22 July 2021
EMA/480638/2021
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on group of an extension of marketing authorisation and an extension of indication variation

Vosevi

International non-proprietary name: sofosbuvir / velpatasvir / voxilaprevir

Procedure No. EMEA/H/C/004350/X/0045/G

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Administrative information

Name of the medicinal product:	Vosevi
MAH:	Gilead Sciences Ireland UC IDA Business & Technology Park Carrigtohill County Cork T45 DP77 IRELAND
Active substance:	sofosbuvir / velpatasvir / voxilaprevir
International Non-proprietary Name:	sofosbuvir / velpatasvir / voxilaprevir
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use; Direct-acting antivirals (J05AP56)
Therapeutic indication(s):	Vosevi is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients aged 12 years and older and weighing at least 30 kg
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	400 mg / 100 mg / 100 mg 200 mg / 50 mg / 50 mg
Route(s) of administration:	Oral use
Packaging:	bottle (HDPE)
Package size(s):	28 tablets

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
APRI	aspartate aminotransferase to platelet ratio index
AST	aspartate aminotransferase
BMI	body mass index
CFU	Colony Forming Units
CSR	clinical study report
CTX	C-type collagen sequence
DAA	direct-acting antiviral
eGFR	estimated glomerular filtration rate
EU	European Union
FAS	Full Analysis Set
FDC	fixed-dose combination
FIB-4	Fibrosis-4
Gilead	Gilead Sciences
GT	genotype
HCV	hepatitis C virus
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL28B	IL28B gene
LDV	ledipasvir (GS-5885)
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
N	number of subjects
NI	nucleoside inhibitor
NLT	Not less than
NMT	Not more than
NS	nonstructural protein (3, 5A, 5B)
P1NP	procollagen type 1 N-terminal propeptide
Peg-IFN	pegylated interferon
Ph. Eur.	European Pharmacopoeia
PI	protease inhibitor
PK	pharmacokinetic(s)
Q1	first quartile
Q3	third quartile
RAV	resistance-associated variant
RBV	ribavirin
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDD	Spray-dried dispersion
SmPC	Summary of Product Characteristics
SOC	system organ class
SOF	sofosbuvir
SOF/VEL/VOX	sofosbuvir/velpatasvir/voxilaprevir (coformulated; Vosevi®)

SVR	sustained virologic response
TSE	Transmissible Spongiform Encephalopathy
uHPLC	ultra-high-performance liquid chromatography
ULN	upper limit of normal
US	United States
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
VEL	velpatasvir (GS-5816)
VOX	voxilaprevir

1. Background information on the procedure

1.1. Submission of the dossier

Gilead Sciences Ireland UC submitted on 14 September 2020 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

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

Extension application to introduce a new strength (200 mg /50 mg /50 mg film-coated tablets). The new presentation is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients aged 12 years and older or weighing at least 30 kg, who cannot swallow the higher strength tablet. In addition, the MAH took the opportunity to implement minor editorial updates in module 3.2.P.

The extension application is grouped with a type II variation (C.I.6.a) to include paediatric use in patients aged 12 years and older or weighing at least 30 kg to the existing presentation. Sections 4.2, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated to support the extended indication. The RMP (version 3.2) is updated in accordance.

The legal basis for this application refers to:

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

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0006/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0006/2020 was completed.

The PDCO issued an opinion on compliance for the PIP P/0006/2020.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Filip Josephson

The application was received by the EMA on	14 September 2020
The procedure started on	29 October 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	19 January 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 January 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 February 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 February 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	19 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	20 April 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	6 May 2021
The CHMP agreed on the consolidated List of Outstanding Issues to be sent to the MAH during the meeting on	20 May 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	22 June 2021
The Pharmacokinetics Working Party experts were convened to address questions raised by the CHMP	1 July 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	07 July 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 July 2021
The Quality Working Party experts were convened to address questions raised by the CHMP	14 July 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vosevi on	22 July 2021

2. Scientific discussion

2.1. Problem statement

The natural history of chronic HCV infection in children is relatively benign. Most children are asymptomatic or have mild nonspecific symptoms; however, cirrhosis has been reported in approximately 1% to 2% of adolescents, and advanced liver disease and decompensated cirrhosis have been reported in children as young as 3 years of age. Disease progression also may occur many years after the initial infection.

Other direct-acting antivirals (DAA) options in children: Sovaldi (SOF) and Harvoni (ledipasvir [LDV]/SOF) have been approved for the treatment of DAA-naive paediatric patients 3 to < 18 years old in the European Union (EU). Epclusa (an FDC of SOF and VEL; SOF/VEL) has also been approved for the treatment of DAA-naive paediatric patients 6 to < 18 years old in EU.

It is anticipated that as more paediatric patients are treated for HCV with DAA-based therapies, the number of patients who fail those treatments will increase. However, retreatment options are limited for patients who fail DAA treatment, particularly regimens that include an NS5A inhibitor and/or NS5B inhibitor.

2.1.1. Disease or condition

Treatment of chronic HCV infection in patients aged 12 years and older.

2.1.2. Epidemiology

Around 71 million individuals worldwide are chronically infected with HCV. The global prevalence in 2018 of HCV infection in children aged 0 to 18 years has been estimated to be 0.13%, or 3.26 million children; over half (1.83 million) were aged 12 to 18 years old. Prevalence also varies by geographic location, with prevalence rates estimated to be 0.04% in Western Europe and 0.06% in the United States (US) compared with rates of 0.40% in Eastern Europe and up to 1.74% in Mongolia. Approximately 50% of the children with HCV infection were estimated to be living in Pakistan, China, India, and Nigeria.

2.1.3. Aetiology and pathogenesis

The HCV has significant genetic (RNA sequence) variability; 8 major genotypes have been identified: genotypes 1 and 3 are the most prevalent globally (46% and 30%, respectively) while genotypes 2, 4, and 6 represent approximately 23% of cases, genotypes 5 and 7 plus recently 8 comprise < 1%. There is a regional predominance of certain genotypes.

Hepatitis C is a blood-borne virus. Most infections occur as a result of sharing needles or other equipment to inject illicit drugs. HCV may or may not cause a short-term illness with features of acute hepatitis at the time of acquisition. About 70%–85% of infected persons do not clear the virus and therefore HCV becomes a long-term chronic infection. Chronic HCV infection is a serious disease that, left untreated, can be fatal due to decompensated liver cirrhosis and/or hepatocellular carcinoma (HCC). Globally, 27% of all cirrhosis and 25% of all HCC are attributable to HCV infection. In addition, persons with chronic HCV infection may develop extra-hepatic manifestations, such as cryoglobulinaemia, renal disease and porphyria cutanea tarda.

2.1.4. Clinical presentation and diagnosis

The natural history of chronic HCV infection in children is generally similar to that in adults, although HCV infection in children is typically relatively mild (Squires 2017). Most children chronically infected with HCV are asymptomatic or have mild, nonspecific symptoms. Clinical symptoms are present in approximately 20% of children in the first 4 years of life, with hepatomegaly being the most frequent sign (10%). Many, but not all, perinatally-infected children will have intermittently or persistently abnormal alanine aminotransferase (ALT) or aspartate aminotransferase levels, particularly in the first 2 years of life. In children with vertical HCV infection who have undergone liver biopsy, the histological spectrum is usually mild, although severe liver disease is encountered {Mohan 2010}. Despite the overall more favourable prognosis compared with adults, approximately 4% to 6% of children with chronic HCV infection have evidence of advanced fibrosis or cirrhosis and some children eventually require liver transplantation as a consequence of HCV infection (Hu 2010), (Wirth 2012). In addition, HCV infection has been reported to negatively affect both the health-related quality of life and cognitive functioning of paediatric patients (Nydegger 2008), (Rodrigue 2009), (Abu Faddan 2015), (Annunziato 2017).

2.1.5. Management

Curing chronic HCV infection is associated with more than 70% reduction in the risk of HCC and 90% reduction in the risk of liver related mortality and liver transplantation.

HCV treatment has been transformed by the development and approval of DAAs that target viral proteins and cellular processes essential to HCV replication and which have activity against multiple HCV genotypes. Several of these agents with different viral targets are now available in fixed-dose combinations (FDC) form for once daily dosing for 12 weeks and have been associated with >90% cure rates.

For patients who fail DAA only treatment with regimens that include an NS5A inhibitor the retreatment options are limited. However, SOF/VEL/VOX is recommended for such patients according to the current HCV treatment guidelines from the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) and European Association for the Study of the Liver (EASL).

The high success rates with DAA regimens in adults with chronic HCV infection are increasingly being replicated in the paediatric population. Interferon and ribavirin exert general and paediatric-specific toxicities (e.g., temporary growth impairment) that do not occur with DAA regimens.

About the product

Vosevi (Sofosbuvir/Velpatasvir/Voxilaprevir) is a fixed-dose combination product currently indicated for the treatment of patients with chronic HCV infection. Sofosbuvir is a nucleotide analogue non-structural protein NS5B polymerase inhibitor approved in EU for use in combination with other medicinal products for the treatment of chronic hepatitis C virus infection in adults and paediatric patients aged 3 years and above. Velpatasvir is an HCV NS5A inhibitor approved in EU for use in combination with SOF for the treatment of chronic hepatitis C virus infection in patients aged 6 years and older. Voxilaprevir is a novel pangenotypic HCV NS3/4A protease inhibitor (PI) with pangenotypic antiviral activity.

Type of Application and aspects on development

There was no scientific advice given from Committee for Medicinal Products for Human Use (CHMP) regarding the development of the new low dose tablet 200/50/50 mg and therapeutic indication for Vosevi in adolescents from 12 years of age and older.

Overall, the design of the paediatric study GS-US-367-1175 was in line with the outline in the CHMP guidance. Efficacy and safety is extrapolated from adults to adolescents based on the principle of comparable systemic exposure (PK bridge) in line with the 2016 EMA draft "Guidelines on the clinical evaluation of direct acting antivirals for the treatment of chronic hepatitis".

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0006/2020 on the agreement of a paediatric investigation plan (PIP). The PIP included a waiver for children less than 12 years old on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments in younger children. At the time of submission of the application, the PIP P/0006/2020 was completed.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 200 mg sofosbuvir, 50 mg velpatasvir and 50 mg voxilaprevir as active substances. This presentation is newly introduced with this line extension (to the already approved film-coated tablets containing 400 mg sofosbuvir, 100 mg velpatasvir and 100 mg voxilaprevir) for use in paediatric patients aged 12 years and older OR weighing at least 30 kg.

Other ingredients are:

Tablet core: colloidal anhydrous silica, copovidone, croscarmellose sodium (E468), lactose monohydrate, magnesium stearate and microcrystalline cellulose (E460).

Film-coating: iron oxide black (E172), iron oxide red (E172), iron oxide yellow (E172), macrogol (E1521), polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171).

The product is available in HDPE bottles with a polypropylene child-resistant closure with polyester coil and a silica gel desiccant as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The active substances sofosbuvir, velpatasvir and voxilaprevir are the same as for the already authorised Vosevi 400 mg sofosbuvir, 100 mg velpatasvir and 100 mg voxilaprevir film-coated tablets. No new information on the active substances has been provided within this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The medicinal product is an immediate release film-coated tablet which contains a fixed dose combination of three active substances. The 200 mg sofosbuvir/ 50 mg velpatasvir/ 50 mg voxilaprevir tablet is presented as a beige, oval-shaped tablet debossed with "GSI" on one side and "SVV" on the other side.

Other ingredients are:

- Tablet core: colloidal anhydrous silica, copovidone, croscarmellose sodium (E468), lactose monohydrate, magnesium stearate and microcrystalline cellulose (E460).
- Film-coating: iron oxide black (E172), iron oxide red (E172), iron oxide yellow (E172), macrogol (E1521), polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171).

The purpose of formulation development was to develop a reduced-strength tablet suitable for use in the paediatric population unable to swallow the approved 400 mg/ 100 mg/ 100 mg strength tablet.

The qualitative composition of the lower strengths 200 mg/ 50 mg/ 50 mg tablets is identical to the approved 400 mg/ 100 mg/ 100 mg tablets. The two tablet strengths are differentiated by tablet size, shape, and debossing.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, except for the film coating material, Opadry II beige, which is tested according to an in-house standard and the colourant, iron oxide, contained in Opadry II beige, which complies with EU regulations. There are no novel excipients used in the finished product formulation. No new information related to excipients was presented with this line extension. The list of excipients is included in section 6.1 of the SmPC.

The formulation used during clinical studies is the same as that intended for marketing.

The 200 mg/ 50 mg/ 50 mg and 400 mg/ 100 mg/ 100 mg strength tablets are manufactured from a common blend and the manufacturing process used is the same as for the approved higher-strength tablets.

For the new 200mg/ 50mg/ 50mg lower-strength tablet, no in vivo data were presented, and the applicant sought a biowaiver of strength based on in vitro dissolution data. The justification for the request for biowaiver of strength as presented in the application was initially judged to be not sufficient and a Major Objection was raised during the procedure. Additional dissolution data were requested at three different pH without the use of surfactant. In response, the applicant presented dissolution profiles generated for sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) tablets, 400/100/100 mg and 200/50/50 mg (three batches of each strength). The dissolution profiles were obtained at the same dose of 400 mg of SOF, 100 mg of VEL, and 100 mg of VOX by comparing one SOF/VEL/VOX 400/100/100 mg tablet per vessel with two SOF/VEL/VOX 200/50/50 mg tablets per vessel. Dissolution profiles were also presented using the conditions of the approved dissolution method.

In summary, the CHMP concluded that the waiver for the additional strength is considered acceptable because of the similarity in dissolution at various pHs and of the QC method. Based on the available data and additional expert consultation, the CHMP concluded that the data presented was sufficient to resolve the Major Objection and to justify the biowaiver of strength for the new lower strength tablet.

The primary packaging is similar for the 200 mg/ 50 mg/ 50 mg tablets and for the approved 400 mg/ 100 mg/ 100 mg tablets and differs only in the bottle size (60 ml rather than 100 ml bottle size). The primary packaging is a high-density polyethylene (HDPE) bottle with a polypropylene child-resistant closure with polyester coil and a silica gel desiccant. The material complies with Ph. Eur. and EC requirements

Manufacture of the product and process controls

The manufacturing process for the new Vosevi film-coated tablets 200 mg/ 50 mg/ 50 mg is similar to the one used for the approved 400 mg/ 100 mg/ 100 mg tablets, except for the differences introduced by tablet size and shape, and scale of the processing equipment. The manufacturing process of the finished product consists of three stages: manufacture of the finished product intermediates velpatasvir spray-dried dispersion (VEL SDD) and voxilaprevir spray-dried dispersion (VOX SDD), and manufacture of the film-coated tablets.

VEL SDD and VOX SDD are finished product intermediates with separate specifications and shelf life. The manufacturing and control of these intermediates was approved with the initial application and subsequent variations and no changes were introduced as part of this line extension.

The manufacturing process of the film-coated tablets consists of the following main steps: powder processing (dispensing, blending, and dry granulation) of sofosbuvir, VEL SDD, VOX SDD, and excipients to yield the final powder blend for compression; tablet compression to yield tablet cores; film coating of tablet cores to yield film coated tablets, and primary packaging of film-coated tablets.

The process is considered to be a standard manufacturing process.

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

The robustness of the process has been demonstrated during development by the manufacture of representative batches. Process validation will be performed prior to commercial distribution of the product. An acceptable process validation scheme has been presented.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form including appearance (visual), identification (HPLC, UV), water content (Ph. Eur.), strength (assay, UPLC), degradation products (UPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur., UPLC) and microbiological examination (Ph. Eur.).

The specification for the new 200 mg/ 50 mg/ 50 mg tablets utilises the same tests and acceptance limits as approved for the 400 mg/ 100 mg/ 100 mg tablets.

The analytical procedures developed for the 400 mg/ 100 mg/ 100 mg strength tablets are used for testing of the 200 mg/ 50 mg/ 50 mg strength tablets. Except for the method for dissolution, sample preparation was proportionally scaled for the 200mg/ 50mg/ 50mg strength tablets.

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

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

elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

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

No new information on reference standards has been presented with this line extension application.

Stability of the product

Stability data from three production scale batches of finished product stored for up to 12 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. The analytical procedures used are stability indicating. No significant changes have been observed.

Manufacture of the new 200 mg/ 50 mg/ 50 mg tablets is from a powder blend common with the approved 400 mg/ 100 mg/ 100 mg tablets, for which a shelf life of 48 months is approved. The 400 mg/ 100 mg/ 100 mg tablets showed little or no change in all quality attributes after storage for up to 48 months at 30 ºC / 75% RH. It was observed that the stability data at accelerated storage conditions are comparable for the 200 mg/ 50 mg/ 50 mg tablets and the 400 mg/ 100 mg/ 100 mg tablets.

The date of tablet manufacture is defined as the date when VEL SDD, VOX SDD and sofosbuvir are combined with the excipients in tablet manufacture. Separate shelf-lives and definitions for the date of manufacture have been approved for VEL SDD and VOX SDD as part of the approval of the 400 mg/ 100 mg/ 100 mg strength tablet marketing authorisation.

Considering the supporting data from the approved 400 mg/ 100 mg/ 100 mg tablets, extrapolating the results from 12 months of stability data at long-term storage conditions and 6 months stability data at the accelerated storage conditions to support the proposed shelf-life and storage conditions of Vosevi 200 mg/ 50 mg/ 50 mg film-coated tablets, can be accepted.

Based on available stability data, the proposed shelf-life of 48 months and with no special storage conditions as stated in the SmPC (section 6.3) is acceptable. The tablets should be stored in the original package (bottle) in order to protect from moisture and this is indicated in section 6.4 of the SmPC.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the

use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure, a Major Objection was raised in relation to the justification for the request for biowaiver of strength and comparative dissolution profiles generated without the use of surfactant were requested. The additional data provided by the applicant was considered sufficient to resolve the Major Objection and justify the biowaiver of strength.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

No new non-clinical studies have been submitted for this procedure.

2.3.1. Ecotoxicity/environmental risk assessment

The EMA guideline on the ERA states that "the evaluation of the environmental impact should be made if there is an increase in the environmental exposure, e.g. a new indication may result in a significant increase in the extent of the use". The prior ERAs for both SOF and VEL predicted environmental concentrations were estimated based on forecasted sales figures provided by the applicant. These forecasts covered the period of 2015 – 2024 for SOF and 2018 – 2024 for VEL and included a reserve/ margin of error that is higher than the small increase in sales that may occur due to the proposed line extension. For VOX, 100% prevalence based on the highest HCV prevalence observed in the European Union (EU) was applied to determine the predicted environmental concentration (PEC) (Italy – 5.2%). Therefore, it can be considered that the sales forecasts and use of prevalence data employed in the previous ERA accounted for the potential sales increase due to the proposed line extension. Hence the estimated PECs are still conservative and no update to the assessment is necessary. As detailed in the ERAs for SOF, VEL and VOX, Risk Quotient (RQ) values for SOF (as GS-331007), VEL, and VOX are less than 1 (highest RQ for SOF = 1.26×10^{-4}, VEL= 1.08×10^{-3}, and VOX = 6.26×10^{-3}) for compartments such as sewage treatment plant, surface water, groundwater, and sediment. An increase in Vosevi sales of greater than 160 times would be required to produce an unacceptable risk. This line extension

grouped with an extension of indication is not expected to significantly increase sales continuing the low RQs.

2.3.2. Discussion on non-clinical aspects

No new non-clinical studies, including juvenile toxicity, have been submitted in support of the current application for use of Vosevi in adolescents 12 - <18 years. This was considered acceptable by the CHMP as the non-clinical data safety data submitted in support of the original Vosevi marketing authorization application did not reveal any hazards specific for adolescents and agrees with the Vosevi paediatric investigation plan (PIP) as stated in the Paediatric Committee (PDCO) decision document, EMEA-001822-PIP01-15. In addition, adverse reactions by Vosevi in patients 12 years and older was studied for 8 weeks in a Phase-2 open-label clinical trial. The observed adverse reactions in this study comprising adolescents were consistent with those observed in clinical studies with Vosevi in adults.

No update of the ERA was submitted in support of the current extension of indication application. This is accepted as the existing ERAs for SOF, VEL, and VOX are considered applicable to this application.

2.3.3. Conclusion on non-clinical aspects

There are no issues with the dossier from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Clinical Study Included in the Update to the SOF/VEL/VOX Marketing Application for Paediatric Subjects (12 to < 18 years old)

Study Number	Study Design	Subject Population	Treatment Regimen[a]	N[b]	Location of Study Summary
GS-US-367-1175	Phase 2, open-label study	Treatment-naive and treatment-experienced subjects 12 to < 18 years old[c] with chronic HCV infection	SOF/VEL/VOX 400/100/100 mg orally once daily for 8 weeks[d]	12 to < 18 years: 21 Genotype 1: 6 Genotype 2: 4 Genotype 3: 9 Genotype 4: 2	**CSR:** GS-US-365-1175 CSR **Narrative:** Section 2.1

CSR = clinical study report; DAA = direct-acting antiviral; HCV = hepatitis C virus; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir

a Selection of tablet strength (400/100/100-mg or 200/50/50-mg tablets) was based on a swallowability assessment using a placebo tablet at screening or baseline. All subjects were able to swallow the 400/100/100-mg tablet.

b N = number of subjects in the Full Analysis Set (ie, all enrolled subjects who received at least 1 dose of study drug).

c A waiver for subjects 3 to < 12 years old was granted by the European Medicines Agency, so this age group was not recruited.

d All subjects were DAA-naive and none had compensated cirrhosis, so the 12-week study drug regimen was not used in this study.

2.4.2. Pharmacokinetics

Relative bioavailability study

No relative bioavailability study was performed in order to investigate interchangeability of two tablets of the 200/50/50 mg strength and one tablet of the 400/100/100 mg strength. Based on the available data and the input from the QWP and PKWP, the CHMP concluded that a biowaiver for the lower-strength was justified, as detailed in section 2.2.3 of the CHMP AR.

PopPK analysis

The objective of the popPk analysis was to:

- update a joint model evaluating the PK of SOF, its primary circulating metabolite (GS-331007), and metabolite GS-566500 in HCV-infected pediatric subjects
- To update a VEL population PK model with additional pediatric data in HCV-infected pediatric subjects administered
- To develop a population PK model for evaluating the PK of VOX in HCV-infected pediatric subjects
- To estimate individual exposures of SOF, GS-331007, GS-566500, VEL, and VOX in the pediatric population

SOF Joint PopPK Model

A total of 85 Subjects in Study GS-US-334-1112, 198 subjects in Study GS-US-337-1116, 179 subjects in Study GS-US-342-1143, and 15 subjects in Study GS-US-367-1175 had at least 1 concentration value for GS-331007 included in the PopPK analysis. Plasma concentrations of SOF, GS-566500, and GS-331007 were best described by a joint 1-compartment (SOF and GS-566500) and a 2-compartment (GS-331007) model, including first-order absorption with zero-order input for SOF and an absorption lag time (ALAG) for both SOF and GS-331007, followed by first-order elimination. The model included the effect of WT (allometric exponents fixed to 0.75 and 1 for clearances and volumes, respectively) on apparent oral clearance of SOF (CLSOF), apparent volume of SOF (VSOF), apparent

oral clearance of GS-566500 (CL500), apparent volume of GS-566500 (V500), apparent oral clearance of GS-331007 (CL007), and apparent volume of GS-331007 (Vc007). Additionally, the model included the separate effect of coadministration of LDV and VEL on relative fraction absorbed for SOF (F1) and co-administration of RBV(ribavirin) on apparent oral clearance ofGS-566500 (CL500) and apparent oral clearance of GS-331007 (CL007).The model also included the effect of age on CL500 and CL007 and sex on CL007.

Table 2: Summary of Parameters for final SOF joint PopPK Model for Paediatric subjects

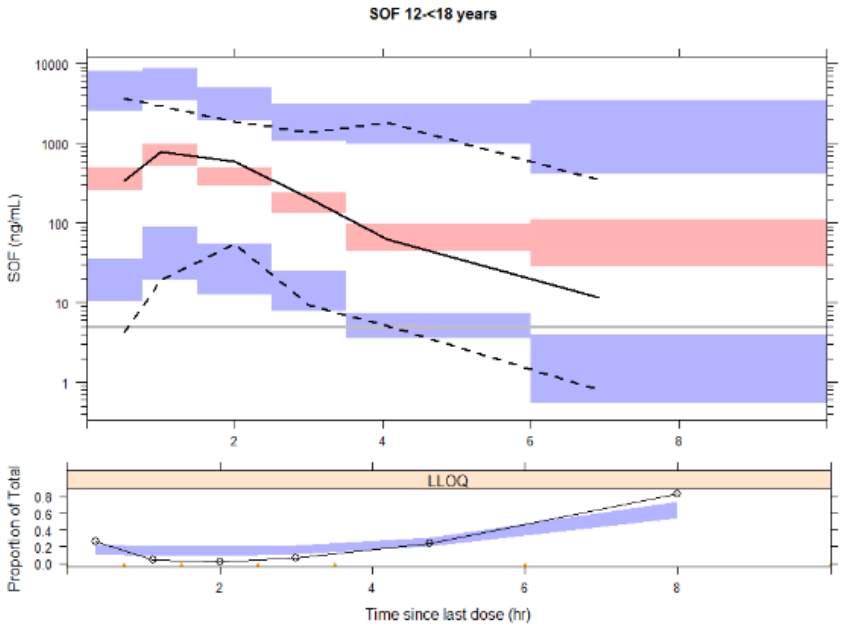
Parameter	Parameter Description		Population Estimate	Change from Typical (%)	IIV (%)
exp(θ1)	Absorption rate for SOF, k_{aSOF} (1/h)		1.22		
exp(θ2)	Absorption rate for GS-566500, k_{a500} (1/h)		0.286		
exp(θ3)	Absorption rate for GS-331007, k_{a007} (1/h)		0.022		
exp(θ4)	Apparent oral clearance of SOF, CL_{SOF} (L/h)		318		81
exp(θ4 + 0.75 × log(WT/42))	Influence of WT on CL_{SOF}	5th %ile of WT	161	-49.4	
		95th %ile of WT	549	72.9	
exp(θ5)	Apparent central volume of SOF, V_{SOF} (L)		161		210
exp(θ5 + 1 × log(WT/42))	Influence of WT on V_{SOF}	5th %ile of WT	65	-59.7	
		95th %ile of WT	335	107.5	
exp(θ6)	Apparent oral clearance of GS-566500, CL_{500} (L/h)	Without RBV	841		32
exp(θ20)		With RBV	1352		
exp(θ6 + 0.75 × log(WT/42))	Influence of WT on CL_{500}	5th %ile of WT	425	-49.4	
		95th %ile of WT	1454	72.9	
exp(θ6 + θ26 × log(AGE/12))	Influence of AGE on CL_{500}	5th %ile of AGE	1019	21.1	
		95th %ile of AGE	792	-5.9	
exp(θ7)	Apparent central volume of GS-566500, V_{500} (L)		1167		
exp(θ7 + 1 × log(WT/42))	Influence of WT on V_{500}	5th %ile of WT	470	-59.7	
		95th %ile of WT	2421	107.5	
exp(θ8)	Apparent oral clearance of GS-331007, CL_{007} (L/h)	Female without RBV	167		28
exp(θ21)		Female with RBV	181	8.2	
exp(θ8) × (1 + θ25)		Male with LDV	184	10.1	
exp(θ8 + 0.75 × log(WT/42))	Influence of WT on CL_{007}	5th %ile of WT	85	-49.4	
		95th %ile of WT	289	72.9	
exp(θ8 + θ24 × log(AGE/12))	Influence of AGE on CL_{007}	5th %ile of AGE	205	22.5	
		95th %ile of AGE	157	-6.2	
exp(θ9)	Apparent central volume of GS-331007, V_{007} (L)		220		
exp(θ9 + 1 × log(WT/42))	Influence of WT on V_{007}	5th %ile of WT	89	-59.7	
		95th %ile of WT	457	107.5	
exp(θ10)	Apparent intercompartmental clearance of GS-331007, Q_{007} (L/h)		49		
exp(θ11)	Apparent peripheral volume of GS-331007, V_{p007} (L)		1005		
exp(θ12)	Duration of zero-order absorption for SOF, D1 (h)		0.56		
Fixed		SOF + RBV	1		

Parameter	Parameter Description		Population Estimate	Change from Typical (%)	IIV (%)
1 + θ14 [Fixed]	Relative fraction absorbed for SOF, F1	LDV/SOF FDC	1.77		
1 + θ23		SOF/VEL FDC	2.52		
θ13 [Fixed]	Relative fraction absorbed for GS-331007, F3		7.18		
θ15 [Fixed]	Relative fraction absorbed for GS-566500, F2		5.32		
exp(θ18)	Absorption lag time for GS-331007, ALAG3 (h)		3		
exp(θ22) [Fixed]	Absorption lag time for SOF, ALAG1 (h)		0.082		
θ19 × 100	Proportional error SD for SOF (%)		92.7		
θ16 × 100	Proportional error SD for GS-566500 (%)		61.4		
θ17 × 100	Proportional error SD for GS-331007 (%)		30.4		
	Elimination half-life SOF (h)		0.35		
	Elimination half-life GS-556500		0.96		
	Elimination half-life GS-331007 (SOF + RBV) (h)		18.2		
	Elimination half-life GS-331007 (LDV/SOF FDC) (h)		18.6		
	Elimination half-life GS-331007 (SOF/VEL FDC) (h)		18.6		
	Elimination half-life GS-331007 (SOF/VEL/VOX FDC) (h)		18.6		

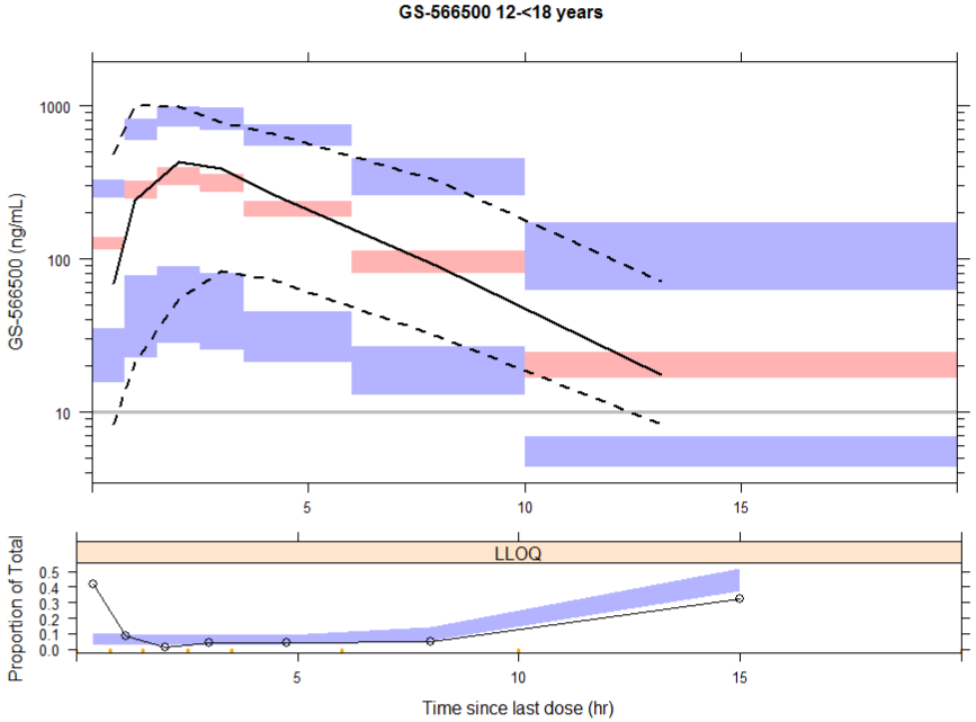
θ = absolute value of the estimate; ω = standard deviation of between-subject variability; %ile = percentile; AGE = baseline age; CV = coefficient of variation; FDC = fixed-dosed combination; IIV = interindividual variability; LDV = ledipasvir; OFV = objective function value; PK = pharmacokinetic; PopPK = population pharmacokinetic; RBV = ribavirin; RV = residual variability; SD = standard deviation; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir; WT = baseline body weight.
Minimum OFV = 91577.471.
The 5th and 95th percentiles of WT are 16.9 and 87.1 kg, respectively; the 5th and 95th percentiles of age are 4 and 17 years, respectively.
Source: sof-run046-gof-final-20200413.R

Prediction-corrected VPC simulations were performed as a validation of the final PopPK model. A total of 1000 replicates of the studies were simulated using the final PopPK model parameter estimates, the estimated subject-specific ETA, and the RV. The pcVPCs of SOF plasma concentration-time profiles and its metabolites are shown in Figure 1 below.

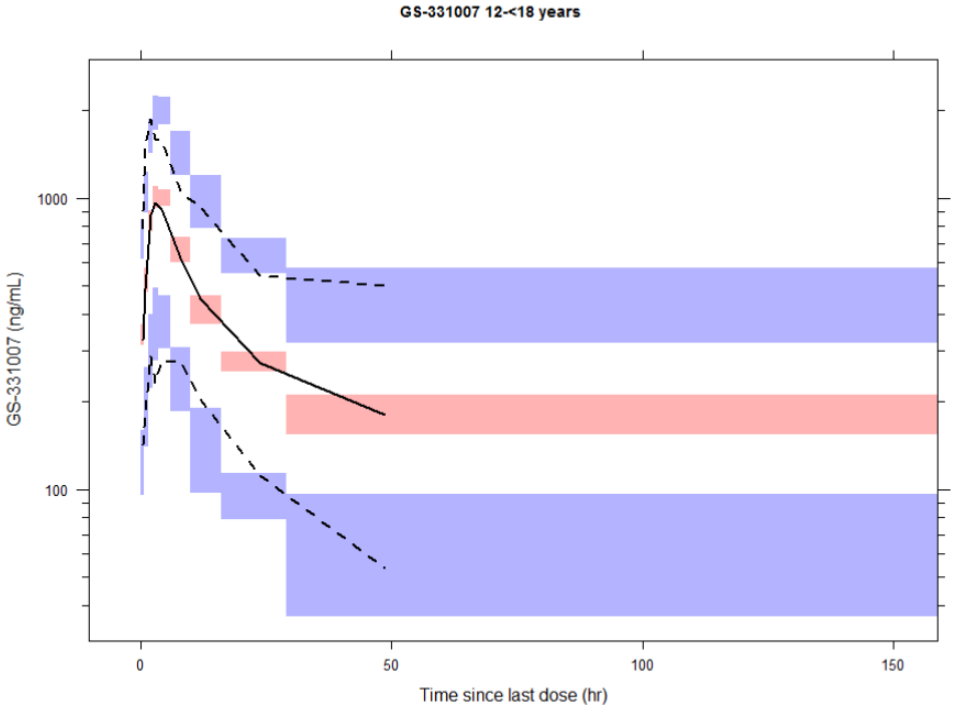
SOF



GS-566500



GS-331007



BLQ = below the limit of quantitation; CI = confidence interval; DV = observed concentrations; LLOQ = lower limit of quantitation; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic; SOF = sofosbuvir; WT = baseline body weight.
Subjects aged 3 to < 6 years old were only in Studies GS-US-334-1112, GS-US-337-1116, and GS-US-342-1143. The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all subjects. The red area is the 95% CI of the simulated median, and the blue area is the 95 CI of the simulated 5th and 95th percentiles. pcVPC is stratified by age category for SOF (top 3 panels), GS-566500 (middle 3 panels), and GS-331007 (bottom 3 panels). For the LLOQ panels, open circles and black solid lines show the observed proportion of BLQ samples, whereas the blue area shows the 95% CI of the simulated BLQ samples.
Source: sof-run046-gof-final-20200413.R

Figure 1: Prediction-corrected VPC simulations of SOF plasma concentration-time profiles and its metabolites

VEL popPK model

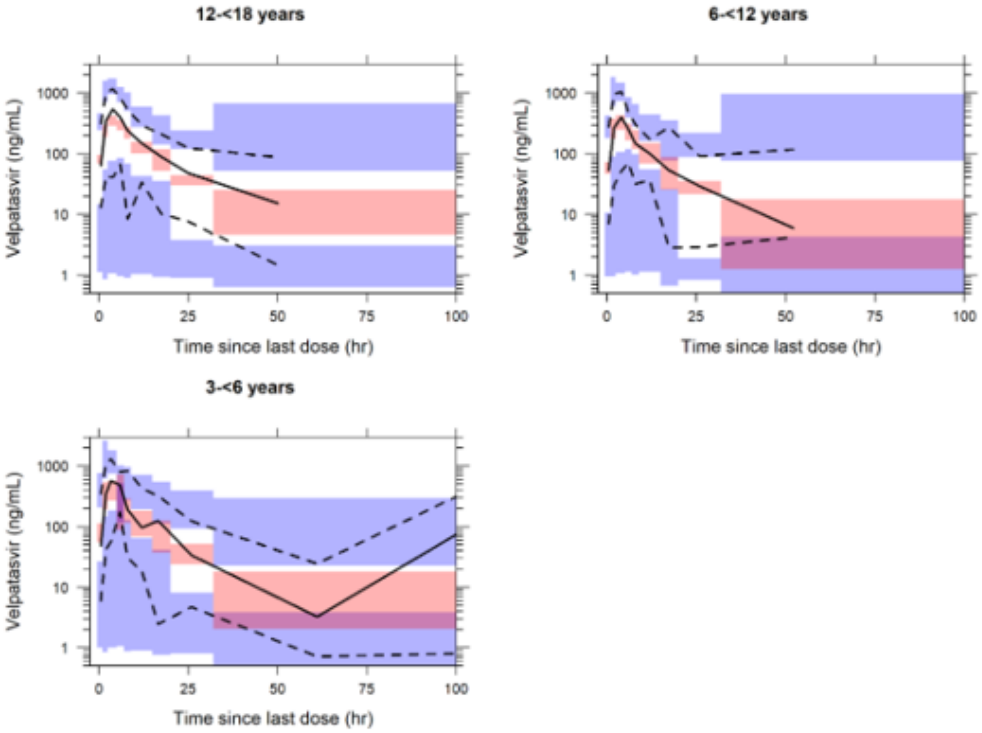
The PopPK data included 209 subjects from Study GS-US-342-1143 and 21 subjects from Study GS-US-367-1175. After all exclusions, a total of 179 subjects in Study GS-US-342-1143 and 15 subjects from Study GS-US-367-1175 had at least 1 measurable concentration value for VEL. The final pediatric VEL model was described by a 2-compartment model with sequential zero-/first-order absorption and first-order elimination, with interindividual variability (IIV) on CL/F, Vc/F, and ka. The effect of WT on CL/F and Vc/F was included using fixed allometric exponents of 0.75 and 1, respectively. VOX was found to affect VEL CL/F (24.4% reduction). No additional covariates were found to significantly affect VEL exposure.

Table 3: Summary of parameters for final VEL PopPK model for paediatric subjects

Parameter	Parameter Description	Population Estimate	Change from Typical (%)	IIV (%)
$\exp(\theta_1)$	Apparent oral clearance, CL/F (L/h)	22.1	--	47
$\exp(\theta_1 + 0.75 \times \log(WT/46))$	Influence of WT on CL/F, 5th %ile of WT	11	-51	--
$\exp(\theta_1 + 0.75 \times \log(WT/46))$	Influence of WT on CL/F, 95th %ile of WT	36	62.8	--
$\exp(\theta_1) \times (1+\theta_9)$	Influence of VOX on CL/F	17	-24.4	--
$\exp(\theta_2)$	Apparent central volume, V_c/F (L)	147	--	66
$\exp(\theta_2 + \log(WT/46))$	Influence of WT on V_c/F, 5th %ile of WT	57	-61.4	--
$\exp(\theta_2 + \log(WT/46))$	Influence of WT on V_c/F, 95th %ile of WT	281	91.5	--
$\exp(\theta_3)$	Intercompartmental clearance, Q/F (L/h)	5.26	--	--
$\exp(\theta_4)$	Apparent peripheral volume, V_p/F (L)	36.9	--	--
$\exp(\theta_5)$	First-order absorption rate constant, k_a (1/h)	1.08	--	84
$\exp(\theta_6)$	Duration of zero-order absorption, D1 (h)	2.11	--	--
$\text{sqrt}(\theta_7)$	Residual proportional error (%)	68	--	--
θ_8	Residual additive	6.6	--	--

θ = absolute value of the estimate; ω = standard deviation of between-subject variability; CL/F = apparent oral clearance; D1 = duration of zero-order absorption; IIV = interindividual variability; k_a = first-order absorption rate constant; OFV = objective function value; PK = pharmacokinetic; PopPK = population pharmacokinetic; V_c/F = apparent central volume; VEL = velpatasvir, VOX = voxilaprevir; V_p/F = apparent peripheral volume; WT = baseline body weight
Minimum OFV = 15038.539.
The 5th and 95th percentiles of WT are 17.8 and 88.0 kg, respectively.
Source: vel-gof-final-run124-20200430.R

Prediction-corrected VPC simulations were performed as a validation of the final PopPK model. A total of 1000 replicates of the studies were simulated using the final PopPK model parameter estimates, the estimated subject-specific ETA, and the RV (residual variability). The pcVPC of VEL plasma concentration-time profiles stratified by age groups are shown in Figure 2 below.



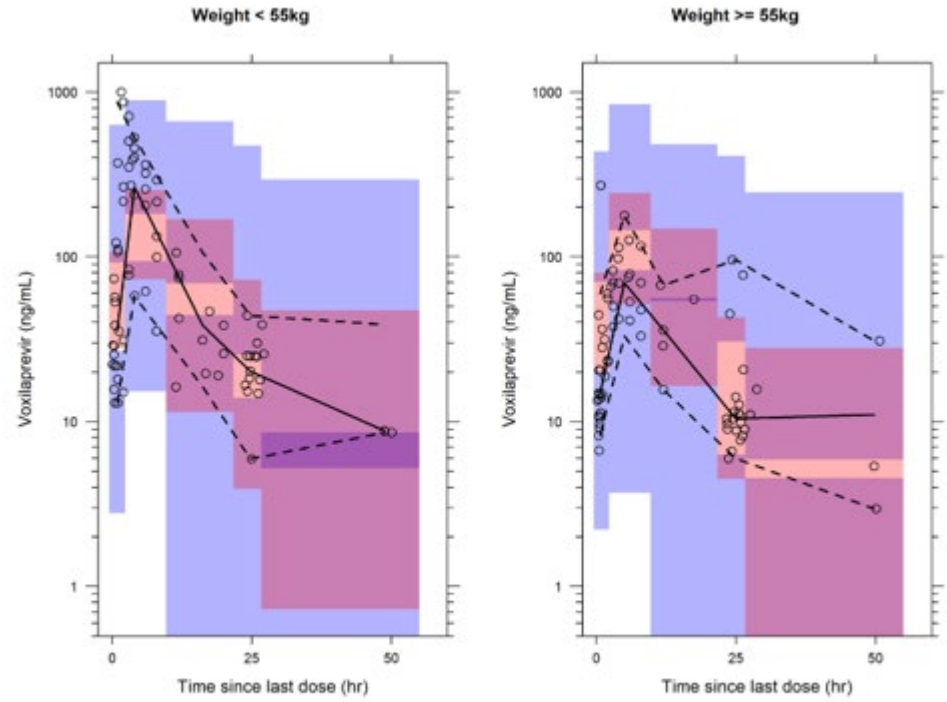
CI = confidence interval; DV = observed concentrations; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic; VEL = velpatasvir.
The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all subjects. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles.
Source: vel-gof-final-run124-20200430.R

Figure 2: pcVPC of the final VEL PopPK model stratified by age

VOX PopPK Model

The PopPK data included 21 subjects from Study GS-US-367 -1175. After all exclusions, a total of 15 subjects in Study GS-US-367 -1175 had at least 1 measurable concentration value for VOX. The final pediatric VOX model was described by a 2-compartment model with sequential zero and first-order absorption and first-order elimination, with IIV on CL/F, Vc/F, ka, and D1. The effect of WT on CL/F and Vc/F was included using fixed allometric exponents of 0.75 and 1, respectively. No additional covariates were found to significantly affect VOX exposure.

Visual Predictive Check simulations were performed as a validation of the final PopPK model. A total of 1000 replicates of the studies were simulated using the final PopPK model parameter estimates, the estimated subject-specific ETA, and the RV. The VPC of VOX plasma concentration-time profiles is shown in Figure 3 below.



CI = confidence interval; DV = observed concentrations; VPC = visual predictive check; PopPK = population pharmacokinetic
The VPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all subjects. The red area is the 95% CI of the simulated median and the blue area is the 95% CI of the simulated 5th and 95th percentiles. Black circles represent the observed data.

Figure 3: VPC with observations of the final VOX paediatric PipPK Models for Low and High Wekght Range

Paediatric exposure:

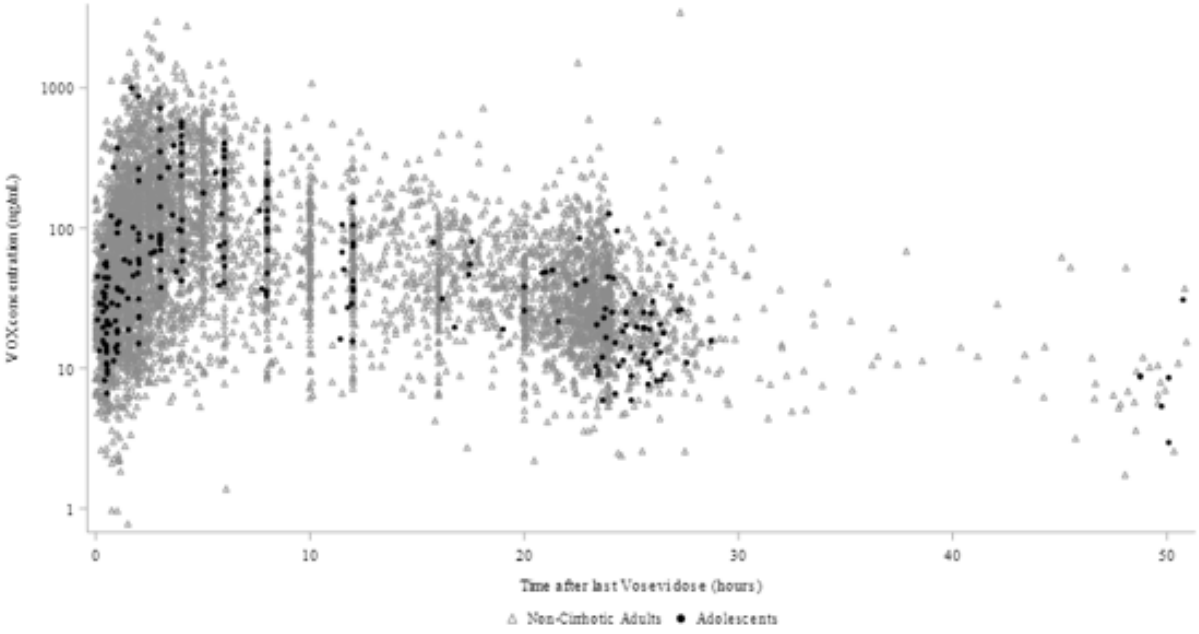
Population PK models derived exposures of SOF, GS-331007, VEL, and VOX using intensive and sparse PK samples from paediatric subjects 12 to < 18 years old in Study GS-US-367-1175 were compared with historical data collected in the adult Phase 2/3 SOF/VEL/VOX clinical studies as presented in Table below.

Table 4: Summary of popPK-based SOF, GS-331007, VEL and VOX exposures in adolescent subjects compared with popPK-based exposures in the adult phase 2/3 SOF/VEL/VOX population (PK analysis set)

		Mean (%CV)		%GMR (90% CI)
Analyte	PK Parameter	Adolescent Subjects SOF/VEL/VOX (400/100/100 mg) 8 Weeks (N = 21)	Adult Phase 2/3 SOF/VEL/VOX Population (N = 1595)	Adolescent Subjects vs Adult Phase 2/3 Population
SOF	AUC_{tau} (h•ng/mL)	2474.8 (50.4)	1665.3 (30.1)	137.75 (123.66, 153.45)
	C_{max} (ng/mL)	1304.7 (69.9)	677.9 (35.4)	162.64 (138.53, 190.94)
GS-331007	AUC_{tau} (h•ng/mL)	14,890.2 (21.0)	12,834.1 (29.0)	118.49 (107.02, 131.19)
	C_{max} (ng/mL)	1278.1 (16.1)	744.3 (28.3)	176.55 (158.98, 196.06)
VEL	AUC_{tau} (h•ng/mL)	6773.0 (35.0)	4041.1 (48.6)	176.53 (147.25, 211.63)
	C_{max} (ng/mL)	621.8 (37.6)	311.1 (56.1)	215.54 (174.79, 265.80)
	C_{tau} (ng/mL)	92.0 (49.6)	51.2 (64.7)	188.51 (154.18, 230.49)
VOX	AUC_{tau} (h•ng/mL)	2205.8 (63.6)	2577.2 (73.7)	89.13 (69.49, 114.32)
	C_{max} (ng/mL)	230.8 (84.3)	191.6 (85.8)	119.68 (89.92, 159.30)
	C_{tau} (ng/mL)	23.7 (71.5)	46.7 (82.0)	51.89 (41.05, 65.59)

CI = confidence interval; %CV = percentage coefficient of variation; FDC = fixed-dose combination; GMR = geometric mean ratio; PK = pharmacokinetic; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir
SOF/VEL/VOX adult population included HCV-infected adult subjects administered SOF 400 mg, VEL 100 mg, and VOX 100 mg as either single agents or FDC in Phase 2 and 3 Studies GS-US-337-1468, GS-US-367-1168, GS-US-367-1169, GS-US-367-1170, GS-US-367-1171, GS-US-367-1172, GS-US-367-1173, or GS-US-367-1871.
C_{min} derived from population PK model is equivalent to C_{tau}.

A qualitative comparison of observed VOX concentration against time after last dose (TALD) in non-cirrhotic adults with adolescents y is shown in Figure 4 below. The observed concentrations of the adolescents are fully contained within the adult range and display a similar trend. This is further corroborated by the corresponding descriptive statistics summarized by TALD windows in Table below, indicating similar distribution of concentrations between the 2 populations within each TALD window.



SOF/VEL/VOX Adult Population = HCV-infected adult subjects administered SOF 400mg, VEL 100mg, VOX 100mg as either single agents or FDC in Phase 2/3
Study GS-US-337-1468, GS-US-367-1168, GS-US-367-1169, GS-US-367-1170, GS-US-367-1171, GS-US-367-1172, GS-US-367-1173, or GS-US-367-1871.

Figure 4: Scatter plot between VOX concentration (ng/mL) and time after last Vosevi dose (hours) Adolescent Population vs SOF/VEL/VOX non-cirrhotic adult population (PK analysis set)

Table 5: Summary Statistics of VOX concentration (ng/mL) and time after last Vosevi Dose (hours) Adolescent subjects vs Noncirrhotic Adult Phase 2/3 SOF/VEL/VOX subjects (Population PK Analysis Set)

	VOX													
TALD (h)	[0,1)		[1,2)		[2,8)		[8,16)		[16,24)		[24,32)		[32,51]	
	Adol	Adult	Adol	Adult	Adol	Adult	Adol	Adult	Adol	Adult	Adol	Adult	Adol	Adult
N	39	685	20	857	63	1850	25	590	26	1270	39	368	6	51
Min	6.7	1.0	13.0	0.8	15.0	1.4	15.6	4.2	6.0	2.2	5.9	2.4	3.0	1.7
Median	21.8	30.0	41.5	69.4	95.3	117.0	77.8	68.3	28.9	31.8	17.9	22.8	8.7	10.5
Max	271.0	1130.0	1000.0	1800.0	869.0	2990.0	292.0	1080.0	126.0	1510.0	95.5	3440.0	30.8	68.5

Adol = adolescent; N = number of observations; SOF = sofosbuvir; TALD = time after last dose; VEL = velpatasvir; VOX = voxilaprevir
SOF/VEL/VOX adult population included HCV-infected adult subjects administered SOF 400 mg, VEL 100 mg, and VOX 100 mg as either single agents or FDC in Phase 2 and 3 Studies GS-US-337-1468, GS-US-367-1168, GS-US-367-1169, GS-US-367-1170, GS-US-367-1171, GS-US-367-1172, GS-US-367-1173, or GS-US-367-1871.

2.4.3. Discussion on clinical pharmacology

Since there is not enough efficacy and safety data in adolescent, the CHMP agreed that efficacy and safety will be extrapolated from adults to adolescents based on the principle of comparable systemic exposure (PK bridge).
The simulated exposure for SOF, the main metabolite of SOF (GS-331007) and VEL show higher exposure in adolescents compared to adults. The proposed posology is the same as what has previously been deemed adequate in paediatric patients for combination including SOF and VEL (Epclusa). The higher exposure in adolescents compared to adults is not considered a concern with regards to safety. Thus, the proposed posology in adolescents regarding SOF and VEL is accepted.

For VOX popPK model, the stratified VPCs show that Cmax is not well captured, underpredicting Cmax for lower body weight patients and overpredicting Cmax for higher body weight patients. Cmin median appears to be fairly well described however the variability is overpredicted, this may be the reason for the 33% lower Cmin in adolescents based on the popPk analysis.

Overall, the VOX popPK model is not optimal and could be further developed/improved. No conclusions here are based on the popPk analysis for VOX. If the VOX model is to be used in the future, improvement of the model is warranted. The CHMP was of the view that this issue does not need to be pursued further in the context of this procedure.

The observed PK data for VOX is deemed rich enough to draw conclusions in adolescents and the exposure is overlapping with adult exposure. The MAH´s conclusion that the VOX exposures in adolescents are similar to those in non-cirrhotic adults for which safety and efficacy have been established was endorsed by the CHMP.

No relative bioavailability study was performed in order to investigate interchangeability of two tablets of the 200/50/50 mg strength and one tablet of the 400/100/100-mg strength. Based on the available data and the input from the QWP and PKWP, the CHMP concluded that a biowaiver for the lower-strength was justified, as detailed in section 2.2.3 of the CHMP AR.

2.4.4. Conclusions on clinical pharmacology

Overall, the PK analyses were considered supportive of the dosing recommendations in the target patient population.

2.5. Clinical efficacy

2.5.1. Dose response studies and main clinical studies

The current application is based on data from the Phase 2, Open-Label, Multicentre, Multi-cohort Study GS-US-367-1175 (the study was conducted in compliance with GCP);

- to support the extension of the indication to paediatric patients 12 to < 18 years old and weighing at least 30 kg by adding clinical data to the existing marketing authorisation (Vosevi 400 mg/ 100 mg/ 100 mg)
- to introduce a new low dose tablet (Vosevi 200 mg/ 50 mg/ 50 mg)

In the current application, the Applicant included data on PK, safety and efficacy of Vosevi in patients 12 years old to <18 years from the GS-US-367-1175 study.

Efficacy and safety is being extrapolated from adults to adolescents based on the principle of comparable systemic exposure (PK bridge) in line with the EMA HCV guidelines.

Main study

Study GS-US-367-1175: *A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Pharmacokinetics, Safety and Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir Fixed-Dose Combination in Adolescents and Children with Chronic HCV Infection*

This was an open-label, multi-cohort study evaluating the PK, safety, and antiviral activity of SOF/VEL/VOX for 8 weeks (DAA-naive without compensated cirrhosis) or 12 weeks (DAA-experienced with or without compensated cirrhosis or treatment-naive with compensated cirrhosis) in paediatric subjects with chronic HCV infection. A total of 21 adolescent subjects 12 to < 18 years old were enrolled in the study and received SOF/VEL/VOX for 8 weeks. All 21 subjects completed study drug and were included in both the FAS and the Safety Analysis Set.

Methods

Study Participants

Main Inclusion Criteria

Eligible subjects were males or nonpregnant females 12 to < 18 years old with chronic HCV infection (HCV RNA ≥ 1000 IU/mL) of any HCV genotype, including indeterminate or mixed genotypes, with or without direct-acting antiviral (DAA) experience.

Main Exclusion Criteria

- Current or prior history of clinical hepatic decompensation
- Any of the following laboratory parameters at screening:
  a) International normalized ratio (INR) > 1.2 x upper limit of normal (ULN)
  b) Platelets < 50,000/mm3
  c) Albumin < 3.5 g/dL
  d) ALT > 10 x ULN
  e) AST > 10 x ULN
  f) Direct bilirubin > 1.5 x ULN
  g) Estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73m^2, as calculated by the Schwartz formula
- Chronic liver disease of a non-HCV aetiology
- Evidence of hepatocellular carcinoma or other malignancy
- Coinfection with HIV, acute hepatitis A virus, or hepatitis B virus (HBV) (hepatitis B surface antigen [HBsAg]-positive at screening)
- Current or prior history of clinically significant illness or major medical disorder
- Clinically relevant alcohol or drug abuse within 12 months of screening.

Approximately 60 subjects were planned to be enrolled into 3 sequential age-based cohorts as follows:

- Cohort 1: at least 20 subjects 12 to < 18 years old
- Cohort 2: at least 20 subjects 6 to < 12 years old
- Cohort 3: at least 20 subjects 3 to < 6 years old

A modification to the original PIP has been agreed with the European Medicines Agency (EMA) Paediatric Committee (PDCO) decision received on 06 January 2020 (EMEA-001822-PIP01-15-M01), waiving the inclusion of subjects 3 to < 12 years old. Thus, there will be no enrolment into Cohort 2 and Cohort 3.

Description of Study Procedures

All subjects were to complete the following visits: screening, Day 1, Weeks 1, 2, 4, and 8 or 12 (depending on treatment assignment) during the treatment phase, followed by posttreatment visits at 4, 12, and 24 weeks after discontinuation of study drug.

At least 10 subjects in each age cohort were to be enrolled in an intensive PK substudy conducted at Week 2 or Week 4 after providing separate consent. Sparse PK samples were also collected at Weeks 1, 2, 4, 8, and 12 depending on treatment duration and intensive PK substudy participation.

Pharmacokinetic and safety data from at least 20 evaluable subjects in each cohort were to be reviewed to confirm the appropriateness of the SOF/VEL/VOX dose used.

Subjects who provided separate and specific consent were eligible for participation in the pharmacogenomics substudy. A blood sample was drawn for this substudy at the Day 1 visit or at any time during the study.

After completing all required study visits, all subjects (those who attained SVR24 and those who did not attain SVR24 and did not initiate other experimental or approved anti-HCV therapy) were eligible to enrol into a registry study (GS-US-334-1113) to be followed every 6 months for the first 2 years, then every 12 months for a total of up to 5 years, for assessments of growth, quality of life, and long-term viral suppression (if applicable).

This study was conducted at a total of 10 study centres in Italy, Poland, and United Kingdom.

Treatments

The marketed dose of SOF/VEL/VOX for the treatment of HCV infection in adults is 400/100/100 mg. The adult clinical dose was evaluated in adolescent subjects (12 to <18 years old) in this study.

Subjects completed a swallowability assessment at screening up to Day 1 using a placebo-to-match (PTM) SOF/VEL/VOX FDC (400/100/100 mg) tablet to determine which formulation each subject could take. Subjects unable to swallow the PTM were to be assigned to wait until a smaller, lower-dose tablet or non-tablet formulation was available.

Following screening and confirmation of eligibility by the investigator, all subjects received the SOF/VEL/VOX FDC (400/100/100 mg) tablet orally once daily with food. Subjects without cirrhosis who were DAA-naive were to receive SOF/VEL/VOX for 8 weeks. Subjects with cirrhosis who were DAA-naive and all DAA-experienced subjects (with or without cirrhosis) were to receive SOF/VEL/VOX for 12 weeks.

All patients were DAA-naïve and without cirrhosis and thus received 8 weeks of treatment.

All subjects were able to swallow the SOF/VEL/VOX FDC (400/100/100 mg) tablet; therefore, information regarding the low-dose tablet is not presented by the Applicant.

Objectives

According to the 2016 EMA draft "Guidelines on the clinical evaluation of direct acting antivirals for the treatment of chronic hepatitis", similar to the case with HIV, it is considered that efficacy data may be bridged from adults to children, provided that similar drug exposure is reached in plasma at the recommended doses. Paediatric studies could primarily focus on the determination of PK, but would also collect, albeit in a rather limited fashion, data on safety and efficacy.

The recommended primary efficacy endpoint for studies aiming at defining cure rate is SVR, defined as HCV-RNA < LLOQ 12 weeks after the planned completion of therapy (SVR12). Both efficacy and safety endpoints are well-established in the field of hepatitis C clinical trials and the objectives are in line with the overall approach to bridge both efficacy and safety from the adult to the paediatric population.

The primary objective of this study was as follows:

- To evaluate the steady-state pharmacokinetics (PK) and confirm the age-appropriate dose of sofosbuvir (SOF)/velpatasvir (VEL)/voxilaprevir (VOX) fixed-dose combination (FDC) in paediatric subjects with chronic hepatitis C virus (HCV) infection

The secondary objectives of this study were as follows:

- To evaluate the safety and tolerability of SOF/VEL/VOX FDC in paediatric subjects with chronic HCV infection
- To evaluate the antiviral efficacy of SOF/VEL/VOX FDC treatment in paediatric subjects with chronic HCV infection, as assessed by the proportion of paediatric subjects with sustained virologic response (SVR) 12 weeks after cessation of treatment (SVR12)
- To evaluate the antiviral efficacy of SOF/VEL/VOX FDC treatment in paediatric subjects with chronic HCV infection, as assessed by the proportion of paediatric subjects with SVR 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of paediatric subjects with virologic failure, including on-treatment virologic failure and relapse
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF, VEL, and VOX during treatment and after cessation of treatment
- To evaluate the effect of SOF/VEL/VOX FDC on growth and development of paediatric subjects during and after treatment
- To evaluate acceptability, including palatability, and swallowability of formulations (as applicable) used in the study
- To assess the effect of treatment with SOF/VEL/VOX FDC on quality of life as measured by the Pediatric Quality of Life Inventory™ v4.0 Short Form 15 (PedsQL™ 4.0 SF15)

The exploratory objective of this study was as follows:

- To identify or validate genetic markers that may be predictive of the natural history of disease, response to therapy, and/or tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics) in subjects who provided their separate and specific consent

Outcomes/endpoints

Safety Assessment

Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, Tanner pubertal stage assessments, height and weight measurements, vital signs measurements, and physical examinations. Additional safety data related to growth were assessed based on radiographic bone age (end of treatment) and bone age biomarkers (posttreatment Week 24). Neuropsychiatric assessment was done using the PedsQL 4.0 SF15.

All enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety data included all data collected on or after the first dose of any study drug up to the date of the last dose of study drug plus 30 days. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.1.

Efficacy Assessment

The key efficacy endpoint was SVR12, defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after discontinuation of the study drug, in the Full Analysis Set. The point estimates of the SVR12 rate and 2-sided 95% exact CIs based on the Clopper-Pearson method were provided by HCV genotype 1 (further broken down to 1a and 1b), 2, 3, 4, 5, 6, or other, as appropriate, and total.

Secondary efficacy endpoints included the proportion of subjects with SVR4 and SVR24, proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through end of treatment, proportion of subjects with virologic failure, proportion of subjects with alanine aminotransferase (ALT) normalization, and characterization of baseline, on-treatment, and posttreatment HCV drug resistance substitutions.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, and maximum). All categorical endpoints were summarized by the number and percentage of subjects who met the endpoint definition.

Sample size

As the efficacy will be bridged through PK, the studies are not powered to allow a precise estimation of neither efficacy nor safety. According to the 2016 EMA draft "Guidelines on the clinical evaluation of direct acting antivirals for the treatment of chronic hepatitis" it is recognised that the number of children and adolescents with chronic hepatitis C eligible for clinical trials is limited. If there are no specific safety concerns relevant to the paediatric population, pre-authorisation studies could be limited in size.

Number of Subjects (Planned and Analysed):

Planned: Approximately 20 subjects 12 to < 18 years old

Analysed:

- Full Analysis Set: 21 subjects
- Safety Analysis Set: 21 subjects
- PK Analysis Set: 21 subjects
- Intensive PK Analysis Set: 14 subjects

At least 10 subjects in each age cohort were to be enrolled in an intensive PK substudy conducted at Week 2 or Week 4 after providing separate consent. Sparse PK samples were also collected from all subjects at Weeks 1, 2, 4, 8, and at end of treatment or early termination, depending on treatment duration and intensive PK substudy participation.

Randomisation and blinding (masking)

Study GS-US-367-1175 was an open-label, single-arm study, hence no randomisation.

Statistical methods

The statistical methods applied are standard for this type of study and they are considered acceptable. The statistical methods were detailed in the SAP, the SAP was however finalised close to the database lock date. Given the open label nature of the study an earlier finalization of the SAP would have been preferred but since the efficacy endpoints are objective in nature this is of less concern.

Sample Size and Power

Assuming similar variability for SOF, GS-331007, VEL, and VOX AUC_{tau} in the paediatric population compared with adults, a sample size of 20 paediatric subjects per cohort provided at least 80% power to target a 90% CI of the geometric mean ratio (GMR) within the bounds of 50% to 200%.

Analysis Sets

The Full Analysis Set (FAS) included all enrolled subjects who took at least 1 dose of study drug (SOF/VEL/VOX FDC). This was the primary analysis set for efficacy analyses.

The Safety Analysis Set included all subjects who were enrolled into the study and took at least 1 dose of study drug (SOF/VEL/VOX FDC). This was the primary analysis set for safety analyses.

Missing data handling

For the analyses of categorical HCV RNA data, missing posttreatment HCV RNA data will have the missing data imputed. Missing on-treatment HCV RNA will have the missing data imputed up to the time of the last dose. If a data point is missing and is preceded and followed in time by values that are "< LLOQ target not detected (TND)," then the missing data point will be set to "< LLOQ TND." If a data point is missing and preceded and followed by values that are "< LLOQ detected," or preceded by "< LLOQ detected" and followed by "< LLOQ TND," or preceded by "< LLOQ TND" and followed by "< LLOQ detected," then the missing value will be set to "< LLOQ detected." In these situations, the data point will be termed a bracketed success; otherwise, the data point will be termed a bracketed failure (i.e., ≥ LLOQ detected). If a data point is missing and is not bracketed, the missing data point will also be termed a failure (i.e., ≥ LLOQ detected) except for SVR24, which will be imputed according to the SVR12 status. Success for SVR12 who have no further HCV RNA measurements collected will be counted as a success for SVR24 due to the high correlation between these 2 endpoints.

Statistical analysis of efficacy endpoint

The proportion of subjects with sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12) was summarized. The point estimates of SVR12 rate and 2- sided 95% exact CI based on Clopper-Pearson method was provided by HCV genotype (1 [further broken down to 1a and 1b], 2, 3, 4, 5, 6, or other, as appropriate, and total).

No adjustments for multiple comparisons were performed.

Results

Participant flow

Table 6: Disposition of Subjects (Screened Subjects)

	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks
Subjects Screened	21
Subjects Enrolled	21
Subjects Enrolled but Never Treated	0
Subjects in Safety Analysis Set	21
Subjects in Full Analysis Set	21
Subjects in PK Analysis Set	21
Subjects in Intensive PK Analysis Set	14
Study Treatment Status	
Completed Study Treatment	21 (100.0%)
No FU-4 HCV RNA Assessment	0
With FU-4 but no FU-12 HCV RNA Assessment	0
Discontinued Study Treatment	0
No FU-4 HCV RNA Assessment	0
With FU-4 but no FU-12 HCV RNA Assessment	0
Study Status	
Completed Study	21 (100.0%)
Discontinued Study	0

FDC = fixed-dose combination; FU-x = follow-up visit at x weeks after discontinuing treatment; HCV = hepatitis C virus; PK = pharmacokinetic; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir
The denominator for percentages is based on the number of subjects in the Safety Analysis Set.
Safety Analysis Set includes subjects who took at least 1 dose of study drug (ie, SOF/VEL/VOX FDC).
Full Analysis Set includes subjects who were enrolled into the study and received at least one dose of study drug.
PK Analysis Set includes all enrolled subjects who received at least one dose of study drug and for whom at least one nonmissing PK concentration data value is available from all types of PK sampling.
Source: Table 15.8.1

Protocol Deviation

A total of 2 important protocol deviations occurred in 2 subjects during the study. One subject was enrolled without completing alcohol or drug abuse screening during the screening visit, so confirmation of this exclusion criterion was not performed prior to enrolment. The other deviation was due to a site failing to electronically transmit an SAE eCRF to the relevant safety group within 24 hours of being informed of the event, as required. Neither of these important protocol deviations affected the overall quality or interpretation of the study data.

Recruitment

Table 7: Key Dates Relevant to the Conduct of Study GS-US-367-1175

Event	Date
First Subject Screened	28 January 2019
First Subject Enrolled	12 February 2019
Last Subject Enrolled	16 July 2019
Last Subject Last Observation for the Primary Endpoint	04 December 2019
Last Subject Last Observation for this Report	19 February 2020
Database Finalization	29 April 2020

Conduct of the study

The protocol was amended once during the course of Study GS-US-367-1175, as indicated in the Table below.

Table 8: Protocol amendments

Protocol/Amendment	Date
Original	08 February 2018
Amendment 1 Summary of Changes	27 March 2019
Amendment 1	27 March 2019
Administrative Amendment 2	11 October 2019

Administrative Amendment 1 (04 March 2019) was incorporated into Amendment 1.

Summary of the major changes made to the Original Protocol dated 08 February 2018 and reflected in Amendment 1.0 dated 27 March 2019 are presented below.:

New Information

- Approximate amount of blood drawn at each visits, which has been reduced to align with the paediatric EMEA guidance "Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate" dated 25 June 2009 which recommends that the trial-related blood loss should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1 % at any single time.
- Weight related inclusion criteria for subjects participating in the Intensive PK Substudy in each cohort, to align with EMEA guidance "Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate" dated 25 June 2009.

Clarifications

- Clarification on possible impact of the IMP on P-gp, BCRP, OATP1B1, OATP1B3, or OATP2B1 substrates, as described in the Investigator Brochure
- Discontinuation criteria related to Grade 3 and Grade 4 adverse events: reference to Appendix 3 table added
- Further details concerning dose calculation for Cohort 2 and 3

Updates

- Change of Gilead Study director and medical Monitor
- Disallowed and Concomitant Medication Table, to align with Vosevi EU SmPC

The statistical analysis plan is dated 10 April 2020 and the study report is dated 24 June 2020.

Baseline data

Table 9: Demographic and Baseline Characteristics (Safety Analysis Set)

Characteristic	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks Total (All Genotypes) (N = 21)
Age at Baseline (Years)	
N	21
Mean (SD)	14 (1.2)
Median	14
Q1, Q3	13, 14
Min, Max	12, 16
Sex at Birth	
Male	8 (38.1%)
Female	13 (61.9%)
Race	
White	16 (76.2%)
Black or African American	1 (4.8%)
Asian	2 (9.5%)
Other	2 (9.5%)

Characteristic	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks Total (All Genotypes) (N = 21)
American Indian or Alaska Native	0
Native Hawaiian or Pacific Islander	0
Ethnicity	
Hispanic or Latino	2 (9.5%)
Not Hispanic or Latino	19 (90.5%)
Baseline Weight (kg)	
N	21
Mean (SD)	54.0 (11.39)
Median	54.2
Q1, Q3	46.1, 57.8
Min, Max	38.2, 86.2

FDC = fixed-dose combination; N = number of subjects; Q1 = first quartile; Q3 = third quartile; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir
Baseline value is the last available value on or prior to first dose date of study drug.
Source: GS-US-367-1175 CSR, Table 15.8.4

Table 1: Baseline Disease Characteristics (Safety Analysis Set)

Characteristic	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks Total (All Genotypes) (N = 21)
Sequence based HCV Genotype	
Genotype 1	6 (28.6%)
Genotype 1a	2 (33.3%)
Genotype 1b	4 (66.7%)
Genotype 2	4 (19.0%)
Genotype 3	9 (42.9%)
Genotype 4	2 (9.5%)
Cirrhosis	
Yes	0
No	21 (100.0%)
FibroScan (Transient Elastography) in kPa	
N	7
Mean (SD)	5.8 (1.08)
Median	5.6
Q1, Q3	4.9, 6.1
Min, Max	4.6, 7.9
Fibrotest Score	
N	21
Mean (SD)	0.2 (0.10)
Median	0.2
Q1, Q3	0.1, 0.3
Min, Max	0.1, 0.5
Fibrotest Stage	
F0, no or minimal fibrosis	15 (71.4%)
F0-F1, no or minimal fibrosis	2 (9.5%)
F1, no or minimal fibrosis	3 (14.3%)
F1-F2, moderate fibrosis	1 (4.8%)
APRI	
N	21
Mean (SD)	0.3 (0.16)
Median	0.2
Q1, Q3	0.2, 0.3
Min, Max	0.2, 0.8
FIB-4	
N	21
Mean (SD)	0.3 (0.10)
Median	0.3
Q1, Q3	0.2, 0.3
Min, Max	0.2, 0.5
Baseline HCV RNA Category	

Characteristic	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks Total (All Genotypes) (N = 21)
< 800,000 IU/mL	10 (47.6%)
≥ 800,000 IU/mL	11 (52.4%)
Baseline HCV RNA (log10 IU/mL)	
N	21
Mean (SD)	5.9 (0.70)
Median	6.0
Q1, Q3	5.5, 6.4
Min, Max	4.3, 7.1
Baseline ALT (U/L)	
N	21
Mean (SD)	39 (27.5)
Median	29
Q1, Q3	19, 41
Min, Max	15, 108
Baseline ALT Category	
≤ 1.5 x ULN	16 (76.2%)
> 1.5 x ULN	5 (23.8%)
Prior HCV Treatment Experience	
Treatment-Naive	16/21 (76.2%)
Treatment-Experienced	5/21 (23.8%)
Direct-Acting Antiviral-Naive	5/5 (100.0%)
Direct-Acting Antiviral-Experienced	0/5
Mode of HCV Infection	
Blood Product Transfusion	1 (4.8%)
Contact with Infected Individual	1 (4.8%)
Unknown	3 (14.3%)
Vertical Transmission	16 (76.2%)

ALT = alanine aminotransferase; APRI = aspartate aminotransferase (AST) to platelet ratio index; FIB-4 = Fibrosis-4; HCV = hepatitis C virus; FDC = fixed-dose combination; N = number of subjects; Q1 = first quartile; Q3 = third quartile; SOF = sofosbuvir; ULN = upper limit of normal; VEL = velpatasvir; VOX = voxilaprevir
Baseline value is the last available value on or prior to first dose date of study drug.
Source:GS-US-367-1175 CSR, Table 15.8.4

The study population had mild disease, which can be anticipated in the paediatric population.

Table 2: Adherence to Study Drug (Safety Analysis Set)

	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks (N = 21)
Study Drug Adherence Rate (%)	
N	21
Mean (SD)	95.2 (14.48)
Median	100.0
Q1, Q3	100.0, 100.0
Min, Max	50.0, 100.0
Study Drug Adherence Rate	
< 80%	2 (9.5%)
≥ 80 to < 90%	0
≥ 90%	19 (90.5%)
At Least 80% Adherence to Study Regimen	19 (90.5%)

FDC = fixed-dose combination; N = number of subjects; Q1 = first quartile; Q3 = third quartile; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir
Adherence to study drug calculated to Day 56.
If a bottle was dispensed but not returned (missing), then it was assumed that no study drug was taken from that bottle.
Source: Table 15.8.5

Numbers analysed

- Full Analysis Set: 21 subjects
- Safety Analysis Set: 21 subjects
- PK Analysis Set: 21 subjects
- Intensive PK Analysis Set: 14 subjects

Outcomes and estimation

Different genotypes were represented in the study population, as shown in Table below.

Table 3: Virologic Outcomes by Genotype (Full Analysis Set)

	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks						
	Total (All Genotypes) (N = 21)	GT-1a (N = 2)	GT-1b (N = 4)	GT-1 Total (N = 6)	GT-2 (N = 4)	GT-3 (N = 9)	GT-4 (N = 2)
SVR12	21/21 (100.0%)	2/2 (100.0%)	4/4 (100.0%)	6/6 (100.0%)	4/4 (100.0%)	9/9 (100.0%)	2/2 (100.0%)
Overall Virologic Failure	0/21	0/2	0/4	0/6	0/4	0/9	0/2
Other	0/21	0/2	0/4	0/6	0/4	0/9	0/2

FDC = fixed-dose combination; GT = genotype; HCV = hepatitis C virus; LLOQ = lower limit of quantitation; N = number of subjects; SOF = sofosbuvir; SVR12 = sustained virologic response at 12 weeks following discontinuation of study drug; VEL = velpatasvir; VOX = voxilaprevir
HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation 15 IU/mL.
Source:GS-US-367-1175 CSR, Table 15.9.2

Table 4: SVR by Visit During Post-treatment Follow-Up (Full Analysis Set)

	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks (N = 21)
SVR4	21/21 (100.0%)
95% CI	83.9% to 100.0%
SVR12	21/21 (100.0%)
95% CI	83.9% to 100.0%
SVR24	21/21 (100.0%)
95% CI	83.9% to 100.0%

FDC = fixed-dose combination; HCV = hepatitis C virus; LLOQ = lower limit of quantitation; N = number of subjects; SOF = sofosbuvir; SVRxx = sustained virologic response at xx weeks following discontinuation of study drug; TND = target not detected; VEL = velpatasvir; VOX = voxilaprevir
HCV RNA was analyzed using COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 with limit of quantitation 15 IU/mL.
SVRxx was sustained virologic response (HCV RNA < LLOQ) xx weeks after stopping study treatment.
A missing SVR value was imputed as a success if it was bracketed by values that were termed successes (ie, "<LLOQ TND" or "<LLOQ detected"); otherwise, the missing SVR value was imputed as a failure.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
Source: Table 15.9.3

Proportion of Subjects with HCV RNA < LLOQ While on Treatment by Visit

The table below presents the proportion of subjects with HCV RNA < LLOQ while on treatment by analysis visit. The total number of subjects with HCV < LLOQ was the sum of the number of subjects with HCV RNA "< LLOQ detected" plus the number of subjects with HCV RNA "< LLOQ target not detected (TND)." Potent and rapid suppression of HCV RNA while on treatment was observed. At Week 4, 90.5% of subjects (19 of 21) had HCV RNA < LLOQ, and 100.0% of subjects (21 of 21) had HCV RNA < LLOQ at Week 8.

Table 5: Proportion of Subjects with HCV RNA < LLOQ (15 IU/mL) While on Treatment by Visit (Full Analysis Set)

Characteristic	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks (N = 21)
Baseline	
< LLOQ	0/21
Week 1	
< LLOQ	11/21 (52.4%)
95% CI	29.8% to 74.3%
< LLOQ detected	8/21 (38.1%)
< LLOQ TND	3/21 (14.3%)
Week 2	
< LLOQ	17/21 (81.0%)
95% CI	58.1% to 94.6%
< LLOQ detected	5/21 (23.8%)
< LLOQ TND	12/21 (57.1%)
Week 4	
< LLOQ	19/21 (90.5%)
95% CI	69.6% to 98.8%
< LLOQ detected	3/21 (14.3%)
< LLOQ TND	16/21 (76.2%)
Week 8	
< LLOQ	21/21 (100.0%)
95% CI	83.9% to 100.0%
< LLOQ detected	1/21 (4.8%)
< LLOQ TND	20/21 (95.2%)

FDC = fixed-dose combination; HCV = hepatitis C virus; LLOQ = lower limit of quantitation; N = number of subjects; SOF = sofosbuvir; TND = target not detected; VEL = velpatasvir; VOX = voxilaprevir
HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation 15 IU/mL.
Missing values for on-treatment visits were imputed up to the time of last dose (if the study day associated with the last dose date is greater than or equal to the lower bound of a visit window, the missing value at the visit was imputed, otherwise, the value was excluded).
Missing values bracketed by values of "< LLOQ TND" were set to "< LLOQ TND"; bracketed by "< LLOQ detected", or "<LLOQ TND" and "<LLOQ detected" were set to "<LLOQ detected"; otherwise, the missing values were set as "≥ LLOQ."
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
Source: Table 15.9.6

ALT Normalization

At baseline, 23.8% of subjects (5 of 21) had ALT > ULN. Normalization of ALT was observed in all of these subjects at Week 4 and in 4 of 4 subjects (1 missing value) through the - Week 4 visit, coincident with suppression of viral replication.

Prevalence of Pre-treatment NS3 and NS5A RAVs and Impact on Treatment Outcome

Pre-treatment full-length NS3 and NS5A deep sequencing data were obtained for all 21 subjects and NS3 and NS5A resistance-associated variants (RAVs) were reported at a 15% assay cut-off. Overall, 1 of 21 subjects (4.8%) had pre-treatment NS3 RAVs without NS5A RAVs. A total of 10 of 21 subjects (47.6%) had pre-treatment NS5A RAVs alone. None of the subjects had both NS3 and NS5A RAVs at baseline. All 11 subjects (52.4%) with baseline NS3 or NS5A RAVs achieved SVR12 and SVR24. Overall, 21 of 21 subjects (100%) achieved SVR12 and SVR24.

Prevalence of Pre-treatment NS5B NI RAVs and Impact on Treatment Outcome

For the purposes of this report, NS5B NI RAVs were defined as follows: S96T, N142T, L159F, E237G, S282ANY, C289I/L, L320F/I/V, and V321A/I, and were reported at a 15% assay cut off. Pre-treatment full-length NS5B sequencing data were obtained for 21 of 21 subjects. Three of 21 subjects (14.3%) had pre-treatment NS5B NI RAVs detected at baseline at a 15% assay cut off. All 3 subjects with baseline NS5B NI RAVs achieved SVR12 and SVR24.

Overall, fourteen of 21 patients had baseline RAVs which did not impact treatment outcome and all the 21 patients reached SVR12 and SVR24.

Acceptability

A total of 21 subjects completed the acceptability questionnaire at Day 1, and 20 subjects and 21 parents or guardians completed the questionnaire at end of treatment (Week 8). Overall, the majority of responses were favourable or neutral with respect to acceptability of the SOF/VEL/VOX FDC (400/100/100 mg) tablet.

Quality of Life Survey

Based on subject and parent/guardian responses to the PedsQL 4.0 SF15 quality of life survey at baseline, end of treatment (Week 8), and posttreatment Weeks 12 and 24, there were no notable changes in overall quality of life or neuropsychiatric status during the study. Based on the subject reports, there was a statistically significant ($p = 0.032$) increase (improvement) at end of treatment compared with baseline in the psychosocial health summary score, followed by non-statistically significant decreases (worsening) during the posttreatment period. The mean psychosocial health summary scores per the subject reports at posttreatment Weeks 12 and 24 were slightly higher than baseline. No other statistically significant changes were observed.

Ancillary analyses

With the 100.0% SVR12 rate observed and no cases of virologic failure, no meaningful interpretation of subgroup analyses can be made.

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive studies

Not applicable.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The GS-US-367-1175 study was not powered for a precise estimate of efficacy and no control arm is available for comparison which is fully acceptable since the main objective of the study is to provide PK data. Furthermore, it was conducted in a population where the contribution of voxilaprevir to the favourable outcomes cannot be ascertained. However, in line with EMA guidance, efficacy can be extrapolated through a PK-bridge as exposure is similar in adolescents and adults.

Efficacy data and additional analyses

The key efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of study drug). Overall, 21 of 21 patients 12 <18 years of age achieved SVR12. No subject had virologic failure, there was no on-treatment breakthrough or relapse observed in subjects through posttreatment Week 12 or posttreatment Week 24.

At Week 4, 90.5% of subjects (19 of 21) had HCV RNA < LLOQ, and 100.0% of subjects (21 of 21) had HCV RNA < LLOQ at Week 8.

Normalization of ALT was observed in all subjects at Week 4 through the posttreatment Week 4 visit (final observation), coincident with suppression of viral replication.

Pre-treatment NS3 and NS5A RAVs were observed in 4.8% and 47.6% of subjects with a virologic outcome that were included in the Resistance Analysis Population, respectively. Pre-treatment NS5B NI RAVs were observed in 14.3% of the subjects. The presence of pre-treatment NS3, NS5A, and/or NS5B RAVs did not impact treatment outcome as all subjects with pre-treatment RAVs achieved SVR12 and SVR24.

2.5.3. Conclusions on the clinical efficacy

The CHMP concluded that Vosevi is effective in the treatment of chronic HCV in adolescent patients 12 < 18 years of age and weighing at least 30 kg.

2.6. Clinical safety

Patient exposure

The mean (SD) duration of exposure was 8.0 (0.08) weeks. All subjects completed their assigned 8-week treatment duration. No subjects were assigned to the 12-week treatment duration.

Table 6: Duration of Exposure to Study Regimen (Safety Analysis Set)

	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks (N = 21)
Duration of Exposure to Study Regimen (Weeks)	
N	21
Mean (SD)	8.0 (0.08)
Median	8.0
Q1, Q3	8.0, 8.0
Min, Max	8.0, 8.3
Cumulative N (%) of Subjects Exposed to Study Regimen Through	
Baseline	21 (100.0%)
Week 1	21 (100.0%)
Week 2	21 (100.0%)
Week 4	21 (100.0%)
Week 8	21 (100.0%)

FDC = fixed-dose combination; N = number of subjects; Q1 = first quartile; Q3 = third quartile; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir
Weeks on study drug = (last dose date of individual study drug - first dose date of individual study drug + 1) divided by 7.
A 3-day window is applied to the last planned on-treatment visit to match with the protocol-specified visit window
Source: Table 15.10.1

Adverse events

The majority of subjects (71.4%, 15 of 21) experienced at least 1 AE, and 42.9% of subjects (9 of 21) had a treatment-related AE, as presented in Table below. All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. One of 21 subjects (4.8%) experienced an SAE, which was assessed as related to study drug. No subject had an AE that led to premature discontinuation or interruption of study drug. No deaths occurred during the study.

Table 7: Overall Summary of Adverse Events (Safety Analysis Set)

	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks (N = 21)
Number (%) of Subjects Experiencing Any	
Adverse Event	15 (71.4%)
Grade 3 or Above Adverse Event	0
Grade 2 or Above Adverse Event	7 (33.3%)
Treatment-Related Adverse Event	9 (42.9%)
Grade 3 or Above Treatment-Related Adverse Event	0
Grade 2 or Above Treatment-Related Adverse Event	1 (4.8%)
Serious Adverse Event	1 (4.8%)
Treatment-Related Serious Adverse Event	1 (4.8%)
Adverse Event Leading to Premature Discontinuation of Study Drug	0
Adverse Event Leading to Interruption of Study Drug	0
All Deaths	0

FDC = fixed-dose combination; N = number of subjects; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir
The denominator for percentages is based on the number of subjects in the Safety Analysis Set.
Source: Table 15.11.1

Common Adverse Events

The Table below presents a summary of AEs reported for ≥5% of subjects by PT. The 3 most commonly reported AEs were abdominal pain and headache (23.8%, 5 subjects each) and nausea (19.0%, 4 subjects).

Table 8: Adverse Events Reported for at Least 5% of Subjects by Preferred Term (Safety Analysis Set)

	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks (N = 21)
Number (%) of Subjects Experiencing Any Adverse Event	15 (71.4%)
Number (%) of Subjects Experiencing Any Adverse Event Occurring in At Least 5% of Subjects by Preferred Term	
Abdominal pain	5 (23.8%)
Headache	5 (23.8%)
Nausea	4 (19.0%)
Diarrhea	3 (14.3%)
Fatigue	3 (14.3%)
Rhinitis	3 (14.3%)
Asthenia	2 (9.5%)
Cough	2 (9.5%)
Dizziness	2 (9.5%)

FDC = fixed-dose combination; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects;
SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir
Adverse events are mapped according to MedDRA Version 22.1.
Subjects are counted once for each AE preferred term.
Data included to last dose date of study drug + 30 days.
Source: Table 15.11.2.1

Overall, the frequency of AEs in Study GS-US-367-1175 are in line with observed AEs in the adult Phase 3 clinical trials. Abdominal pain is more frequently reported in the adolescent population (23.8%) compared to the adult population (3.4% abdominal pain in the Phase 3 program). However, all AEs were Grade 1 (mild) or Grade 2 (moderate) in severity.

Adverse Events by Severity

All AEs reported in this study were Grade 1 (mild) or Grade 2 (moderate) in severity. No Grade 3 (severe) or Grade 4 (life threatening) AEs were reported.

Adverse Events by Relationship to Study Drug

The Table below presents a summary of treatment-related AEs reported for ≥ 5% of subjects by PT. The most common treatment-related AEs reported were headache (14.3%, 3 subjects), nausea (14.3%, 3 subjects), and abdominal pain, diarrhoea, and fatigue (9.5%, 2 subjects each).

Table 18: Treatment-Related Adverse Events Reported for at Least 5% of Subjects by Preferred Term (Safety Analysis Set)

	12 to < 18 Years Old SOF/VEL/VOX FDC (400/100/100 mg) 8 Weeks (N = 21)
Number (%) of Subjects Experiencing Any Treatment-Related Adverse Event	9 (42.9%)
Number (%) of Subjects Experiencing Any Treatment-Related Adverse Event Occurring in at Least 5% of Subjects by Preferred Term	
Headache	3 (14.3%)
Nausea	3 (14.3%)
Abdominal pain	2 (9.5%)
Diarrhea	2 (9.5%)
Fatigue	2 (9.5%)

AE = adverse event; FDC = fixed-dose combination; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir
Adverse events are mapped according to MedDRA Version 22.1.
Subjects are counted once for each AE preferred term.
AEs are related to treatment if Related to Study Treatment = 'Related' on the AE case report form.
Data included to last dose date of study drug + 30 days.
Source: Table 15.11.5.1

Discontinuations Due to Adverse Events

No subject discontinued study drug due to an AE.

Adverse Events Leading to Interruption of Study Drug

There were no AEs leading to interruption of study drug during this study.

Analysis of Adverse Events by Organ System or Syndrome

Adverse events of interest were defined as treatment-emergent AEs that have historically been associated with administration of some nucleoside/nucleotide inhibitors or other DAAs including cardiac events, dermatologic events, pancytopenia, psychiatric events relevant to suicide ideation or attempt, pancreatitis events, rhabdomyolysis/myopathy events, renal failure events and hepatic events.

Cardiac Safety

Cardiac safety assessments included analysis of cardiac failure events, cardiac arrhythmia/bradycardia events, events during the first 2 weeks of study treatment in subjects taking or not taking beta blockers and calcium channel blockers, and any safety events in subjects with amiodarone use during treatment.

Cardiac Failure Events*:* Given historical potential toxicities associated with some antiviral nucleoside/nucleotide inhibitors, an analysis of cardiac failure/cardiomyopathy events was performed. No cardiac failure/cardiomyopathy AEs were reported.

Cardiac Arrhythmias/Bradycardia: A subject experienced a Grade 1 AE of bradycardia on Day 8, which resolved on posttreatment Day 168. The event was assessed as related to study drug and study drug was not interrupted. The subject was hospitalized for 1 day on Day 10 for an SAE of Grade 2 hypotension.

Adverse Events During the First 2 Weeks of Treatment for Subjects Using a Beta Blocker, a Calcium Channel Blocker, or Neither: No subject had on-treatment beta blocker or calcium channel blocker use. One subject without on-treatment beta blocker or calcium channel blocker use had a Grade 1 AE of dizziness during the first 2 weeks of treatment, and 1 subject had a Grade 1 AE of bradycardia.

Amiodarone Use: No subject received amiodarone during treatment with SOF/VEL/VOX.

Other Adverse Events of Interest

There were no reports of other adverse events of interest defined as follows: dermatologic events (defined as events within the skin and subcutaneous tissue disorders SOC that were serious, Grade 3 or above, or resulted in discontinuation of SOF/VEL/VOX), pancytopenia (including aplastic anemia) events, psychiatric events relevant to suicide ideation or attempt, pancreatitis events, rhabdomyolysis/myopathy events, renal failure events, and hepatic events (serious hepatic failure events, hepatic AEs leading to discontinuation of SOF/VEL/VOX, or subjects requiring liver transplantation).

Vital Signs, Physical Findings, and Other Observations Related to Safety

The effects of study treatment on development and growth were assessed by changes from baseline in Tanner pubertal stage, bone age assessments, height, weight, and BMI. No notable effects of Vosevi on development, growth or vital signs as assessed by changes from baseline through posttreatment Week 24, were observed.

Tanner Pubertal Staging

Male

At baseline, the majority of male subjects were at Tanner stage 4 or 5 for pubic hair and genitalia development (75.0%, 6 of 8 subjects). At end of treatment and at posttreatment Weeks 12 and 24, no male subjects (8 subjects) had a decrease from baseline in their Tanner stage for pubic hair and genitalia development.

Female

At baseline, the majority of female subjects were at Tanner stage 4 or 5 for pubic hair and breast development (69.2%, 9 of 13 subjects). At end of treatment and at posttreatment Weeks 12 and 24, no female subjects (13 subjects) had a decrease from baseline in their Tanner stage for pubic hair and breast development.

Height, Weight, and Body Mass Index

Height

The median (Q1, Q3) body height at baseline was 162.0 (158.0, 166.0) cm. At posttreatment Week 24, the median (Q1, Q3) change from baseline in body height was 1.8 (0.8, 3.0) cm. The median (Q1, Q3) body height percentile at baseline was 47.9 (32.4, 63.2). At posttreatment Week 24, the median (Q1, Q3) change in body height percentile was −0.2 (−3.1, 4.3). This minor negative change in body height percentile was not considered clinically relevant and could reflect variability in how height was assessed.

Weight

The median (Q1, Q3) body weight at baseline was 54.2 (46.1, 57.8) kg. At posttreatment Week 24, the median (Q1, Q3) change from baseline in body weight was 2.7 (1.0, 3.5) kg. The median (Q1, Q3) body weight percentile at baseline was 54.0 (30.9, 75.9). At posttreatment Week 24, the median (Q1, Q3) change in body weight percentile was −1.6 (−5.2, 4.3).

Body Mass Index

The median (Q1, Q3) BMI at baseline was 19.8 (18.5, 22.0) kg/m2. At posttreatment Week 24, the median (Q1, Q3) change from baseline in BMI was 0.2 (−0.2, 0.8) kg/m2. The median (Q1, Q3) BMI percentile at baseline was 57.4 (30.2, 73.6). At posttreatment Week 12, the median (Q1, Q3) change in BMI percentile was −2.8 (−7.1, 2.5).

Bone Age Assessments

Radiographic Bone Age Assessments

The median (Q1, Q3) radiographic bone age at baseline was 14.5 (13.7, 16.0) years. At end of treatment (Week 8), the median (Q1, Q3) change from baseline was 0.0 (0.0, 0.5) years.

Bone Age Biomarkers

The median (Q1, Q3) CTX at baseline was 1.35 (1.05, 2.35) ng/mL. At posttreatment Week 24, the median (Q1, Q3) change from baseline was −0.22 (−0.55, −0.04) ng/mL, and was not considered clinically relevant.

The median (Q1, Q3) P1NP at baseline was 383.25 (175.00, 944.20) ng/mL. At posttreatment Week 24, the median (Q1, Q3) change from baseline was –101.50 (−359.00, −24.98) ng/mL, and was not considered clinically relevant.

Vital Signs

No notable changes from baseline in vital signs (temperature, pulse, respiration, systolic blood pressure, or diastolic blood pressure) were observed during the study.

Pregnancies

No pregnancies were reported during this study.

Serious adverse event/deaths/other significant events

Serious Adverse Events

One subject had a Grade 2 SAE of hypotension on Day 10, which was assessed as related to study drug and resolved the same day. Study drug was not interrupted. No relevant medical history or concomitant medication use was reported. This subject experienced multiple AEs of mostly Grade 1 nausea, drowsiness, diarrhea, and dyspnea with a duration of 1 day beginning on Day 1 through Day 46. The subject experienced a Grade 2 AE of abdominal pain with unknown start and end dates during the first month of treatment as well as a Grade 1 AE of dizziness after Day 46 with unknown start and end dates. No medications were administered for any of these events. Most of the AEs were assessed as related to study drug, and study drug dosing was not changed. This subject also experienced an AE of Grade 1 bradycardia that started on Day 8 and resolved Day 224.

Deaths

No deaths were reported during this study.

Laboratory findings

Overall, 28.6% of subjects (6 of 21) had a Grade 1 laboratory abnormality, no subjects had Grade 2 or 3 laboratory abnormalities, and 4.8% of subjects (1 of 21) had a Grade 4 laboratory abnormality.

Laboratory findings do not indicate a different safety profile compared to adults. Overall, ALT and AST decreased with the duration of treatment and no change from baseline in bilirubin was observed.

Haematology

No Grade 3 or 4 haematologic laboratory abnormalities were reported during the study. No subject experienced a postbaseline haemoglobin value < 10 g/dL or < 8.5 g/dL. No clinically meaningful changes from baseline in neutrophils, lymphocytes, haemoglobin or platelets were observed.

Chemistry

An isolated Grade 4 increase in potassium (hyperkalemia) was reported for 1 subject (4.8%) at Week 1. The subject had no relevant medical history and was asymptomatic, and the value was within normal limits on repeat testing.

On-Treatment Liver-Related Abnormalities

No subject met any of the criteria for on-treatment liver-related laboratory abnormalities. The 3 liver-related laboratory criteria assessed were as follows:

- AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- ALT > 5 x ULN
- Total bilirubin > 2 x ULN

Total Bilirubin

No Grade 3 or 4 elevations in total bilirubin were reported and no notable changes from baseline in total bilirubin were observed.

Alanine Aminotransferase

No graded ALT laboratory abnormalities were reported during this study. Coincident with suppression of viral replication, all subjects had ALT normalization by Week 4. During treatment, median changes from baseline ranged from −10 to −14 U/L.

Aspartate Aminotransferase

No Grade 3 or 4 AST elevations were reported during this study. Laboratory results for AST were similar to those for ALT. Coincident with suppression of viral replication, median AST decreased from baseline for the duration of the treatment period and at the posttreatment Week 4 visit.

Safety in special populations

Not applicable.

Safety related to drug-drug interactions and other interactions

As the drug interaction profile of SOF/VEL/VOX in subjects 12 to < 18 years old is not expected to differ from that in adult subjects, no additional drug interaction studies of SOF/VEL/VOX were conducted for subjects 12 to < 18 years old. No new findings relevant to the coadministration of SOF/VEL/VOX with other drugs are submitted with this update to the marketing application. From a clinical perspective, this application raised no new safety issues regarding interactions.

Discontinuation due to adverse events

No subject had an AE that led to premature discontinuation or interruption of study drug.

Post marketing experience

No post marketing data were submitted with this application. Any off-label use of SOF/VEL/VOX in patients 12 to < 18 years old and any associated trends are routinely monitored by the MAH and documented in the PSURs.

2.6.1. Discussion on clinical safety

The Vosevi paediatric study was not powered to generate a comprehensive safety database in children and no control arm was available for comparison. This is considered acceptable since the main objective of the study is to provide PK data.

As exposure is comparable, safety can be extrapolated from the adult safety database through a PK-bridge, in line with the EMA guidance. The CHMP also considered that eligible patients will enrol in a registry study GS-US-334-1113 for a total of up to 5 years for assessments of growth, quality of life, and long-term viral suppression (if applicable), as these issues are particular causes of concern in the paediatric population.

From the limited safety dataset, there were no findings indicating a different safety profile compared to adults, which was considered reassuring by the CHMP.

Further to the request from the CHMP, the MAH amended the indication statement to "patients aged 12 years and older and weighing at least 30 kg" to avoid patients below 30 kg being dosed with Vosevi (400 mg /100 mg /100 mg) and risk overexposure.

2.6.2. Conclusions on the clinical safety

The CHMP concluded that Vosevi is safe in the treatment of chronic HCV in adolescent patients 12 < 18 years of age and weighing at least 30 kg.

2.7. Risk Management Plan

Safety concerns

The summary of safety concerns as per RMP version 5 is provided below

Important Identified Risks	Severe bradycardia and heart block when used with concomitant amiodarone
	HBV reactivation in HBV/HCV coinfected patients
Important Potential Risks	Recurrence of HCC
	Emergence of HCC
Missing Information	Safety in pregnant women
	Safety in patients with previous HCC
	Safety in patients with moderate or severe hepatic impairment

Pharmacovigilance plan

The following Table outlines the ongoing and planned additional pharmacovigilance activities in the RMP.

Table Part III.3. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
DAA-PASS: A post-authorisation safety study of early recurrence of hepatocellular carcinoma in HCV-infected patients after direct-acting antiviral therapy	To evaluate the impact of DAA treatment on the incidence of HCC recurrence, relative to no DAA therapy	*Important potential risk*: Recurrence of HCC *Missing information*: Safety in patients with previous HCC	Submission of final report	Final study report Q3 2021
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
De Novo DAA PASS: 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	To evaluate among compensated cirrhotic patients, whether DAA therapy for chronic HCV infection increases the risk of incident HCC compared to no treatment or treatment with IFN-based regimens	*Important potential risk*: Emergence of HCC	Submission of updated joint protocol	02 April 2019
			End of Data Collection	18 months after protocol approval by IRB and PRAC
			Final Report	12 months after end of data collection

Risk minimisation measures

Routine risk minimisation activities proposed to manage the safety concerns of the medicinal product are provided in the table below.

Table Part V.2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
Severe bradycardia and heart block when used with concomitant amiodarone	Routine risk minimization measures: SmPC section 4.4, 4.5, and 4.8 PL section 2. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire for bradyarrhythmia Additional pharmacovigilance activities: None
HBV reactivation in HBV/HCV coinfected patients	Routine risk minimization measures: SmPC Section 4.4 PL Section 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important potential risk(s)		
Recurrence of HCC	Routine risk minimization measures: None Additional risk minimization measures: None The need for risk minimization measures will be reassessed following the availability of the results from a study for HCC recurrence.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study to assess the impact of DAA treatment on the incidence of HCC recurrence, relative to no DAA therapy
Emergence of HCC	Routine risk minimization measures: None Additional risk minimization measures: None The need for risk minimization measures will be reassessed following the availability of results from a study to investigate the impact of DAA therapies on the incidence and type of de novo HCC.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study to evaluate the risk of de novo HCC in patients with compensated cirrhosis treated with DAAs for chronic hepatitis C
Missing information		
Safety in pregnant women	Routine risk minimization measures SmPC section 4.6 PL section 2. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Proactive follow-up to obtain information on maternal and paternal profile including medical history, risk factors, trimester and duration of exposure, and expected delivery date. Proactive follow-up on course and outcome of pregnancy and lactation. Additional pharmacovigilance activities: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Safety in patients with previous HCC	Routine risk minimization measures: None Additional risk minimization measures: None The need for risk minimization measures will be reassessed following the availability of the results from a study for HCC recurrence.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study to assess the impact of DAA treatment on the incidence of HCC recurrence, relative to no DAA therapy
Safety in patients with moderate or severe hepatic impairment	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 5.2 PL Section 3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 5.0 is acceptable.

2.8. Pharmacovigilance

Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

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.

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Vosevi 400/100/100mg film-coated tablets. The bridging report submitted by the MAH has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vosevi (sofosbuvir / velpatasvir / voxilaprevir) is included in the additional monitoring list as it had a PASS imposed at the time of

authorisation.

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

HCV infection has an estimated global prevalence of 1%, i.e. a total of 71 million individuals chronically infected with HCV. Although data on the global prevalence of HCV in children are limited, approximately 3.3 million children worldwide, aged 0 to 18 years, were estimated to be with viraemic HCV infection in 2018.

The natural history of chronic HCV infection in children is relatively benign. Most children are asymptomatic or have mild nonspecific symptoms; cirrhosis development within childhood/adolescence is rare but has been reported.

The HCV has significant genetic (RNA sequence) variability; 8 major genotypes have been identified: genotypes 1 and 3 are the most prevalent globally (46% and 30%, respectively) while genotypes 2, 4, and 6 represent approximately 23% of cases. Genotypes 5 and 7 comprise < 1%, and genotype 8 has only recently been identified.

3.1.2. Available therapies and unmet medical need

HCV treatment for adults has been transformed by the development and approval of DAA agents, including sofosbuvir-based compounds. Despite the high sustained virologic response rates with DAAs in clinical studies, as well as real-world studies, there are patients who fail multi-DAA–based therapies.

Some of the DAAs have recently been approved for the treatment of adolescents and children. Although DAA failures in the paediatric population currently represent a small unmet medical need, this is anticipated to increase over time as DAA treatment in this population increases and retreatment options become limited for patients who fail DAA treatment. Vosevi would offer a treatment regimen for adolescents, regardless of genotype, prior treatment failure, or presence of compensated cirrhosis.

3.1.3. Main clinical studies

Study GS-US-367-1175 was an open-label study evaluating the PK, safety and antiviral activity of SOF/VEL/VOX in adolescent subjects with chronic HCV infection. A total of 21 subjects were enrolled and received SOF/VEL/VOX for 8 weeks (all subjects were DAA-naive without compensated cirrhosis). All 21 subjects completed study drug and were included in both the FAS and the Safety Analysis Set.

3.2. Favourable effects

The favourable effects of Vosevi are well-known from the adult pivotal trials. In this paediatric application, the efficacy is established through a PK-bridge.

The proposed posology in adolescents regarding SOF and VEL has previously been approved (i.e. Epclusa). The popPK analysis supports the posology.

With regards to clinical outcomes, 21 of 21 patients 12 <18 years of age achieved SVR12. No subject had virologic failure, there was no on-treatment breakthrough or relapse observed in subjects through posttreatment Week 12 or posttreatment Week 24. However, it is not evident that this outcome could not have been reached without voxilaprevir.

Vosevi is expected to be effective in the treatment of HCV in adolescents from 12 years of age and weighing at least 30 kg.

3.3. Uncertainties and limitations about favourable effects

The VOX popPK model was not deemed optimal. However, based on observed PK data for VOX, the exposure, including Cmin, was overlapping with the adult exposure. The MAH´s conclusion that the VOX exposures in adolescents are similar to those in non-cirrhotic adults, for which safety and efficacy have been established, was agreed by the CHMP.

Given that the pharmacologic targets of SOF/VEL/VOX are viral and not host-related, the PK-PD relation is expected to be unchanged without additional uncertainty being introduced in adolescents other than potential age-related differences in treatment adherence.

3.4. Unfavourable effects

The safety profile of Vosevi is well-established in adults and it is not expected to be substantially different in a paediatric setting. The limited paediatric safety dataset did not raise any age-specific issues. The treatment was well-tolerated and all reported AEs were mild to moderate (Grade 1 or Grade 2). One of 21 subjects experienced a Grade 2 SAE of hypotension assessed as related to study drug, which resolved the same day.

3.5. Uncertainties and limitations about unfavourable effects

This product contains three active substances: SOF, VEL and VOX. The simulated exposure for SOF and VEL showed slightly higher exposure in adolescents compared to adults. The proposed posology is the same as what has been previously deemed satisfactory in paediatric patients for combinations including SOF and VEL (Epclusa). The CHMP considered that the higher exposure of SOF and VEL does not raise concerns with regards to safety in paediatric patients weighing above 30 kg.

3.6. Effects Table

Favourable effects					
SOF/VEL/VOX (400/100/100 mg)					
		Mean (%CV)		%GMR (90% CI)	
Analyte	PK Parameter	Adolescent Subjects ≥ 30 kg	Adult Phase 2/3 SOF/VEL/VOX Population	Adolescent Subjects vs Adult Phase 2/3 Population	Uncertainties / Strength of evidence
SOF	AUC_{tau} (h•ng/mL)	2474.8 (50.4)	1665.3 (30.1)	137.75 (123.66, 153.45)	Model predicted
	C_{max} (ng/mL)	1304.7 (69.9)	677.9 (35.4)	162.64 (138.53, 190.94)	Model predicted
GS-331007	AUC_{tau} (h•ng/mL)	14,890.2 (21.0)	12,834.1 (29.0)	118.49 (107.02, 131.19)	Model predicted
	C_{max} (ng/mL)	1278.1 (16.1)	744.3 (28.3)	176.55 (158.98, 196.06)	Model predicted
VEL	AUC_{tau} (h•ng/mL)	6773.0 (35.0)	4041.1 (48.6)	176.53 (147.25, 211.63)	Model predicted
	C_{max} (ng/mL)	621.8 (37.6)	311.1 (56.1)	215.54 (174.79, 265.80)	Model predicted
	C_{tau} (ng/mL)	92.0 (49.6)	51.2 (64.7)	188.51 (154.18, 230.49)	Model predicted
VOX					
		Adolescent Subjects ≥ 30 kg median (min-max)	Adult Phase 2/3 SOF/VEL/VOX Population median (min- max)	Adolescent Subjects vs Adult Phase 2/3 - ratio	
	$C_{16\text{-}24h}$(ng/mL)	28.9 (6.0-126)	31.8(2.2-1510)	0.91	Observed
	$C_{24\text{-}32h}$ (ng/mL)	17.9(5.9-95.5)	22.8(2.4-3440)	0.79	Observed

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The favourable effects of Vosevi in terms of sustained virologic response are well-known from the adult pivotal trials and can be extrapolated to adolescents.

Extrapolating from the safety profile in adults, the risks associated with Vosevi use are expected to be relatively mild also in adolescents.

3.7.2. Balance of benefits and risks

Given the natural course of chronic HCV infection, the high cure rate and the safety profile of Vosevi, the favourable effects are considered to outweigh the unfavourable effects.

3.8. Conclusions

The overall B/R of Vosevi is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vosevi 200/50/50 mg film-coated tablets is favourable in the following indication:

- Vosevi is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients aged 12 years and older and weighing at least 30 kg.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Vosevi subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to evaluate the recurrence of hepatocellular carcinoma associated with Vosevi, the MAH shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol. The final study report shall be submitted by:	Q3 2021

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0006/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

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

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

Extension of indication to include paediatric use in patients aged 12 years and older and weighing at least 30 kg. Sections 4.2, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated to support the extended indication. The RMP (version 5.0) is updated in accordance. Furthermore, the MAH took the opportunity to implement minor editorial updates in module 3.2.P and minor editorial updates throughout the Product Information, and to update the list of local representatives in the Package Leaflet.