post marketing experience

The post-marketing data for the pediatric population are limited. However, a review of these data do not identify new safety issues.

The EBR/GZR FDC tablet was first approved in Canada on 19-JAN-2016 (IBD) and has been approved in 79 countries as of 18-JUL-2020. The single-entity tablets of EBR and GZR are currently approved in 1 country (Japan) and are indicated in combination. There are no records of any registration being revoked or withdrawn for safety reasons.

The MAH’s safety database was queried for valid, spontaneous and non-interventional study reports for EBR/GZR from 19-JAN-2016 to 18-JUL-2020. A total of 7783 reports with 16,087 events were identified. Of these, 7 concerned pediatric patients; 2 reports were serious, and 5 were non-serious. Of these 7 reports, 3 pertained to adolescent patients.

Table 16: *Adverse Events by System Organ Class in Patient <18 years of age 19-JAN-2016 to 18-JUL-2020*

Event System Organ Class	Event Preferred Term	Non-Serious (Event Count)	Serious (Event Count)
Congenital, familial and genetic disorders	Microcephaly	0	1
Congenital, familial and genetic disorders	**Subtotal**	**0**	**1**
Gastrointestinal disorders	Nausea	1	0
Gastrointestinal disorders	**Subtotal**	**1**	**0**
General disorders and administration site conditions	Adverse event	1	0
	Treatment noncompliance	1	0
General disorders and administration site conditions	**Subtotal**	**2**	**0**
Injury, poisoning and procedural complications	Circumstance or information capable of leading to medication error	1	0
	Foetal exposure during pregnancy	3	0
	Inappropriate schedule of product administration	1	0

Event System Organ Class	Event Preferred Term	Non-Serious (Event Count)	Serious (Event Count)
	Product use issue	1	0
Injury, poisoning and procedural complications	**Subtotal**	**6**	**0**
Investigations	Alpha 1 foetoprotein amniotic fluid increased	0	1
Investigations	**Subtotal**	**0**	**1**
Pregnancy, puerperium and perinatal conditions	Low birth weight baby	2	0
	Premature baby	1	0
	Small for dates baby	1	0
Pregnancy, puerperium and perinatal conditions	**Subtotal**	**4**	**0**
Psychiatric disorders	Dependence	0	1
Psychiatric disorders	**Subtotal**	**0**	**1**
Total		**13**	**3**

2.5.1. Discussion on clinical safety

The safety assessment for the extension of the indication to adolescents is based on the safety data from 22 patients 12 <18 years of age. This sample size is not sufficient to generate a comprehensive safety database. This is not considered an issue since the primary objective of the study was to generate PK data. Efficacy and safety are extrapolated based on the comparable exposure in adolescents and adults.

All 22 participants in Age Cohort 1 completed 12 week treatment period with the FDC tablet (50 mg EBR and 100 mg GZR). One participant took less than 12 weeks (84 days) of therapy and missed 8 doses between Day 1 (first day of dosing) and Day 84 (last day of dosing). Despite the missed doses, this participant achieved sustained virologic response at follow-up weeks 12 and 24. These missed doses are not explained by difficulty with swallowing or taste as the participant reported favourable and neutral responses on the acceptability/palatability questionnaire.

Treatment-related adverse events were reported by 6/22 patients. The most common were headache and nausea. These ADRs are known for EBR/GZR and are adequately covered in the current SmPC. Furthermore, fatigue, arthralgia, somnolence, flatulence, asthenia and chills occurred. All ADR's were mild and resolved without sequelae; therefore, no action is necessary to adjust section 4.8 of the SmPC.

No deaths and treatment-related serious AEs were reported. No discontinuations due to the study drug occurred.

There were no clinically relevant changes in ALT, AST and bilirubin.

Although limited, the post-marketing safety database in adolescents did not raise safety concerns.

2.5.2. Conclusions on clinical safety

From a clinical safety perspective, no issues are identified.

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 an updated RMP version 5.0 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 5.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

Safety concerns

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Drug resistance development
Important potential risks	• Emergence of Hepatocellular Carcinoma (*de novo* HCC) • Recurrence of Hepatocellular Carcinoma
Missing information	• Exposure in patients with previous hepatocellular carcinoma

Pharmacovigilance plan

Table III.3.1: On-Going and Planned Additional Pharmacovigilance Activities

StudyStatus	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Protocol 135 - DAA-PASS: A Post-Authorization Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy	The primary objective of the DAA PASS is to estimate the risk of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort. Secondary objectives are to:	Recurrence of HCC Exposure in patients with previous hepatocellular carcinoma	Protocol (version 3.3) endorsed by PRAC	14-JUN-2018

Table III.3.1: On-Going and Planned Additional Pharmacovigilance Activities

StudyStatus	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Status: Ongoing	1. Compare the adjusted incidence of early HCC recurrence (within the follow-up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort; 2. Estimate the risk of early HCC recurrence (within the follow-up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC; 3. Compare the adjusted incidence of early HCC recurrence (within the follow-up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC. The exploratory objective is to describe in a non-comparative summary the cumulative risk of HCC recurrence over time for the historical cohort alone.			
			Amended protocol (version 4.2) endorsed by PRAC	11-JUN-2020
			Date of Final study report Submission	3Q 2021
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Table III.3.1: On-Going and Planned Additional Pharmacovigilance Activities

StudyStatus	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Protocol 149 - A study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C (De Novo DAA PASS) Status: Ongoing	The primary objectives of this retrospective cohort study are as follows: 1. Estimate the risk of de novo HCC associated with DAA therapy exposure in cirrhotic HCV patients compared to no anti-HCV therapy exposure in cirrhotic HCV patients. 2. Estimate the risk of de novo HCC in cirrhotic HCV patients treated with DAA therapy compared to those treated with IFN-based therapy. The secondary objective is to compare, in a subset of patients with available data recorded in the VA CCR, tumor characteristics (i.e., tumor size, tumor number, tumor stage, tumor type) of the de novo HCC cases observed following initiation of DAA therapy to those of de novo HCC cases observed (a) following initiation of IFN-containing regimens and (b) in untreated patients.	Emergence of HCC (*de novo HCC)*	PRAC endorsed joint PASS protocol (version 3.0)	14-JUN-2019
			Date of Final Study Report Submission	14-DEC-2021

Table III.3.1: On-Going and Planned Additional Pharmacovigilance Activities

StudyStatus	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Protocol 017: A Long-Term Follow-up Study to Evaluate the Durability of Virologic Response and/or Viral Resistance Patterns of Subjects With Chronic Hepatitis C Who Have Been previously Treated with MK-5172 in a Prior Clinical Trial Status: Ongoing	Adult Population: In HCV-infected subjects who received at least 1 dose of GZR in a previous study: Objectives: To evaluate the durability of response in subjects who achieved SVR24 in the prior treatment study and at the time of entry into PN017 were HCV rRNA < lower limit of quantification (either target not detected or target detected, unquantifiable). To evaluate the presence of treatment emergent antiviral resistance to NS3/4A, NS5A and/or NS5B regions, (as applicable) and determine if there is a reversion to wild-type pattern with the 3 year time frame of this long-term follow-up study (or 5 year time frame for subjects from P052) in subjects with virologic failure in the prior treatment study and with HCV RNA ≥1000 IU/mL in P017. To evaluate the long-term safety. Pediatric Population: In HCV-infected subjects who received at least 1 dose of GZR in a previous study: To evaluate the persistence of treatment-emergent antiviral resistance to NS3 and NS5A regions within the 3 year time frame of this long-term follow-up study.	Drug resistance development	Date of initiation (First Subject First Visit)	23-JAN-2013
			Interim report	September 2016 (submitted September 2016)
			Date of completion (Last Subject Last Visit)	31-MAR-2021
			Date of Final Clinical Study Report Submission	1Q 2022

Risk minimisation measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Drug resistance development	Routine risk minimisation measures: Listed under SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Not applicable	Routine pharmacovigilance activities Additional pharmacovigilance activities: Study short name and title: Protocol 017 - A Long-Term Follow-up Study to Evaluate the Durability of Virologic Response and/or Viral Resistance Patterns of Subjects With Chronic Hepatitis C Who Have Been previously Treated with MK-5172 in a Prior Clinical Trial Final study report submission date: 1Q 2022
Emergence of Hepatocellular Carcinoma (*de novo* HCC)	Routine risk minimisation measures: Not applicable. Additional risk minimisation measures: Not applicable	Routine pharmacovigilance activities Additional pharmacovigilance activities: Study short name and title: Protocol 149 - A study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C (De Novo DAA PASS) Final study report submission date: 14-DEC-2021
Recurrence of Hepatocellular Carcinoma	Routine risk minimisation measures: Not applicable. Additional risk minimisation measures: Not applicable	Routine pharmacovigilance activities Additional pharmacovigilance activities: Study short name and title: Protocol 135 - DAA-PASS (Category 1): A Post-Authorization Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy Final study report submission date: 3Q 2021
Exposure in patients with previous hepatocellular carcinoma	Routine risk minimisation measures: Not applicable. Additional risk minimisation measures: Not applicable	Routine pharmacovigilance activities Additional pharmacovigilance activities: Study short name and title: Protocol 135 - DAA-PASS (Category 1): A Post-Authorization Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy Final study report submission date: 3Q 2021

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being

updated to reflect the inclusion of adolescents in the indication. 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 BE/LU, DE, and UK (Northern Ireland).

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 reason:

The proposed revisions do not constitute significant changes that would require the need to conduct a new user consultation.

2.7.1. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zepatier is included in the additional monitoring list as it has a PASS imposed either at the time of authorisation or afterwards.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Hepatitis C virus causes both acute and chronic infection. New HCV infections are usually asymptomatic. Around 30% (15–45%) of infected persons spontaneously clear the virus within 6 months of infection without any treatment. The remaining 70% (55–85%) of persons will develop chronic HCV infection (CHC). Of those with chronic HCV infection, the risk of cirrhosis ranges between 15% and 30% within 20 years (WHO).

CHC has similar clinical features and risks for complications (progression to advanced fibrosis, cirrhosis, end-stage liver disease, hepatocellular carcinoma) in both adults and adolescents. It is estimated that between 40% and 60% of HCV-antibody-positive adolescents are chronically infected and viraemic.

3.1.2. Available therapies and unmet medical need

Perinatal (vertical) transmission is the most common source of CHC in paediatrics. However, in adolescents, the incidence of CHC increases due to high-risk behaviours such as IV drug use and shared tattoo equipment. In particular, the opioid epidemic has resulted in an increasing incidence of CHC among adolescents. Therefore, within the paediatric population, adolescents are the group in greatest need of treatment options.

The therapeutic goal of treatment of chronic HCV is the eradication of the virus as measured by a sustained virologic response with a halt in the progression of liver damage.

The current standard of care for the treatment of CHC in adolescents is the use of all-oral combination DAA regimens (e.g., sofosbuvir/velpatasvir or glecaprevir/pibrentasvir). Treatment with DAAs is usually

very effective, and treatment duration is short (usually 12 to 24 weeks), depending on the absence or presence of cirrhosis.

3.1.3. About the product

EBR/GZR is an FDC of 2 DAAs with distinct mechanisms of action and non-overlapping resistance profiles targeting HCV at multiple steps in the viral lifecycle (see section 2.3.3.).

3.1.4. Main clinical studies

The indication extension to adolescents is supported by study P079, a single arm, open label study in 3 age cohorts. Age cohort 1 consisted of 22 adolescents aged 12 <18 years of age that received the FDC tablets (50 mg EBR/100 mg GZR) for 12 weeks. After the end of treatment, patients were followed up for 24 weeks.

The primary objective was to generate PK data for PK-bridging. Secondary objectives were efficacy, measured by sustained virologic response 12 weeks after the end of treatment (SVR12), and safety.

3.2. Favourable effects

Based on the PK bridge, efficacy can be extrapolated from adults to adolescents.

With regard to the clinical outcomes, all patients enrolled in cohort 1 achieved SVR12 (22/22, 100%).

3.3. Uncertainties and limitations about favourable effects

This study was not designed and powered to provide comprehensive efficacy data.

3.4. Unfavourable effects

Most common side effects were headache (occurring in 3/22 patients) and nausea (2/22 patients). Other ADRs occurring were arthralgia, flatulence, chills and somnolence (all reported in 1/22 patients).

3.5. Uncertainties and limitations about unfavourable effects

The size of the safety database is limited, including 22 patients.

One out of 22 patients did not complete the 12 weeks of therapy, but the reason is unclear.

3.6. Effects Table

Table 1. . Effects Table for Zepatier for the treatment of CHC in adolescents aged 12 <18 years of age.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
SVR12	Proportion of patients achieving SVR 12 weeks after end of	n/N	22/22		SoE: Supported by the 95% SVR 24 weeks after treatment.	Study P079

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	treatment.					
Unfavourable Effects						
headache		n/N	3/22		SoE: in line with the known safety profile of zepatier.	Study P079
nausea		n/N	2/22		SoE: in line with the known safety profile of zepatier.	Study P079

Abbreviations: SVR12; sustained virologic response 12 weeks after the end of treatment.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The paediatric study P079 was not powered to provide comprehensive safety and efficacy data in adolescents. However, this is not of concern since the main objective was to generate PK data for PK bridging. Efficacy and safety can be extrapolated on the basis of similar systemic exposure in line with the "Guidelines on the clinical evaluation of direct-acting antivirals for the treatment of chronic hepatitis" from the EMA.

Given that viral clearance aims to treat chronic HPV infections, SVR12 is an appropriate and clinically relevant endpoint. The sustained virologic response 12 weeks after treatment was maintained 24 weeks after treatment.

The safety profile in adolescents is in line with the safety profile known from adults.

3.7.2. Balance of benefits and risks

Based on PK bridging, the proposed dose of EBR/GZR can be assumed to be effective and safe.

Sustained virologic response 12 weeks after the end of treatment was achieved in 22/22 adolescents enrolled in the study.

The safety profile in adolescents is in line with the safety profile known from adults and is relatively mild, with headache and nausea as most common ADRs.

3.8. Conclusions

The overall B/R of Zepatier is positive.

4. Recommendations

Outcome

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

change:

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

Extension of indication to include treatment of chronic hepatitis C (CHC) in paediatric patients 12 years of age and older who weigh at least 30 kg for Zepatier; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.0 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0255/2017 and the results of these studies relevant to the agreed paediatric indication are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Zepatier-H-C-004126-II-0029'

Attachments

1. SmPC, Package Leaflet (changes highlighted) as adopted by the CHMP on 16 September 2021.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 6th October 2021. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 6th October 2021. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.