25 June 2020
EMA/379603/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Epclusa

International non-proprietary name: sofosbuvir / velpatasvir

Procedure No. EMEA/H/C/004210/X/0043/G

Note

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

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AS	active substance
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BMI	body mass index
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CLCRSW	creatinine clearance estimated by the Schwartz formula
C_{max}	maximum observed concentration of drug
CoA	Certificate of Analysis
CQA	Critical quality attribute
CSR	clinical study report
DAA	direct-acting antiviral
EC	European Commission
eGFR	estimated glomerular filtration rate
EMEA	European Medicines Evaluation Agency
EU	European Union
FDA	Food and Drug Administration
FDC	fixed-dose combination
GC	Gas chromatography
GCP	Good Clinical Practice
Gilead	Gilead Sciences
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IFN	Interferon
IL28B	IL28B gene
IND	investigational new drug (application)
IPC	In-process control
LDV	Ledipasvir
LDV-SDD	Ledipasvir spray-dried dispersion

LDV/SOF	ledipasvir/sofosbuvir (coformulated; Harvoni)
LLOQ	lower limit of quantitation
MAH	Marketing Authorisation holder
N or n	number of subjects in a population (N) or subset (n)
NA	not applicable
NDA	new drug application
NF	National formulary
NI	nucleoside inhibitor
NS (3/4A/5A/5B)	nonstructural protein (3/4A/5A/5B)
PAR	Proven acceptable range
PBRER	Periodic Benefit-Risk Evaluation Report
pcVPC	Prediction corrected visual predictive check
PDCO	Paediatric Development Committee
PDE	Permitted Daily Exposure
PE	Polyethylene
Peg-IFN	pegylated interferon
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PREA	Paediatric Research Equity Act
PSUR	Periodic Safety Update Report
QbD	Quality by design
QC	Quality control
RAV	resistance-associated variant
RBV	Ribavirin
RH	Relative humidity
RNA	ribonucleic acid
rpm	Revolutions per minute
SAE	serious adverse event
SD	standard deviation
SDD	spray-dried dispersion
SLS	Sodium lauryl sulfate
SmPC	Summary of product characteristics
SOF	sofosbuvir (Sovaldi)
SOF/VEL	sofosbuvir/velpatasvir (Epclusa)
SVR, SVRxx	sustained virologic response, sustained virologic response at "xx" weeks following completion of all treatment
TSE	Transmissible spongiform encephalopathy
uHPLC	ultra-high performance liquid chromatography
UK	United Kingdom
ULN	upper limit of normal
US, USA	United States, United States of America

USP	United States Pharmacopoeia
UV	Ultraviolet
VEL	Velpatasvir
WHO	World Health Organization
WR	Written Request

1. Background information on the procedure

1.1. Submission of the dossier

Gilead Sciences Ireland UC submitted on 14 October 2019 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 (200/50 mg film-coated tablets). The new presentation is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients 6 years and older.

The extension application is grouped with a type II variation (C.I.6.a) to include paediatric use in patients aged 6 to < 18 years to the existing strength of 400/100 mg film-coated tablets. 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 5.1) is updated in accordance.

In addition, the MAH took the opportunity to implement minor editorial updates throughout the Product Information.

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

Not applicable

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	14 October 2019
The procedure started on	31 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	21 January 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	28 January 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2020
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	27 February 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	23 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	26 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 June 2020
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 Epclusa on	25 June 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

2.1.1.1. Epidemiology

Hepatitis C virus infection is a global health challenge with an estimated global prevalence of 1%, for a total of 71 million individuals worldwide chronically infected with HCV (The Polaris Observatory HCV Collaborators 2017), (World Health Organization (WHO) 2018b). In the US, over 3 million people are estimated to be chronically infected with HCV (Center for Disease Control and Prevention 2016), and in Europe an estimated

10 to 14 million people have chronic HCV infection (The Polaris Observatory HCV Collaborators 2017), (World Health Organization (WHO) 2018c). Up to 85% of individuals infected with HCV fail to clear the virus and progress to chronic infection; over the ensuing 20 years, as many as 20% of patients with chronic HCV infection are estimated to develop complications, including cirrhosis, end stage liver disease, and hepatocellular carcinoma (HCC). Curing HCV infection is associated with numerous health benefits, including more than 70% reduction in the risk of HCC and 90% reduction in the risk of liver-related mortality and liver transplantation (Morgan 2013), (van der Meer 2012), (Veldt 2007), (Poynard 2002).

The estimated prevalence of HCV infection in children is up to 0.4% in Europe and the US and up to 6% in resource-limited countries (El-Shabrawi 2013), (Khaderi 2014). Globally, it is estimated that approximately 2.1 to 3.5 million individuals 15 years of age or younger are chronically infected with HCV (Nwaohiri 2018), (European Association for the Study of the Liver (EASL) 2018).

2.1.1.2. Aetiology and pathogenesis

The primary mechanism of HCV infection in children is vertical transmission, with parenteral transmission secondary. Following vertical transmission of HCV, in the absence of treatment, approximately 20% to 40% of children clear the infection spontaneously, usually in the first 4 to 7 years of life, whereas the remaining 60% to 80% develop chronic infection that persists into adulthood (Mack 2012), (Indolfi 2018).

2.1.1.3. Clinical presentation

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).

2.1.1.4. Management

The goal of HCV treatment in both paediatric and adult populations is viral eradication, thereby preventing progressive hepatic inflammation, hepatic fibrosis, cirrhosis, and liver failure that result in the need for liver transplantation. Over the past 7 years, the development and approval of safe and effective direct-acting antivirals (DAAs) have transformed the treatment and course of HCV infection in adults. Several DAA therapies containing sofosbuvir have been approved for the treatment of adults with chronic HCV infection (Sovaldi, Harvoni, Epclusa and Vosevi).

2.1.2. About the product

Epclusa was approved in 2016 for the treatment of chronic hepatitis C in adults. It is a fixed dose combination of sofosbuvir, an HCV polymerase inhibitor, and velpatasvir, an NS5A-inhibitor. It is pangenotypic, indicated regardless of HCV genotype.

Type of Application and aspects on development

In the EU, a paediatric investigation plan (PIP) for SOF/VEL was agreed on 08 May 2015 (EMEA-001646-PIP01-14). Minor modifications to the original PIP have been agreed since that time, most recently on 18 May 2018 (EMEA-001646-PIP01-14-M02). The design of GS-US-342-1143 reflected the PIP Decision agreed with the Paediatric Development Committee (PDCO) as part of the assessment of the PIP.

2.2. Quality aspects

2.2.1. Introduction

This application is a line extension to the already approved Epclusa 400 mg/100 mg film-coated tablets. This line extension involves the addition of a 200/50 mg strength film-coated tablets and an extension of indication.

The finished product is presented as film-coated tablets containing 200 mg sofosbuvir and 50 mg velpatasvir as active substances.

Other ingredients are:

Tablet core: copovidone, microcrystalline cellulose, croscarmellose sodium, magnesium stearate.

Film-coating: polyvinyl alcohol, titanium dioxide (E171), polyethylene glycol, talc and iron oxide red (E172).

The product is available in high density polyethylene (HDPE) bottle with a polypropylene child-resistant closure containing 28 film-coated tablets with polyester coil as described in section 6.5 of the SmPC.

2.2.2. Active Substance – Sofosbuvir, Velpatasvir

General information

This application is a line extension and contains the same active substances, sofosbuvir and velpatasvir, used to manufacture the already-approved film-coated tablets. The information presented by the Applicant in the dossier was already assessed in the original submission and includes updates from any subsequent variations. The active substances are sourced from the same manufacturers, are manufactured by the same processes and are released in accordance with the same active substance specifications.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Epclusa 200 mg/50 mg film-coated tablets are pink, oval-shaped, film-coated tablets of dimensions 14 x 7 mm, debossed on one side with "GSI" and "S/V" on the other side.

The aim of development was to identify a lower strength solid oral dosage form for use in paediatric patients. Development was based on the already approved 400/100 mg film-coated tablets, including the use of the same manufacturing process, adapted to the smaller tablet size, utilizing the identical formulation composition that is dose-proportional. Subsequent to the commercialization of the 400/100 mg strength, the reduced-strength 200/50 mg tablet was developed for use by paediatric patients unable to swallow a larger tablet. The 200/50 mg tablet was used to support Phase 2 paediatric studies and primary stability studies.

The qualitative composition of the 200/50 mg film-coated tablets and existing Epclusa 400/100 mg film-coated tablets is identical. The quantitative composition for the 200/50 mg film-coated tablets is proportional to the existing Epclusa 400/100 mg film-coated tablets for all the components. The dose strengths can be differentiated by different sizes, shape and dimensions.

The active substances are the same as those used in the approved higher strength tablets. Velpatasvir free base is a stable amorphous solid, no stable crystalline forms have been isolated. It exhibits pH-dependent solubility over the physiological pH range of 2 to 8. Velpatasvir solubility increases with decreasing pH. Velpatasvir is considered to have low solubility and low apparent intestinal permeability based on low oral bioavailability (BCS class IV).

Sofosbuvir is a crystalline solid, routinely manufactured as the most stable polymorphic form containing small quantities of an equivalent polymorphic form. Sofosbuvir exhibits pH-independent solubility across the physiological pH range. Sofosbuvir is highly soluble but has low apparent intestinal permeability (BCS class III).

The excipients used in the 200/50 mg film-coated tablets are the same as those used in the 400/100 mg film-coated tablets and their compatibility with the active substance was demonstrated in stability studies. They are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. Standards, except for the film-coating material, Opadry II Pink tested according to an in-house standard. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The dissolution method is the same as used for the already-approved 400/100 mg film-coated tablets.

The existing 400 mg/100 mg tablets and 200 mg/50 mg tablets are both manufactured using the same manufacturing process train. The manufacturing process for VEL SDD was assessed in connection with the approval of Epclusa tablets, 400 mg/100 mg. No new information is provided in this application and no further assessment is made at this stage.

The manufacturing process for the 200 mg/50 mg tablets was developed and optimized at the proposed manufacturing site. The development and optimization of the manufacturing process involved a tablet compression study and a film-coating study to define the commercial process parameters. The results of these studies were used to establish proposed targets and PARs for the commercial process. For the drying and dry granulation steps, the manufacturing processes and associated operating parameters were within the ranges defined in the current SOF/VEL tablet, 400 mg/100 mg, process and no additional work was

conducted. A confirmation study was performed to verify the suitability of the dry granulation process parameter ranges for the SOF/VEL tablet, 200 mg/50 mg. The parameter ranges used in these studies are considered as PARs and were summarized in the dossier.

The primary packaging is HDPE bottle and a polypropylene (PP) continuous thread child-resistant cap lined with an induction activated aluminium foil liner. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of two parts: manufacture of velpatasvir spray-dried dispersion (VEL-SDD) and then production of the film-coated tablets.

The first part of the manufacturing process (manufacture of VEL-SDD) consists of four main steps: feed solution preparation, drying, secondary drying, and packaging of VEL SDD.

The manufacturing process for the VEL-SDD is identical to that used for the approved 400/100 mg film-coated tablets. The controls applied to the VEL-SDD intermediate have previously been assessed in the context of the original MAA and are considered appropriate.

The tablet manufacturing process consists of three main steps: (1) powder processing (dispensing, blending, and dry granulation), (2) tablet compression, and (3) film-coating of tablet cores to yield film-coated tablets. IPCs are carried out to monitor the critical steps of the manufacturing process. The IPCs are adequate for this type of manufacturing process and pharmaceutical form.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this film-coated tablet manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identity (UPLC, UV), water content (Ph. Eur., USP), assay (UPLC), degradation products (UPLC), uniformity of dosage units (Ph. Eur., USP), dissolution (Ph. Eur., USP) and microbiological enumeration (Ph. Eur., USP).

The specification for the 200 mg/50 mg tablets utilizes the same tests and acceptance limits as approved for Epclusa film-coated tablets, 400 mg/100 mg. The proposed specification is considered acceptable.

The potential presence of class 1, 2A and selected class 3 elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on seven representative pilot scale batches and three primary stability batches using a validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. 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. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The finished product is released onto the market based on the above release specifications, through traditional final product release testing.

A risk assessment concerning the presence of nitrosamine impurities was performed for the finished product based on the combined recommendations from health authorities, including EMA communication EMA/189634/2019; it was concluded that there is no risk related to the presence of nitrosamine impurities in the product. Therefore, no changes to the control strategy for Epclusa are necessary to mitigate potential contamination by nitrosamines. The nitrosamine impurities risk assessment of the finished product included evaluating contributions from sofosbuvir and velpatasvir active substances, VEL spray-dried dispersion, excipients, finished product manufacturing facilities, and packaging components.

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.

Stability of the product

Stability data from 3 production scale batches 200/50 mg film-coated tablets stored for up to 6 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 identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, water content, assay, degradation products, dissolution, total aerobic microbial count, total combined yeasts and moulds count, and *Escherichia coli*. No significant changes were observed to any of the measured parameters under any conditions and the results were comparable to the data from the approved 400/100 mg film-coated tablets at each time-point.

A further consideration is that the already-marketed 400/100 mg film-coated tablets have a 48-month shelf-life based on extensive stability data which revealed little or no change in any of the measured quality attributes, and that the two strengths of tablet are manufactured from a common blend. Photostability data was generated for the 400/100 mg film-coated tablets indicating that Epclusa film-coated tablets are not photosensitive. Additional stability data reveals that the product is not impacted by freezing or temporary exposure to high temperature (60 ºC), which means that temperature excursions outside the normal temperature range which may be encountered during shipping will not have an adverse effect on product quality.

Based on available stability data, the proposed shelf-life of 4 years without any special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Satisfactory information has been provided in regard of the new presentation intended for treatment of paediatric patients. The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the 200mg/50mg film-coated tablet 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

Regarding the ecotoxicological aspects of Epclusa, the environmental risk assessment (ERA) for SOF has been conducted for its major metabolite (GS-331007) with the conclusion that the use of SOF is not expected to pose a risk to the environment.

No conclusion on the environmental risk of VEL was made for Epclusa as VEL has been found to be persistent in sediments and there was data missing on the potential for bioaccumulation in sediment-dwelling organisms. This was to some extent resolved with a study on bioaccumulation in sediment-dwelling benthic oligochaetes (OECD TG315, a study with adult Lumbriculus variegatus that is considered to provide indications of bioaccumulation potential) in procedure EMEA/H/C/004210/IB/0013. The outcome was a normalized BAF of 0.122, indicating that VEL is rapidly eliminated and has very little potential for bioaccumulation in sediment-dwellers. That being said, as no definite equilibrium or kinetic bioaccumulation factor (BAFss; BAFk) could be determined in the study and as there are (at the present time) no formal criteria for bioaccumulation for OECD TG315 data, some uncertainty remains.

2.3.2. Discussion and conclusion on non-clinical aspects

No new non-clinical studies have been submitted for this procedure. This is in line with the agreed paediatric investigation plan for sofosbuvir / velpatasvir (SOF/VEL, product name Epclusa), (EMEA-01646-PIP01-14-M02) and therefore acceptable.

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 Marketing Application for Paediatric Subjects (6 to < 18 years old)

Study Number	Study Design	Subject Population	Treatment Regimen[b]	N[c]
GS-US-342-1143[a]	Phase 2, open-label, multicohort, 2-part study	Treatment-naive and treatment-experienced subjects 3 to < 18 years old with chronic HCV infection	SOF/VEL for 12 weeks	12 to < 18 years: 102 Genotype 1: 75 Genotype 2: 6 Genotype 3: 12 Genotype 4: 2 Genotype 5: 0 Genotype 6: 6 Missing: 1[d]
				6 to < 12 years: 73[e] Genotype 1: 56 Genotype 2: 2 Genotype 3: 11 Genotype 4: 4 Genotype 5: 0 Genotype 6: 0

a Only data for subjects 12 to < 18 years old and 6 to < 12 years old are discussed in this summary.
b The doses and formulations of SOF/VEL were based on age group as follows:
- Adolescent subjects 12 to < 18 years old received SOF/VEL 400/100 mg orally, once daily (1 × 400/100-mg tablet or 2 × 200/50-mg tablets).
- Pediatric subjects 6 to < 12 years old received SOF/VEL 200/50 mg orally, once daily (1 × 200/50-mg tablet or 4 × 50/12.5-mg packets containing granules).

The selection of SOF/VEL formulation was based on a swallowability assessment using a placebo tablet at baseline.
c N = Number of subjects in the Safety Analysis Set, which included all subjects who received at least 1 dose of study drug.
d Based on BLAST analysis the subject was determined to have genotype 1b HCV infection.
e Of the 73 subjects enrolled in the study and received at least 1 dose of study drug, 71 subjects received the SOF/VEL FDC tablet formulation.

2.4.2. Clinical pharmacology

2.4.2.1. Population pharmacokinetics

The objectives of the Population Pharmacokinetic Analysis for Sofosbuvir, GS 331007, and Velpatasvir after Administration of Sofosbuvir + Ribavirin, Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin, or Sofosbuvir/Velpatasvir Fixed-Dose Combination in Pediatric Subjects with Hepatitis C Virus Infection were:

- To update a joint model evaluating the PK of SOF, GS-566500, and its primary metabolite, GS-331007, in HCV-infected pediatric subjects administered SOF+ RBV, ledipasvir (LDV)/SOF FDC ±RBV, or SOF/VELFDC
- To develop a PopPK model for evaluating the PK of VEL in HCV-infected pediatric subjects administered SOF/VELFDC
- To evaluate the effects of demographic
- To support a simplified dosing recommendation for SOF/VEL FDC in pediatric subjects based on weight band.

Dataset

Three Phase 2 studies (GS-US-334-1112, GS-US-337-1116 and GS-US-342-1143) in pediatric subjects with chronic HCV infection were used in the population PK modeling and are presented in the table below. Study GS-US-334-1112 evaluated SOF (administered once daily) + RBV for a treatment duration of 12 or 24 weeks in subjects aged 3 to < 18 years old with chronic genotype 2 or 3 HCV infection. Study GS-US-337-1116 evaluated LDV/SOF FDC (administered once daily) ± RBV for a treatment duration of 12 or 24 weeks in subjects aged 3 to <18 years old with chronic genotype 1, 3, 4, 5, or 6 HCV infection. Study GS-US-342-1143 evaluated SOF/VEL FDC (administered once daily) for a treatment duration of 12 weeks in subjects aged 6 to < 18 years with chronic HCV infection. PK sampling included a combination of intensive and sparse sampling. After all exclusions, a total of 69 subjects in Study GS-US-334-1112, 160 subjects in Study GS-US-337-1116, and 148 subjects in Study GS-US-342-1143 had at least one measurable SOF concentration value included in the SOF joint model population PK analysis. A total of 70 subjects in Study GS-US-334-1112, 197 subjects in Study GS-US-334-1116, and 148 subjects in Study GS-US-334-1143 had at least one concentration value for GS-566500 included in the population PK analysis. A total of 85 Subjects in Study GS-US-334-1112, 198 subjects in Study GS-US-337-1116, and 153 subjects in Study GS-US-342-1143 had at least one concentration value for GS-331007 included in the population PK analysis.

The population PK data included 173 subjects from Study GS-US-342-1143 for VEL. After all exclusions, a total of 153 subjects in Study GS-US-342-1143 had at least one measurable concentration value for VEL.

Table 2 Phase 2 studies (GS-US-334-1112, GS-US-337-1116 and GS-US-342-1143) in paediatric subjects with chronic HCV infection used in the population PK modelling

Study	Age Group [yrs]	Study Phase	Subjects with PK Sampling (Intensive [Int] and/or Sparse)[a]	Dosing Regimen (mg)[b]
GS-US-334-1112 SOF + RBV[c]	12 to < 18	PK lead-in	N = 10 (Int + Sparse in Treatment phase)	400 SOF
		Treatment	N = 42 (Sparse only)	
	6 to < 12	PK lead-in	N = 12 (Int + Sparse in Treatment phase)	200 SOF
		Treatment	N = 29 (Sparse only)	
	3 to < 6	PK lead-in	N = 11 (Int + Sparse in Treatment phase)	> 17 kg: 200 SOF ≤ 17 kg: 150 SOF
		Treatment	N = 1 (Sparse only)	
GS-US-337-1116 LDV/SOF ± RBV[d]	12 to < 18	PK lead-in	N = 10 (Int + Sparse in Treatment phase)	90/400 LDV/SOF
		Treatment	N = 90 (Sparse only)	
	6 to < 12	PK lead-in	N = 12 (Int + Sparse in Treatment phase)	45/200 LDV/SOF
		Treatment	N = 80 (Sparse only)	
	3 to < 6	PK lead-in	N = 14 (Int + Sparse in Treatment phase)	> 17 kg: 45/200 LDV/SOF ≤ 17 kg: 33.75/150 LDV/SOF
		Treatment	N = 8 (Sparse only) N = 12[e] (Int + Sparse in Treatment phase)	
GS-US-342-1143 SOF/VEL[f]	12 to < 18	PK lead-in	N = 17 (Int + Sparse in Treatment phase)	400/100 SOF/VEL
		Treatment	N = 85 (Sparse only)	
	6 to < 12	PK lead-in	N = 20 (Int + Sparse in Treatment phase)	200/50 SOF/VEL
		Treatment	N = 51 (Sparse only)	

Int = intensive; LDV = ledipasvir; N = number of subjects; PK = pharmacokinetic; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir.

[a] For sparse PK sampling, single blood samples were collected at all on-treatment study visits.

[b] Protocol-defined dosing regimen based on defined age and weight cutoff.

[c] Intensive PK sampling included 8 time points for pediatric subjects 6 to < 18 years old and 5 time points for pediatric subjects 3 to < 6 years old.

[d] Intensive PK sampling included 9 time points for pediatric subjects 6 to < 18years old and 6 time points for pediatric subjects 3 to < 6 years old. Pediatric subjects 3 to < 6 years old could have participated in an optional intensive PK substudy that included 9 time points at Week 4 or 8 of treatment.

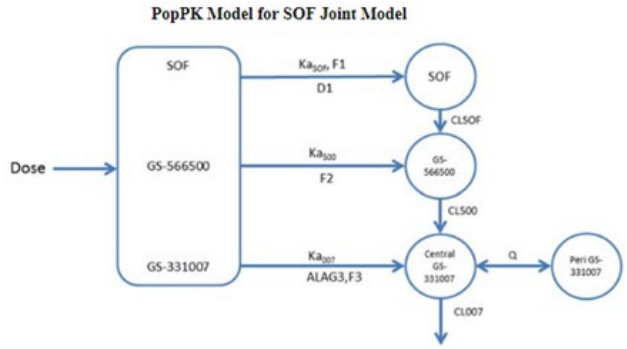
[e] One subject participated in both the PK lead-in phase and the intensive PK substudy during the treatment phase.

[f] Intensive PK sampling included 9 time points for pediatric subjects 6 to < 18 years old.

SOF popPK model development

A previously developed PopPK models using 2 of the 3 studies (GS-US-334- 1112 and GS-US-337- 1116) was updated with data from GS-US-342-1143 also included in the dataset. The structural model is a joint model for parent and metabolites, depicting the metabolism of SOF to the intermediate metabolite, GS-566500, which is subsequently metabolized to and cleared from the body as GS-331007, is illustrated in figure below (Figure 1). The model included, a priori, the effect of baseline WT (allometric exponents fixed to 0.75 and 1 for clearances and volumes, respectively) on CLSOF, VSOF, CL500, V500, CL007, and Vc007. Based on previous population PK analysis and the expected effect of LDV, VEL, and RBV on the PK of SOF and its metabolites, the model also included (a priori) coadministration of LDV and VEL separately on SOF F1 and coadministration of RBV on CL500and CL007. Following the covariate search, statistically significant covariates of age on CL500and CL007and also sex on CL007were included in the model. Bootstrap resampling techniques were used to evaluate the model stability and confidence interval (CI) of the final parameter estimates (Table 5). This model evaluation consisted of repeatedly fitting the model to a large number (n= 1000) of bootstrap replicates of the dataset.

Figure 1 Population PK Model Diagram for SOF and SOF Metabolites



ALAG = absorption lag time; CL_{007} = clearance of GS-331007; CL_{500} = clearance of GS-566500; CL_{SOF} = clearance of SOF; D1 = duration of zero order input; F1 = relative fraction absorbed; Ka007 = first-order absorption rate constant of GS-331007; Ka500 = first-order absorption rate constant of GS-566500; KaSOF = first-order absorption rate constant of SOF; PopPK = population pharmacokinetic; SOF = sofosbuvir.

Table 3 Comparison of final model estimates and bootstrap results for SOF

Comparison of Final Model Estimates and Bootstrap Results

Parameter	Parameter Description	Estimate [RSE*]	Bootstrap Estimate Median [2.5th, 97.5th Percentiles]	SIR Median [2.5th, 97.5th Percentiles]
$\exp(\theta_1)$	Absorption rate for SOF (1/hr)	1.25 [2]	1.27 [1.14;1.4]	1.25 [1.19;1.3]
$\exp(\theta_2)$	Absorption rate for GS-566500 (1/hr)	0.292 [3]	0.291 [0.274;0.313]	0.292 [0.281;0.304]
$\exp(\theta_3)$	Absorption rate for GS-331007 (1/hr)	0.0225 [7]	0.023 [0.0201;0.0264]	0.0229 [0.0202;0.0268]
$\exp(\theta_4)$	Apparent oral clearance of SOF (L/hr)	304 [6]	302 [268;341]	305 [276;339]
$\exp(\theta_5)$	Apparent central volume of SOF (L)	148 [15]	154 [110;203]	156 [120;196]
$\exp(\theta_6)$	Apparent oral clearance of GS-566500 (L/hr)	811 [3]	811 [766;855]	822 [772;871]
$\exp(\theta_7)$	Apparent central volume of GS-566500 (L)	1190 [4]	1180 [1010;1370]	1180 [1110;1270]
$\exp(\theta_8)$	Apparent oral clearance of GS-331007 (L/hr)	169 [2]	167 [160;174]	166 [160;173]
$\exp(\theta_9)$	Apparent central volume of GS-331007 (L)	212 [5]	212 [180;285]	213 [190;232]
$\exp(\theta_{10})$	Apparent intercompartmental clearance of GS-331007 (L/hr)	47.6 [9]	52.2 [39.6;74.8]	49.4 [42.4;57]
$\exp(\theta_{11})$	Apparent peripheral volume of GS-331007 (L)	1030 [21]	1100 [172;1840]	1090 [707;1540]
$\exp(\theta_{12})$	Absorption duration for SOF (hr)	0.609 [7]	0.61 [0.482;0.8]	0.597 [0.507;0.688]
	F1 for SOF	1 [Fixed]	--	--
θ_{13}	F1 for GS-331007	7.18 [Fixed]	7.18 [7.18;7.18]	--
θ_{14}	Ledipasvir on F1 for SOF	0.769 [Fixed]	0.769 [0.769;0.769]	--
θ_{15}	F1 for GS-566500	5.32 [Fixed]	5.32 [5.32;5.32]	--
θ_{16}	Proportional error SD for GS-566500	0.603 [2]	0.602 [0.577;0.628]	0.602 [0.585;0.625]
θ_{17}	Proportional error SD for GS-331007	0.306 [1]	0.305 [0.292;0.317]	0.305 [0.296;0.313]
$\exp(\theta_{18})$	Absorption lag time for GS-331007	3 [2]	3 [0.5;11.5]	3.01 [2.91;3.12]
019	Proportional error SD for SOF	0.93 [3]	0.927 [0.888;0.968]	0.934 [0.873;0.979]
$\exp(\theta_{20})$	Oral clearance of GS-566500*RBV (L/hr)	1240 [4]	1260 [1170;1350]	1240 [1160;1360]
$\exp(\theta_{21})$	Oral clearance of GS-331007*RBV (L/hr)	188 [3]	186 [174;197]	186 [175;197]
$\exp(\theta_{22})$	Absorption lag time for SOF (hr)	0.0821 [Fixed]	0.0821 [0.0821;0.0821]	--
θ_{23}	Velpatasvir on F for SOF	1.4 [9]	1.41 [1.05;1.79]	1.42 [1.17;1.61]
θ_{24}	Age effect on clearance of GS-331007	-0.17 [19]	-0.184 [-0.24;-0.123]	-0.181 [-0.249;-0.115]
θ_{25}	Sex effect on clearance of GS-331007	0.101 [31]	0.105 [0.0521;0.16]	0.0998 [0.0417;0.163]
θ_{26}	Age effect on clearance of GS-566500	-0.239 [20]	-0.241 [-0.332;-0.163]	-0.255 [-0.341;-0.192]
ω^2_{11}	Between subject variance on clearance of SOF	80% [11]	76.7 [64.9;87.4]	80 [69.5;91.1]
ω^2_{22}	Between subject variance on volume of SOF	224% [13]	204 [151;337]	212 [190;237]
$\omega^2_{12,12}$	Between subject variance on clearance of GS-566500	32% [22]	32.3 [27.9;40.3]	33.7 [29.5;37.7]
$\omega^2_{13,13}$	Between subject variance on clearance of GS-331007	27% [9]	27.2 [25.2;29.3]	27.7 [25;29.3]

F1 = relative fraction absorbed; RBV = ribavirin; RSE = residual standard error; SD = standard deviation; SE = standard error; SIR = sampling importance resampling; SOF = sofosbuvir.

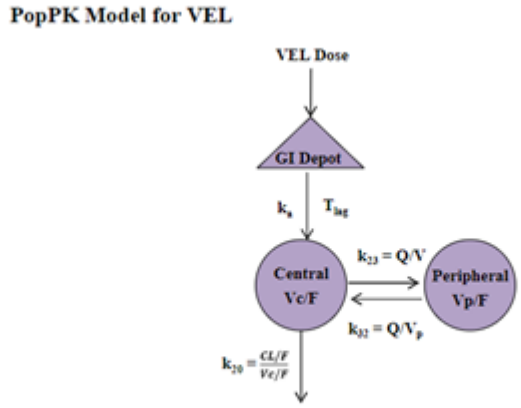
* RSE is defined as the SE divided by the absolute value of the estimate (θ) × 100% for nontransformed parameters and as SE × 100% for log-transformed parameters.

Source: sof-rum053-gof-final-20190706.R

VEL popPK model development

A previous popPK model developed for VEL based on adult data was used as a starting point. The model was a 2-compartment model with first-order absorption, first-order elimination from the central compartment, and an absorption lag time (ALAG) (Figure 2). The model was updated using the updated dataset with data from Study GS-US-342-1143 added. The effect of WT on CL/F and Vc/F were included using fixed allometric exponents of 0.75 and 1, respectively. No additional covariates were included in the updated model. Bootstrap resampling techniques were used to evaluate the model stability and confidence interval (CI) of the final parameter estimate (N=1000) (Table 6).

Figure 2 Population PK Model Diagram for VEL



GI = gastrointestinal; k_a = first-order absorption rate constant; k_{20} = elimination rate constant; k_{23} = rate constant from central to peripheral; k_{32} = rate constant from peripheral to central; CL/F = apparent central oral clearance; PopPK = population pharmacokinetic; Q/F = apparent inter-compartmental clearance; Vc/F = apparent central volume; VEL = velpatasvir; Vp/F = apparent peripheral volume.

Table 4 Table x Comparison of final model estimates and bootstrap results for VEL

Comparison of Final Model Estimates and Bootstrap Results for VEL

Parameter	Parameter Description	Final PopPK Model Estimates [RSE%]	Bootstrap Final Model Median [2.5th, 97.5th Percentiles]	SIR Median [2.5th, 97.5th Percentiles]
$\exp(\theta_1)$	Apparent oral clearance for VEL, CL/F (L/hr)	23.5 [5]	22.6 [9.71;25.8]	23.5 [21.7;25.7]
$\exp(\theta_2)$	Apparent central volume for VEL, Vc/F (L)	25.3 [13]	25.4 [19.5;33.3]	25.3 [20.2;30.7]
$\exp(\theta_3)$	Apparent inter-compartment clearance for VEL, Q/F (L/hr)	1.09 [48]	1.51 [0.405;11.9]	1.11 [0.598;1.92]
$\exp(\theta_4)$	Apparent peripheral volume for VEL, Vp/F (L)	577 [91]	713 [43.2;562000]	621 [163;3280]
$\exp(\theta_5)$	Absorption rate constant for VEL, k_a (hr^{-1})	0.116 [6]	0.116 [0.103;0.133]	0.116 [0.107;0.126]
$\exp(\theta_6)$	Absorption lag time for VEL, ALAG (hr)	0.457 [2]	0.458 [0.44;0.479]	0.457 [0.443;0.473]
—	Residual error for VEL (%)	79 [3]	79.5 [76.1;82.8]	79.5 [77.6;81.7]
$\omega_{CL/F}$	IIV of CL/F (%)	52 [27]	54.7 [38;113]	52.4 [45.4;61.3]
$\omega_{Vc/F}$	IIV of Vc/F (%)	83 [25]	80.9 [59.6;101]	84.1 [64;101]
ω_{Ka}	IIV of k_a (%)	21 [37]	20.3 [11.1;27.7]	21.1 [14.3;27.8]

CL/F = apparent central clearance; IIV = interindividual variability; k_a = first-order absorption rate constant; PopPK = population pharmacokinetic; Q/F = apparent intercompartmental clearance; RSE = residual squared error; SIR = sampling importance resampling; Vc/F = apparent central volume; VEL = velpatasvir; Vp/F = apparent peripheral volume.
Source: vel-gof-final-20190606.R

Model evaluation

The pcVPC evaluated the ability of the model to reproduce the distribution of the data despite variable dosing/sampling regimens. Prediction-corrected 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 residual variability.

The pcVPC of SOF plasma concentration-time profiles and its metabolites stratified by age group are shown in Figure 3. The pcVPC plots show that the final SOF joint PopPK model adequately predicted the central tendency and variability of plasma SOF, GS-566500, and GS-331007 concentrations in the paediatric patient population.

The pcVPC of VEL plasma concentration-time profiles are shown Figure 4. The pcVPC plots show that the final VEL PopPK model adequately predicted the central tendency and variability of the plasma VEL concentrations in the pediatric patient population. The 5th percentile associated with the second bin in both age categories is found to be outside the 95% CI of the model-predicted 5th percentile; this is explained by few individual observations that deviate significantly from the overall population at that specific time interval.

Figure 3 Prediction-corrected VPC of Plasma Concentration-Time Profiles for SOF and SOF Metabolites Stratified by Age Groups

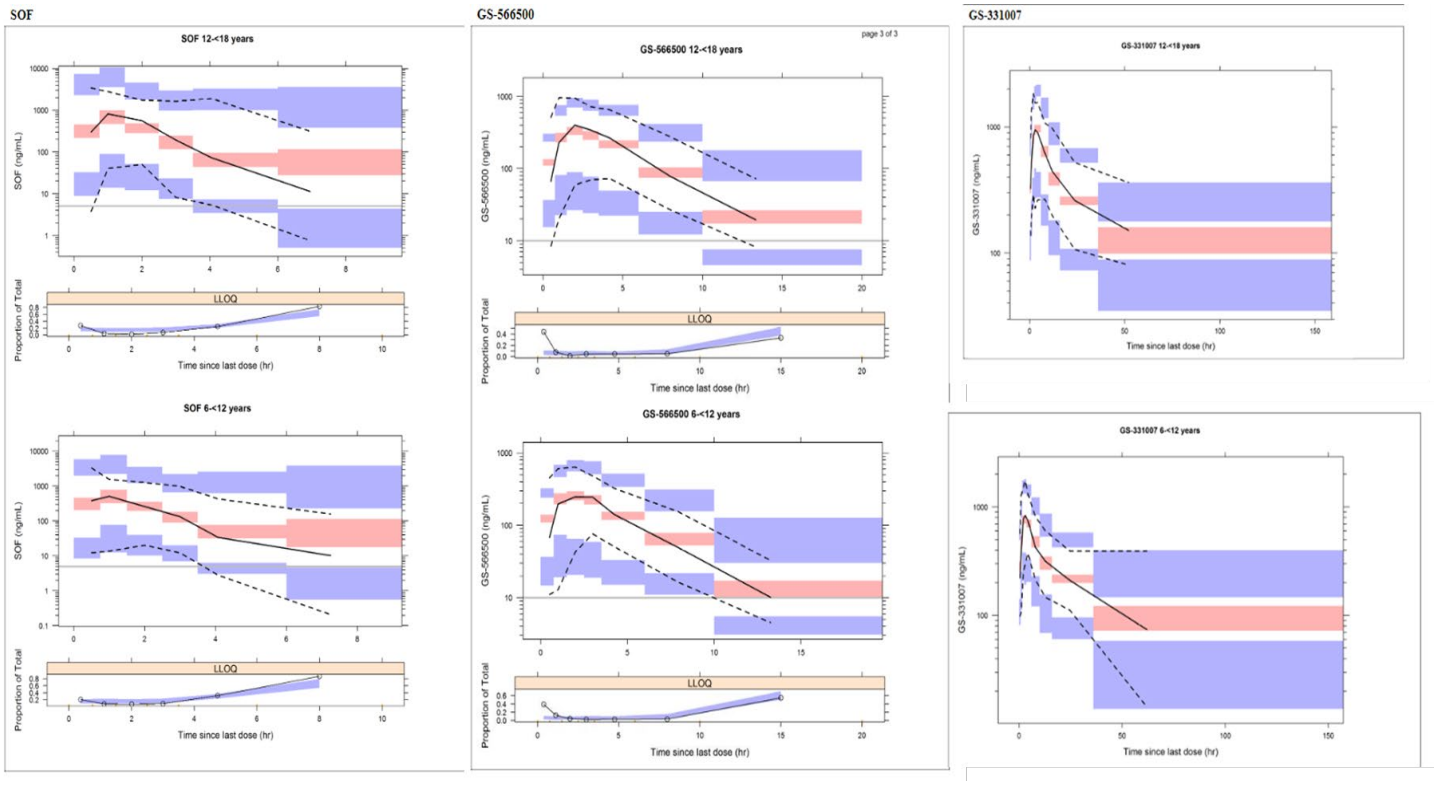
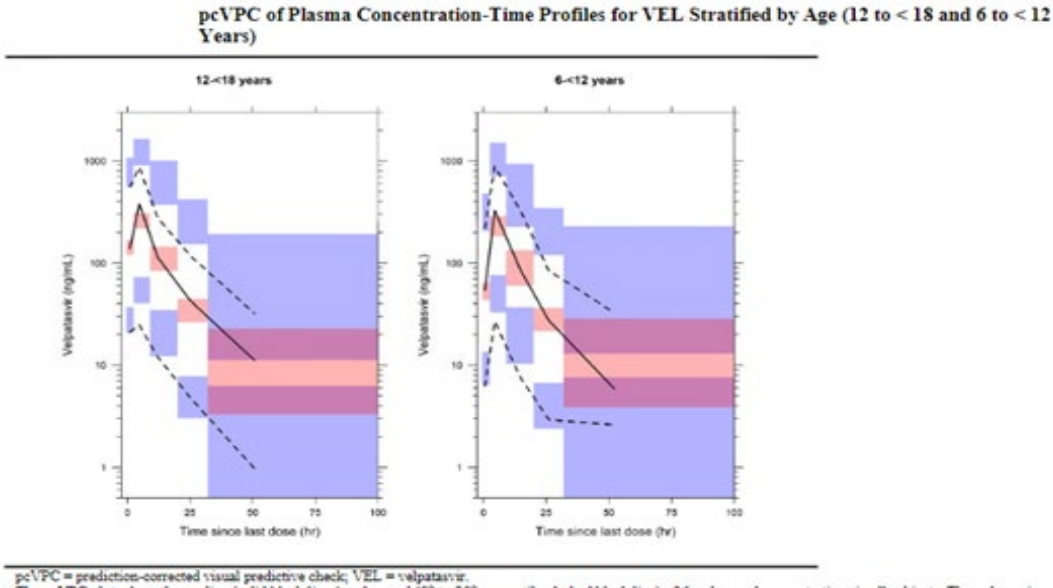


Figure 4 Prediction-corrected VPC of Plasma Concentration-Time Profiles for VEL Stratified by Age



pcVPC = prediction-corrected visual predictive check; VEL = velpatasvir.
The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the observed concentrations in all subjects. The red area is the 95% confidence interval of the simulated median, and the blue area is the 95% confidence interval of the simulated 5th and 95th percentiles. The pcVPC for adolescents (12 to < 18yr) is presented in the left panel, and the pcVPC for subjects 6 to < 12 years old is presented in the right panel.
Source: vel-gof-final-20190606.R

Simulated exposures for SOF/VEL in paediatric subjects following the proposed WT-band based dosing regimen were largely contained within the range of exposure observed in the adult Phase 2/3 population. Sofosbuvir and GS-331007 exposures were inversely correlated with WT, with a percent change in SOF/GS-331007 exposures ranging from −42.2% to +119% (relative to the median exposures) for subjects with extreme covariate values (ie, 5th and 95th WT percentile, respectively).

Figure 5 Simulated SOF Exposures by Proposed Weight Band-Based Dosing

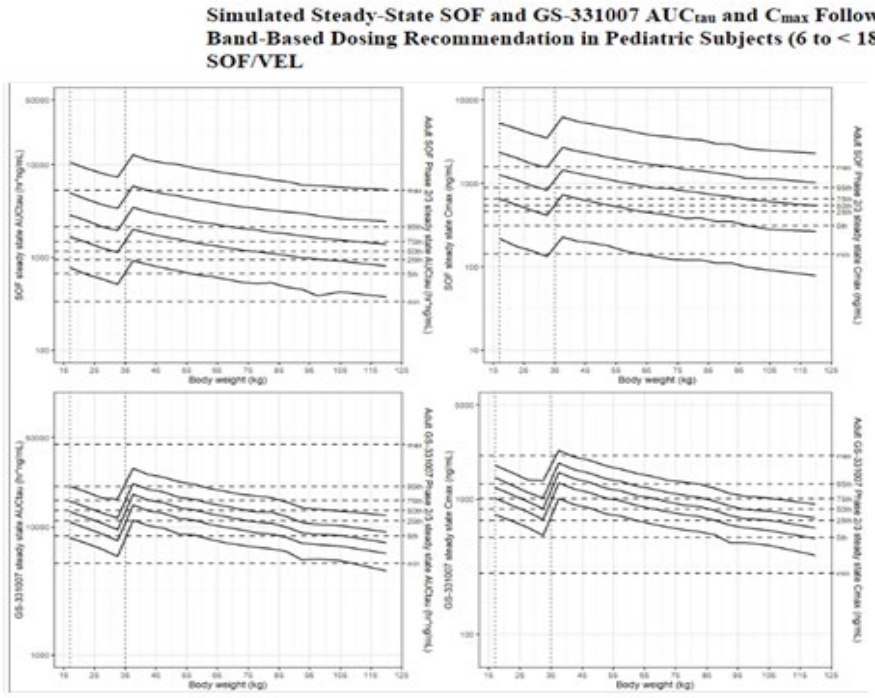
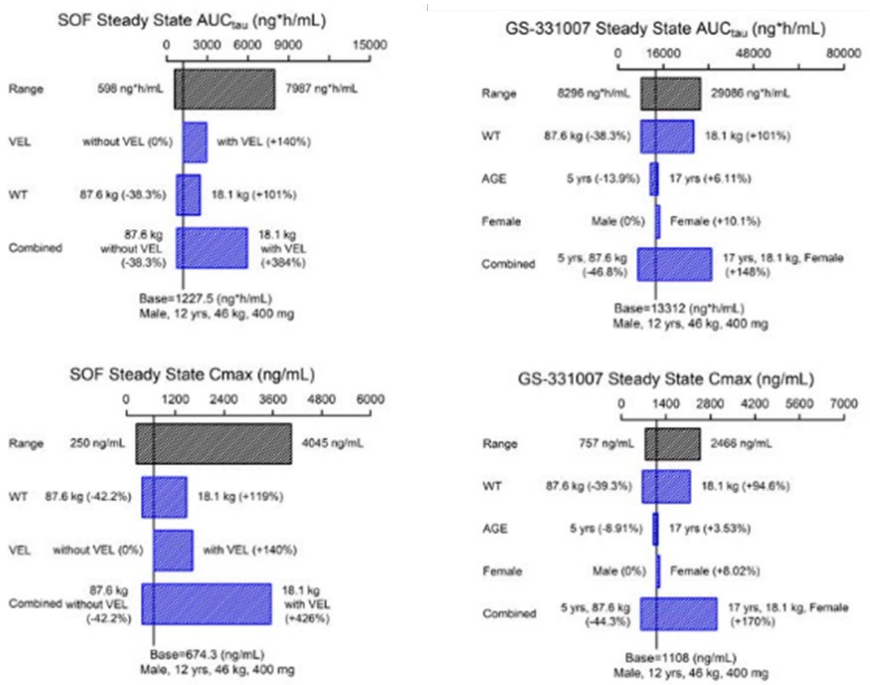
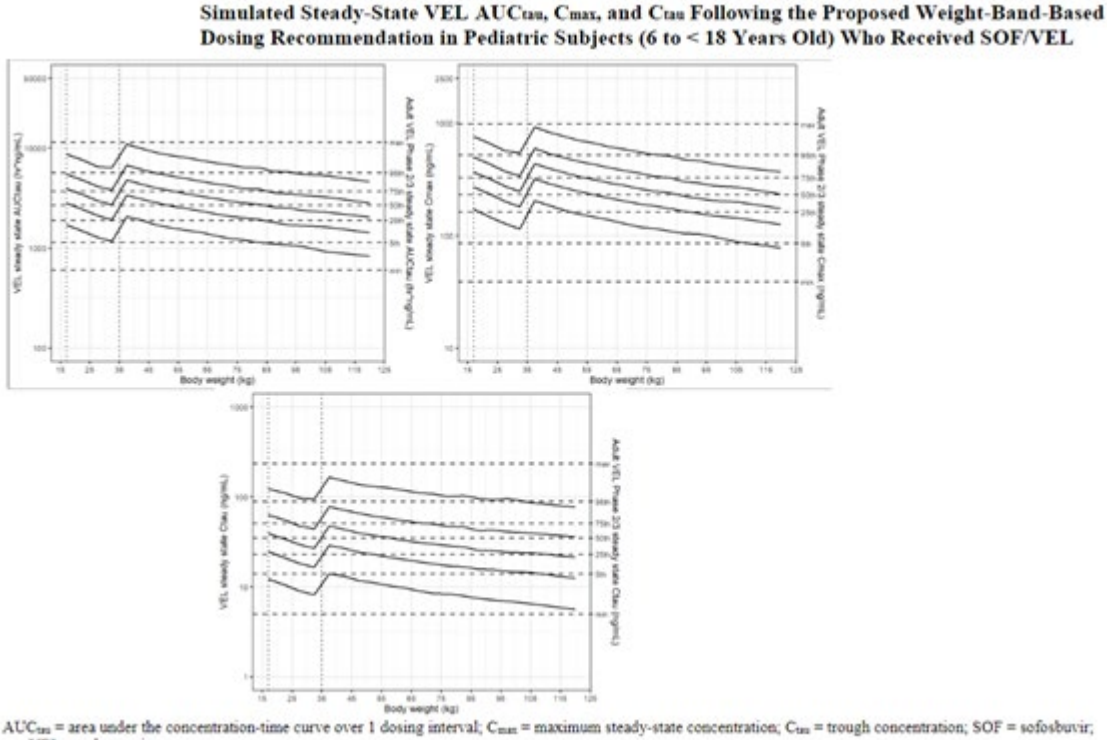


Figure 6 Sensitivity Plot for SOF and GS-331007 AUC_{tau} and C_{max}



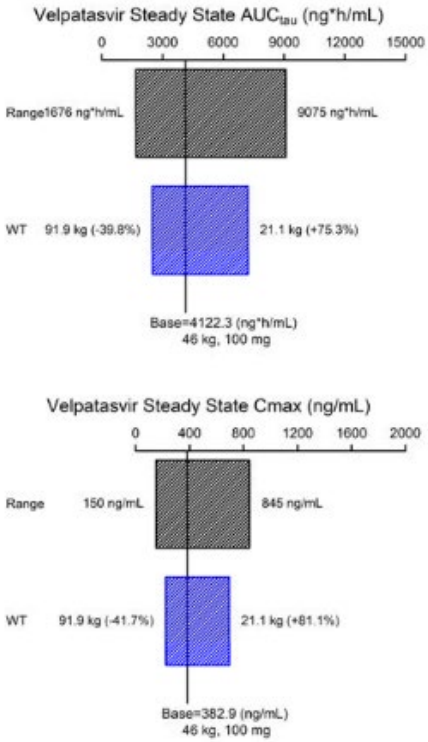
Velpatasvir exposures were inversely correlated with WT, with a percent change in VEL exposures ranging from −41.7% to +81.1% (relative to the median exposures) for subjects with extreme covariate values (ie, 5th and 95thWT percentile, respectively).

Figure *7 Simulated SOF Exposures by Proposed Weight Band-Based Dosing*



AUC_{tau} = area under the concentration-time curve over 1 dosing interval; C_{max} = maximum steady-state concentration; C_{tau} = trough concentration; SOF = sofosbuvir; VEL = velpatasvir.

Figure 8 Sensitivity Plot for VEL AUC_{tau} and C_{max}



Weight based dosing

Exposures within the adult range have been shown to be associated with high SVR rates, a favorable safety profile, and a lack of association between exposures and AEs.

During the ongoing procedure, Gilead proposes an update to the dosing regimen to allow administration of the SOF/VEL400/100mg tablet to children weighing ≥ 30kg in lieu of limiting treatment to those weighing ≥35 kg. Gilead believes the data presented herein supports the lower weight band and does not impact the safety profile of SOF/VEL in pediatric patients within the 30 to 35kg weight range. The CHMP agreed to assess this new data within the current extension. The simulations presented below and the accompanying changes to the SmPC to incorporate the 30 kg cut-point and ensure a greater proportion of children in the 30 to <35kg weight range have VEL Ctau values within the range of those observed in the adult population. Simulated exposures of SOF, GS-331007, and VEL in children weighing ≥30 kg administered SOF/VEL 400/100mg and children weighing 17 to <30 kg administered SOF/VEL 200/50mg are shown graphically in Figure 9, Figure 10, and Figure 11, respectively along with their corresponding comparison to the observed exposures in adults in Table 7, Table 8, and Table 9, respectively. These comparisons show that administration of the 400/100mg dose to children weighing >30 kg will decrease the percentage of children (in the applicable weight band of 30 to 40 kg) with Ctau values below the 5th percentile of adults from 12% to 4% for VEL. A modest increase is projected in the percentage of children with AUCtau and Cmax above the 95th percentile of adults for all analytes (SOF, GS-331007, and VEL).

Figure 9 Original and Proposed Epclusa Weight-Band Simulations for SOF

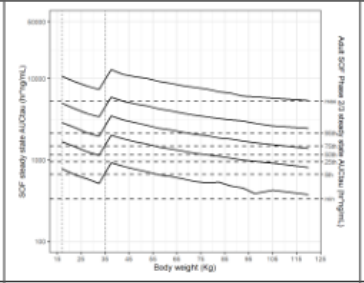
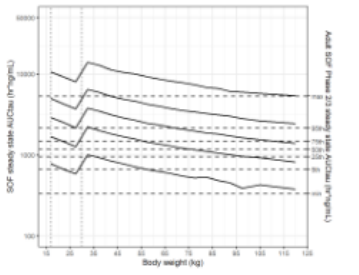
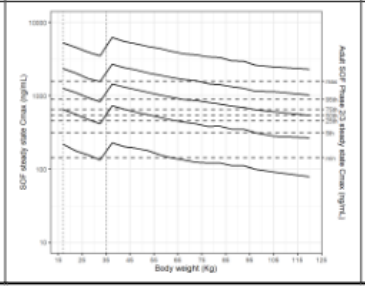
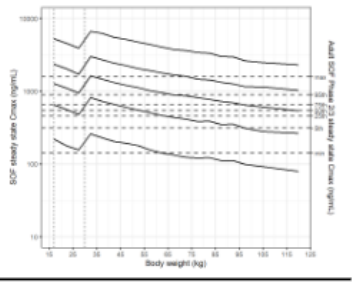
SOF PK Parameter	Original Weight-Band Simulation	Proposed Weight-Band Simulation
	• Children ≥35 kg: 400/100 mg • Children 17 to <35 kg: 200/50 mg	• Children ≥30 kg: 400/100 mg • Children 17 to <30 kg: 200/50 mg
AUC_{tau}		
C_{max}		

Table 5 Proposed Epclusa Weight Band Simulations for SOF AUC_{tau} and C_{max}

Table 1. Proposed Epclusa Weight Band Simulations for SOF AUC_{tau} and C_{max}

Weight Group	SOF PK Parameter	Percentage of Pediatric Subjects Outside of Adult Exposure (%)									
		Outside 90% Confidence Interval		Above Max		Above 95th Percentile		Below 5th Percentile		Below Min	
		17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg
17-20 kg	AUC_{tau}	67.8	67.8	22.4	22.4	64.3	64.3	3.5	3.5	0.3	0.3
20-30 kg		60.1	60.1	15.2	15.2	54.2	54.2	6	6	0.8	0.8
30-40 kg		**63.5**	**75.9**	**19.3**	**31.4**	**57.6**	**74.2**	**5.9**	**1.7**	**0.9**	**0.1**
40-50 kg		69	69	22.9	22.9	65.9	65.9	3.1	3.1	0.3	0.3
50-60 kg		63.5	63.5	18.4	18.4	58.8	58.8	4.7	4.7	0.5	0.5
60-70 kg		59.1	59.1	14.6	14.6	52.9	52.9	6.2	6.2	0.9	0.9
70-80 kg		55.9	55.9	11.1	11.1	47.2	47.2	8.7	8.7	1.3	1.3
80-90 kg		52.2	52.2	9	9	42	42	10.2	10.2	1.6	1.6
90-100 kg		51.4	51.4	6.8	6.8	37.7	37.7	13.7	13.7	3	3
100 kg+		47.8	47.8	5.6	5.6	31.8	31.8	16	16	3.4	3.4
17-20 kg	C_{max}	73.3	73.3	40.6	40.6	64.2	64.2	9.1	9.1	2.3	2.3
20-30 kg		68.7	68.7	31.8	31.8	55.5	55.5	13.2	13.2	3.8	3.8
30-40 kg		**70.4**	**77.8**	**34.6**	**48.9**	**56.9**	**70.4**	**13.5**	**7.4**	**4**	**1.8**
40-50 kg		73.5	73.5	40.1	40.1	63.2	63.2	10.3	10.3	2.7	2.7
50-60 kg		70.1	70.1	33.6	33.6	57	57	13.1	13.1	3.8	3.8
60-70 kg		67.2	67.2	28.4	28.4	51.1	51.1	16.2	16.2	5.2	5.2
70-80 kg		65.6	65.6	24	24	47	47	18.6	18.6	6.5	6.5
80-90 kg		63	63	20.1	20.1	42	42	21	21	7.4	7.4
90-100 kg		60.9	60.9	16.2	16.2	36.7	36.7	24.2	24.2	8.5	8.5
100 kg+		61	61	12.8	12.8	32.2	32.2	28.8	28.8	10.9	10.9

Figure 10 Original and Proposed Epclusa Weight-Band Simulations for GS-331007

Figure 2. Original and Proposed Epclusa Weight-Band Simulations for GS-331007

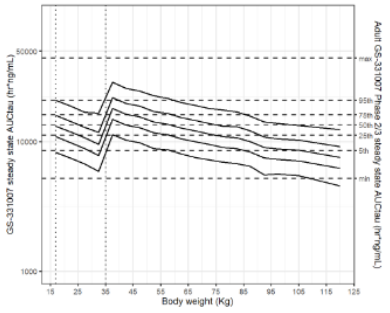
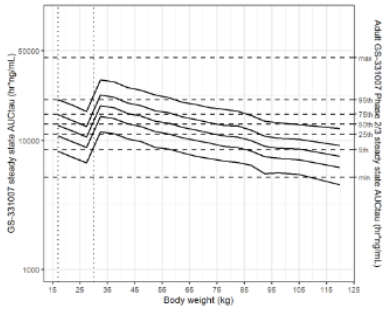
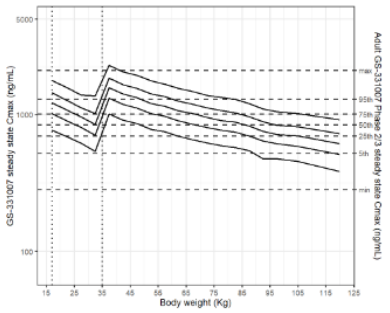
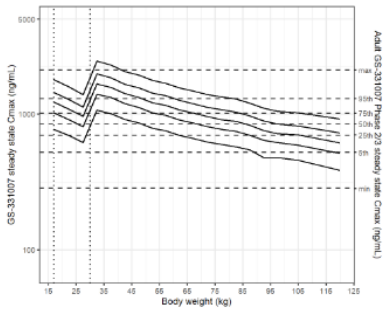
GS-331007 PK Parameter	Original Weight-Band Simulation	Proposed Weight-Band Simulation
	• Children ≥35 kg: 400/100 mg • Children 17 to <35 kg: 200/50 mg	• Children ≥30 kg: 400/100 mg • Children 17 to <30 kg: 200/50 mg
AUC_{tau}		
C_{max}		

Table 6 Proposed Epclusa Weight Band Simulations for GS-331007 AUC_{tau} and C_{max}

Weight Group	GS-331007 PK Parameter	Percentage of Pediatric Subjects Outside of Adult Exposure (%)									
		Outside 90% Confidence Interval		Above Max		Above 95th Percentile		Below 5th Percentile		Below Min	
		17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg
17-20 kg	AUC_{tau}	11.5	11.5	0	0	5.2	5.2	6.3	6.3	0	0
20-30 kg		18.2	18.2	0	0	1.6	1.6	16.6	16.6	0.4	0.4
30-40 kg		**34.3**	**33.5**	**0**	**0.1**	**14.8**	**33.1**	**19.5**	**0.4**	**1**	**0**
40-50 kg		17.8	17.8	0	0	16.4	16.4	1.5	1.5	0	0
50-60 kg		11.8	11.8	0	0	7.5	7.5	4.2	4.2	0	0
60-70 kg		12.3	12.3	0	0	3.2	3.2	9.2	9.2	0.1	0.1
70-80 kg		17.8	17.8	0	0	1.4	1.4	16.4	16.4	0.3	0.3
80-90 kg		26.4	26.4	0	0	0.6	0.6	25.8	25.8	0.7	0.7
90-100 kg		45.1	45.1	0	0	0.2	0.2	44.9	44.9	3.2	3.2
100 kg+		57.7	57.7	0	0	0.1	0.1	57.7	57.7	7	7
17-20 kg	C_{max}	40.8	40.8	0.7	0.7	40.7	40.7	0.1	0.1	0	0
20-30 kg		17.5	17.5	0.1	0.1	16.7	16.7	0.8	0.8	0	0
30-40 kg		**41.4**	**80.4**	**5.1**	**13.7**	**39.2**	**80.4**	**2.2**	**0**	**0**	**0**
40-50 kg		58.1	58.1	2.7	2.7	58.1	58.1	0	0	0	0
50-60 kg		35.2	35.2	0.5	0.5	35.1	35.1	0.1	0.1	0	0
60-70 kg		18.7	18.7	0.1	0.1	18.2	18.2	0.5	0.5	0	0
70-80 kg		9.3	9.3	0	0	8	8	1.4	1.4	0	0
80-90 kg		6.2	6.2	0	0	3.2	3.2	3	3	0	0
90-100 kg		9.6	9.6	0	0	0.5	0.5	9.1	9.1	0	0
100 kg+		20.6	20.6	0	0	0.3	0.3	20.3	20.3	0.3	0.3

Figure 11 Original and Proposed Epclusa Weight-Band Simulations for VEL

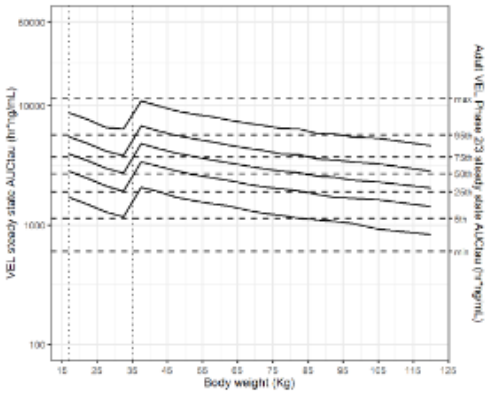
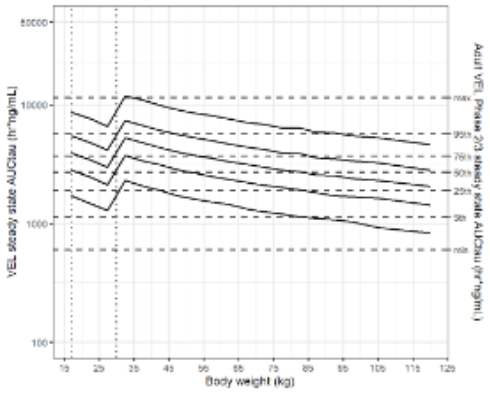
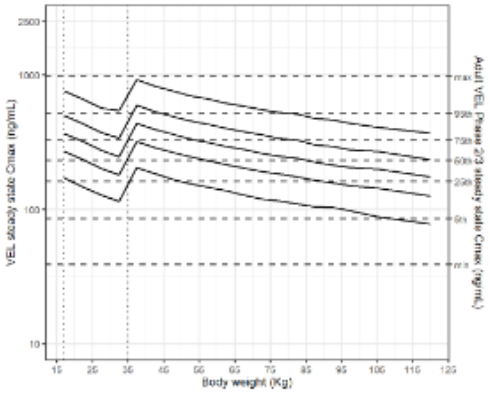
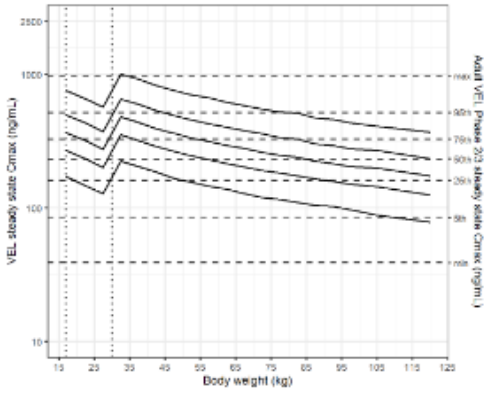
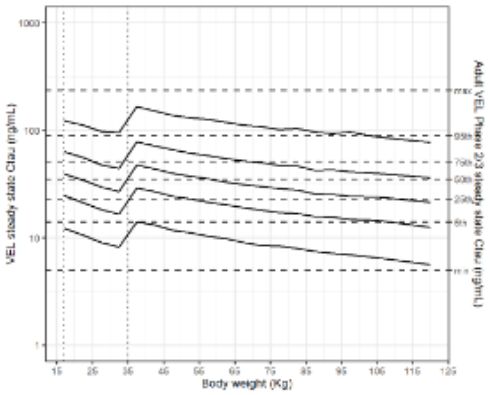
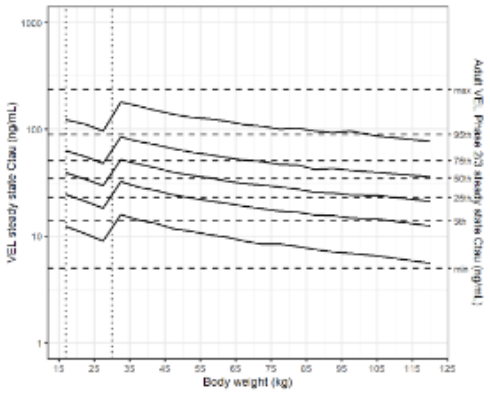
VEL PK Parameter	Original Weight-Band Simulation	Proposed Weight-Band Simulation
	• Children ≥35 kg: 400/100 mg • Children 17 to <35 kg: 200/50 mg	• Children ≥30 kg: 400/100 mg • Children 17 to <30 kg: 200/50 mg
AUC_{tau}		
C_{max}		
C_{tau}		

Table 7 Proposed Epclusa Weight Band Simulations for VEL AUC_{tau}, C_{max} and C_{tau}

Weight Group	VEL PK Parameter	Percentage of Pediatric Subjects Outside of Adult Exposure (%)									
		Outside 90% Confidence Interval		Above Max		Above 95th Percentile		Below 5th Percentile		Below Min	
		17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg
17-20 kg	AUC_{tau}	23.1	23.1	1.1	1.1	22.4	22.4	0.7	0.7	0	0
20-30 kg		14.7	14.7	0.4	0.4	12.7	12.7	2	2	0.1	0.1
30-40 kg		**23.8**	**41**	**2**	**5**	**21.3**	**40.8**	**2.5**	**0.2**	**0.1**	**0**
40-50 kg		27.5	27.5	2.1	2.1	26.9	26.9	0.6	0.6	0	0
50-60 kg		20.2	20.2	1.1	1.1	19	19	1.2	1.2	0	0
60-70 kg		15.3	15.3	0.6	0.6	13.1	13.1	2.2	2.2	0.1	0.1
70-80 kg		12.8	12.8	0.2	0.2	9.2	9.2	3.6	3.6	0.2	0.2
80-90 kg		11.8	11.8	0.2	0.2	6.6	6.6	5.2	5.2	0.2	0.2
90-100 kg		11.9	11.9	0.2	0.2	4.6	4.6	7.3	7.3	0.4	0.4
100 kg+		14.6	14.6	0	0	2.8	2.8	11.8	11.8	1.1	1.1
17-20 kg	C_{max}	22	22	1.2	1.2	21.9	21.9	0.1	0.1	0	0
20-30 kg		11.5	11.5	0.4	0.4	11	11	0.4	0.4	0	0
30-40 kg		**20.2**	**39.5**	**1.8**	**4.7**	**19.5**	**39.5**	**0.7**	**0**	**0**	**0**
40-50 kg		23.6	23.6	1.6	1.6	23.6	23.6	0.1	0.1	0	0
50-60 kg		15.2	15.2	0.7	0.7	15	15	0.2	0.2	0	0
60-70 kg		10.1	10.1	0.3	0.3	9.5	9.5	0.6	0.6	0	0
70-80 kg		6.9	6.9	0.1	0.1	5.9	5.9	1	1	0	0
80-90 kg		5.2	5.2	0.1	0.1	3.7	3.7	1.6	1.6	0	0
90-100 kg		5	5	0	0	2.4	2.4	2.6	2.6	0	0
100 kg+		7.1	7.1	0	0	1.2	1.2	5.9	5.9	0.1	0.1

Weight Group	VEL PK Parameter	Percentage of Pediatric Subjects Outside of Adult Exposure (%)									
		Outside 90% Confidence Interval		Above Max		Above 95th Percentile		Below 5th Percentile		Below Min	
		17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg	17 to <35 kg and ≥35 kg	17 to <30 kg and ≥30 kg
17-20 kg	C_{tau}	19.3	19.3	0.6	0.6	12.2	12.2	7	7	0.2	0.2
20-30 kg		20.2	20.2	0.3	0.3	7.8	7.8	12.4	12.4	0.6	0.6
30-40 kg		**24.3**	**25.6**	**1**	**2.1**	**12.2**	**21.5**	**12.1**	**4.1**	**0.7**	**0.1**
40-50 kg		22	22	1.2	1.2	15.1	15.1	7	7	0.3	0.3
50-60 kg		21.5	21.5	0.9	0.9	11.7	11.7	9.8	9.8	0.4	0.4
60-70 kg		21.8	21.8	0.5	0.5	9.1	9.1	12.7	12.7	0.7	0.7
70-80 kg		23.9	23.9	0.4	0.4	7.5	7.5	16.5	16.5	1.1	1.1
80-90 kg		25.9	25.9	0.2	0.2	6.3	6.3	19.6	19.6	1.4	1.4
90-100 kg		28.3	28.3	0.2	0.2	6	6	22.3	22.3	2.1	2.1
100 kg+		31.3	31.3	0.2	0.2	4.2	4.2	27.1	27.1	3.1	3.1

2.4.3. Discussion on clinical pharmacology

A population PK analysis was performed where all sofosbuvir data has been pooled, and a joint model of SOF and metabolites and a separate popPK model for VEL were developed. Adequate non-linear mixed effects modelling methods have been used.

There is a slight overprediction of SOF trough concentration in the paediatric subjects, which would result in more conservative estimates of exposures with respect to safety. There is also a slight underprediction of the

absorption phase for GS-566500 in the 12 < 18-year-old age group. However, overall the model diagnostics indicate that the sofosbuvir model adequately represents the observed data in the paediatric population and the model is considered adequate to use in simulations to support the dose selection.

The population PK simulated exposures metrics have been compared with the corresponding observed exposure ranges in the adult population.

The CHMP considered that the AUC and Cmax for SOF are higher than the adult exposures. However, much higher exposures in adults with renal impairment have been observed with no dose adjustment required. Overall, given the safety profile of SOF and associated metabolites, the exposure levels in the paediatric population are acceptable.

Simulated velpatasvir exposures were similar to the ones in adults. Patients with extreme covariate values had 81 % higher Cmax and 75 % higher AUC. Based on a favourable clinical safety profile, these changes in exposure for VEL are not deemed clinically significant.

During this procedure, the applicant proposed an update to the dosing regimen to allow administration of the SOF/VEL400/100mg tablet to children weighing ≥ 30kg instead of the previously proposed ≥35 kg weight cut off. The simulations for the new proposed weight cut-off show that administration of the 400/100mg dose to children weighing >30 kg will decrease the percentage of children in the weight band of 30 to 40 kg with Ctau values below the 5th percentile of adults from 12% to 4% for VEL. Since dosing in the paediatric study was based on age rather than weight, low weight subjects in group 1 achieved high exposures, and high weight subjects in group 2 quite low exposures. The high exposures seen in children at low weight subjects did not seem to be associated with any specific safety concerns in this study. Overall, the slightly higher exposures expected with regards to this change of weigh cut off from ≥ 30kg instead of ≥35 kg, are considered unlikely to have a relevant impact on the safety profile, having in mind the wide therapeutic index for sofosbuvir and velpatasvir. To simplify the safety follow-up, a specific subsection on AEs reported for the paediatric population will be presented in coming PSURs, with adequate narratives to allow for a proper assessment.

2.4.4. Conclusions on clinical pharmacology

Overall, the population PK analysis provides an adequate description of sofosbuvir and velpatasvir exposure in children 6-18 years of age. Given the range of weight bands studied and no data on posology in patients below 17 kg, the CHMP considered that the product use should be limited to patients aged 6 years and older and weighing at least 17 kg.

2.5. Clinical efficacy

2.5.1. Main study

The present application is based on the results of an ongoing study GS-US-342-1143, a phase 2, open-label, multicentre, multi cohort study to investigate the safety and efficacy of sofosbuvir/velpatasvir in adolescents and children with chronic HCV infection. The study is evaluating SOF/VEL in children aged 3 to <17 years old, the data presented with this application pertain to ages 12 to <17 (group 1) and 6 to <12 (group 2).

2.5.1.1. Methods

- **Study participants**

Main inclusion criteria

- Parent or legal guardian was able to provide written informed consent prior to any screening evaluations
- Chronic HCV infection (≥ 6 months) as documented by prior medical history or liver biopsy, with HCV RNA ≥ 1000 IU/mL at screening
- Treatment naive to an approved or experimental DAA based regimen; prior IFN-based theray with or without an HCV protease inhibitor was allowed)

Main exclusion criteria

- Current or prior history of clinical hepatic decompensation
- The following laboratory parameters at screening:
  a) International normalized ratio (INR) > 1.2×upper limit of normal (ULN)
  b) Platelets<50,000/mm3
  c) Albumin<3.5 g/dL
  d) Alanine aminotransferase (ALT)> 10 ×ULN
  e) Aspartate aminotransferase (AST) > 10 ×ULN
  f) Direct bilirubin > 1.5 ×ULN
  g) eGFR <90 mL/min/1.73m2, as calculated by the SchwartzFormula
- Chronic liver disease of a non-HCV etiology
- Coinfection with HIV or HBV co-infection
- Substantial psychiatric illness
- Clinically relevant alcohol or drug abuse within 12 months of screening.

- **Treatments**

Group 1 (12-<17 years): SOF/VEL 400/100 mg qd, taken as one 400/100 FDC tablet or as two 200/50 mg FDC tablets. The selection of tablet strength was based on a swallowability assessment using matching placebo tablets prior to start of therapy, where 92/102 were able to swallow the adult size tablet, and the other 11 were able to swallow the 200/50 mg tablet.

Both tablets are film-coated; the adult tablet is diamond shaped of dimensions 20 x 10 mm, the 200/50 mg tablet is oval-shaped and 14 x 7 mm.

Group 2 (6-<12 years): SOF/VEL 200/50 mg qd, taken as one 200/50 mg FDC tablet, or as oral granule formulation (4 x 50/12.5-mg packets). The children completed a swallowability assessment at screening up to Day 1 using placebo tablets, to determine which formulation to choose; 71/73 subjects were treated with tablets, 2 with the oral granule formulation.

Disposition

All enrolled subjects that received at least 1 dose of study drug and were included in both the Safety Analysis Set and FAS. All but 1 subject of the enrolled subjects completed study treatment, this 1 subject prematurely discontinued study treatment due to pregnancy, table x below.

Table 8 Subject disposition

Subject Disposition	Group 1 12-<17 SOF/VEL (400/100 mg)	Group 2 6-<12 SOF/VEL (200/50mg)
Screened	103	73
Not Enrolled	1	0
Enrolled	102	73
Enrolled Never Treated	0	0
Safety Analysis Set	102	73
FAS	102	73
Lead-in Phase PK Analysis Set	17	20
Completed Study Treatment	101 (99%)	69 (95%)
No FU-4 HCV RNA Assessment	3	1
With FU-4 but no FU-12 HCV RNA	1	2
Discontinued Study Treatment	1	4 (5%)
No FU-4 HCV RNA Assessment	0	2
With FU-4 but no FU-12 HCV RNA	0	0
Reason for Premature Discontinuation		
Pregnancy	1	
AE		2
Investigator´s discretion		1
Lack of efficacy		1

In group 1 (12-18 years old), all but 1/102 treated subjects completed the study regimen. In group 2 (6-12 years old) 4/73 subjects discontinued treatment, two of whom due to adverse events,

Baseline characteristics are summarised in the table 11 below. The gender mix is quite even in both groups. The majority had normal transaminases at baseline. The study subjects had very mild HCV-infection; HCV-infection has a mild course in the paediatric ages in the vast majority of cases.

Table 9 Baseline characteristics

Characteristic		Group 1 SOF/VEL FDC (400/100 mg) (102)	Group 2 SOF/VEL FDC (200/50 mg) (73)
Age at Baseline (Years)			
	Mean (SD)	15 (1.9)	8 (1.6)
	Median	15	8
	Q1, Q3	13, 17	7, 9
	Min, Max	12, 17	6, 11
Male gender		50 (49%)	35 (48%)
Race	White	74 (72%)	66 (90%)
	Asian	11 (11%)	1 (1.4%)
	Black or African American	9 (8.8%)	4 (5.5%)
	Other	5 (4.9%)	2 (2.7%)
	American Indian or Alaska Native	2 (2.0%)	0
	Not Disclosed	1 (1.0%)	0
	Native Hawaiian or Pacific Islander	0	0
Weight	Mean (kg)	60.6	29.7
	Median	56.9	26.7
	Q1, Q3	47.5, 67.0	23.0, 35.0
	Min, Max	21.5, 146.5	18.4, 77.9
Cirrhosis			
Yes		0	0
No		40 (39.2%)	31 (42.5%)
Not Determined		62 (60.8%)	42 (57.5%)
Baseline ALT Category≤ 1.5 x ULN		(80.4%)	47 (64.4%)
Treatment-Experienced		22/102 (21.6%)	4/73 (5.5%)

Table 10 Table x Baseline weight

Baseline Weight (kg) Group 1, 12<17 years (400/100 mg, adult dose)		
25 subjects in interval	21-47 kg	25 subjects aged 12-13
25	47-57 kg	25 subjects aged 13-15
25	57-67 kg	50 subjects aged 15-17
25	67-147 kg	

Baseline Weight (kg) Group 2, 6-<12 years given tablet 200/50 mg		
17 subjects in interval	18-23 kilo	17 subjects aged 6-7
17	23-27 kilo	17 subjects aged 7-8
17	27-35 kilo	17 subjects aged 8-9
17	35-78 kilo	17 subjects aged 9-11

2.5.1.2. Results

Two subjects in group 2 did not take tablets but were treated with the granule formulation. The efficacy evaluation therefore concerns 71/73 in group 2. The SVR12 rate is high, in line with that seen in the adult population.

Table 11 Efficacy outcomes

	Group 1 12-<17 years 400/100 mg (N = 102)	Group 2 6-<12 years 200/50 mg (FDC tablet) (N=71)
SVR12	97/102 (95.1%)	66/71 (93.0%)
Overall Virologic Failure	1/102	1/71 (1.4%)
Relapse	1/102	0/69
Completed Study Treatment	0/101	-
Discontinued Study Treatment	1/1	-
On-Treatment Virologic Failure	0/102	1/71 (1.4%)
Other	4/102 (3.9%)	4/71 (5.6%)

Group 1: 5/102 patients did not achieve SVR12. 1 subject relapsed, she stopped treatment at day 29 due to pregnancy. 4 subjects were categorized as "Other". 3 subjects were "lost to follow-up". All 3 completed therapy, had rapid viral responses and were negative at EOT, but did not come back for the planned follow-up visits EOT. 1 subject (TE) was pending a posttreatment Week 12 visit at the time of analysis.

Group 2: 5/71 subjects did not achieve SVR12. 1 had "non-response" (10 year-old white female). Although compliance was 100% according to pill count, viral load over time indicating low adherence (including stop of therapy for a period from week 1 to week 4). 4 subjects were categorized as "other". As for group 1, 3 were "lost to follow-up": all 3 completed therapy, with rapid adequate response to treatment. One did not return after EOT, 2 had SVR4 and did not return for the 3 months follow-up. The fourth subject did not return after the BL visit.

2.5.2. Discussion on clinical efficacy

While the study treatments (dosing) were based on age, the dosing schedule that is proposed as part of the application, is based on weight, which is considered a more adequate parameter. This is supported by the weight baseline data in the in the two age groups. Of note, at least some subjects in group 2 (200/50 mg qd) had a baseline weight where the adult dose (400/100 mg) would appear more adequate. However, the study

data showed no true virological failures. Conversely, some subjects in group 1, with a low weight, were given the adult dose. However, the safety data in the study were re-assuring and did not raise any concerns.

In summary, although it is apparent that dosing by weight is more reasonable, the overall data confirm the wide therapeutic index of the drugs, both efficacy and safety wise.

The SVR12 rate in adolescents (dosed 400/100 mg) and children 6- <12 (dosed 200/50 mg) was around 95%, fully in line with results obtained in adults, despite the fact that a proportion of the younger group (with a higher weight for their age) achieved a lower dose.

The children studied had mild disease characteristics; however, this is considered typical of the paediatric population. Different HCV subtypes were represented, which the CHMP considered reassuring.

2.5.3. Conclusions on the clinical efficacy

The CHMP concluded that SOF/VEL is effective in the treatment of chronic HCV in children aged 6 years and older and weighing at least 17 kg.

2.6. Clinical safety

2.6.1. Patient exposure

Subjects 12 to < 18 Years

The mean (SD) duration of exposure to SOF/VEL for subjects 12 to < 18 years old in Group 1 was 12.0 (0.80) weeks, and 99.0% of subjects (101 of 102) received SOF/VEL for 12 weeks.

Subjects 6 to < 12 Years

The mean (SD) duration of exposure to SOF/VEL for subjects 6 to < 12 years old in Group 2 was 11.7 (1.90) weeks, and 94.5% of subjects (69 of 73) received SOF/VEL for 12 weeks.

2.6.2. Adverse events

Treatment was to be well tolerated, and severe AEs distinctly uncommon. In group 1, 1 subject experienced Grade 3 suicidal ideation, and 1 experienced Grade 3 suicidal ideation and worsening of bipolar disorder II and Grade 4 suicide attempt; these AEs were assessed as not related. In group 2, the grade 3 AE concerns a case with auditory hallucinations, judged as related to treatment by the investigator.

Table 12 Number (%) of subjects experiencing AEs

Number (%) of Subjects Experiencing	Group 1 12-<17 (102)	Group 2 6-<12 (73)
Any Adverse Event	77 (75.5%)	59 (80.8%)
Grade 3	1 (1%)	1 (1.4%)
Grade 4	1 (1%)	0
Treatment-Related AE	41 (40.2%)	25 (34.2%)
Grade ≥3 Treatment-Related Adverse Event	0	1 (1.4%)
Serious AE	2 (2.0%)	2 (2.7%)
Treatment-Related	0	1 (1.4%)
AE Leading to stopping therapy	0	2 (2.7%)
AE Leading to interruption	0	3 (4.1%)
All Deaths	0	0

Table 13 Adverse Events Reported for ≥ 5% of Subjects

Group 1 (400/100 mg) 12-<17 (N = 102)		Group 2 (200/50 mg) 6-<12 (N = 73)	
Event	frequency	Event	frequency
Any Adverse Event	77 (75.5%)	Any Adverse Event	59 (80.8%)
Headache	30 (29.4%)	Vomiting	12 (16.4%)
Fatigue	22 (21.6%)	Cough	11 (15.1%)
Nausea	17 (16.7%)	Headache	11 (15.1%)

Abdominal pain upper	10 (9.8%)	Abdominal pain	9 (12.3%)
Pyrexia	10 (9.8%)	Fatigue	9 (12.3%)
Cough	9 (8.8%)	Pyrexia	8 (11.0%)
Dizziness	9 (8.8%)	Nasopharyngitis	7 (9.6%)
Oropharyngeal pain	9 (8.8%)	Rash	7 (9.6%)
Vomiting	9 (8.8%)	Upper RTI	7 (9.6%)
Diarrhoea	7 (6.9%)	Diarrhoea	6 (8.2%)
Abdominal pain	6 (5.9%)	Epistaxis	6 (8.2%)
Nasal congestion	6 (5.9%)	Nausea	5 (6.8%)
Nasopharyngitis	6 (5.9%)	Arthralgia	4 (5.5%)
		Nasal congestion	4 (5.5%)
		Rhinorrhoea	4 (5.5%)

Table 14 Treatment-Related Adverse Events Reported for > 1 subject

Group 1 12-<17 (N = 102)		Group 2 6-<12 (N = 73)	
Event	frequency	Event	frequency
Any Treatment-Related AE	41 (40.2%)	Any Treatment-Related AE	25 (34.2%)
Headache	18 (17.6%)	Fatigue	8 (11.0%)
Fatigue	16 (15.7%)	Headache	5 (6.8%)
Nausea	15 (14.7%)	Abdominal pain	3 (4.1%)
Dizziness	5 (4.9%)	Abdominal pain upper	3 (4.1%)
Abdominal pain	4 (3.9%)	Diarrhoea	3 (4.1%)
Abdominal pain upper	4 (3.9%)	Irritability	2 (2.7%)
Diarrhoea	2 (2.0%)	Product use issue	2 (2.7%)

2.6.3. Serious adverse event/deaths/other significant events

There were two cases of SAEs in group 1, both considered treatment unrelated. One subject, with attention deficit/hyperactivity disorder (treated with lisdexamfetamine, Vyvanse) experienced a Grade 3 SAE of suicidal ideation, assessed as not related to study drug on Day 55, which resolved on Day 57 without interruption of study drug. One patient had an ongoing Grade 3 SAE of exacerbated bipolar disorder II on Day 1 of the study and a Grade 3 SAE of suicidal ideation on Day 69 of the study, which resolved 12 days later on Day 80. On Day 75, the subject had a Grade 4 SAE of suicide attempt. The SAEs were assessed as not related to study drug and there was no interruption of the study drug. Medical history of ongoing bipolar disorder II, frequent suicidal thoughts, anorexia, bulimia, emotional abuse, attention deficit hyperactivity disorder, and oral and receptive language disorders, and a prior history of suicidal ideation, suicide attempt, and sexual abuse.

There were two cases of SAEs in group 2. One subject with a medical history of ongoing chronic constipation experienced a Grade 2 SAE of constipation on Day 3, which was assessed as not related to study drug. Resolved day 5, after in-ward treatment. The SAE was considered treatment unrelated. One subject with a medical history of asthma, seasonal allergies, allergic shiners experienced "negative thoughts" (grade 2) and a grade 3 SAE of "auditory hallucinations", assessed as related to study drug by the investigator.

AEs and drug levels

Sofosbuvir levels in the paediatric patients in study GS-US-342-1143 are well covered by levels seen in patients with severe renal impairment, studied without particular safety issues. The main metabolite is not higher in the paediatric population than in adults with normal renal function.

Velpatasvir levels are higher in the lower age spans in group 1 and 2 as compared to levels seen in the adult population. These levels are not increased in the adult special populations (neither in those with severe renal impairment (not studied at large), nor in those with severely impaired liver function (studied at large), i.e. "not covered" by adult safety data.

Summary statistics of SOF and VEL exposure parameters by the presence or absence of common AEs by age groups are shown in Figure 12, Figure 13, Figure 14 and Figure 15 below (SOF for group 1 and 2, followed by VEL for group 1 and 2, respectively). No relevant differences in exposures by presence or absence of the common AEs (headache, fatigue, nausea, vomiting or cough) are seen.

Figure 12 Summary statistics of SOF exposure by the presences of common AEs (group 1)

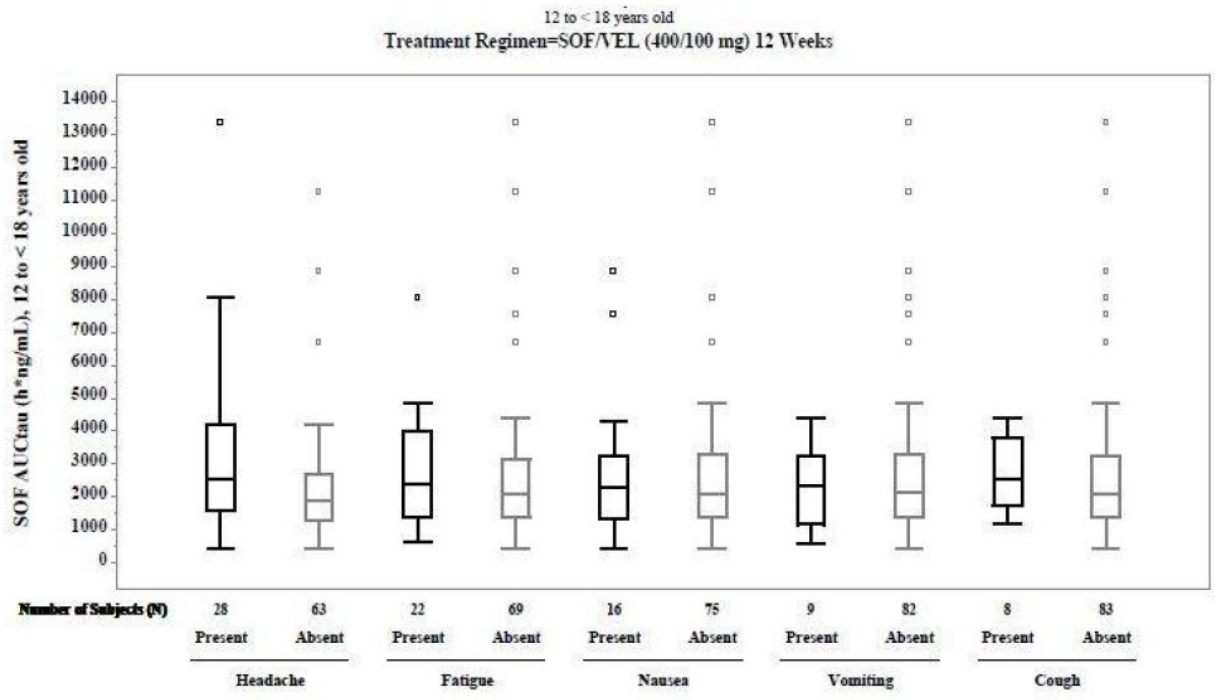


Figure 13 Summary statistics of SOF exposure by the presences of common AEs (group 2)

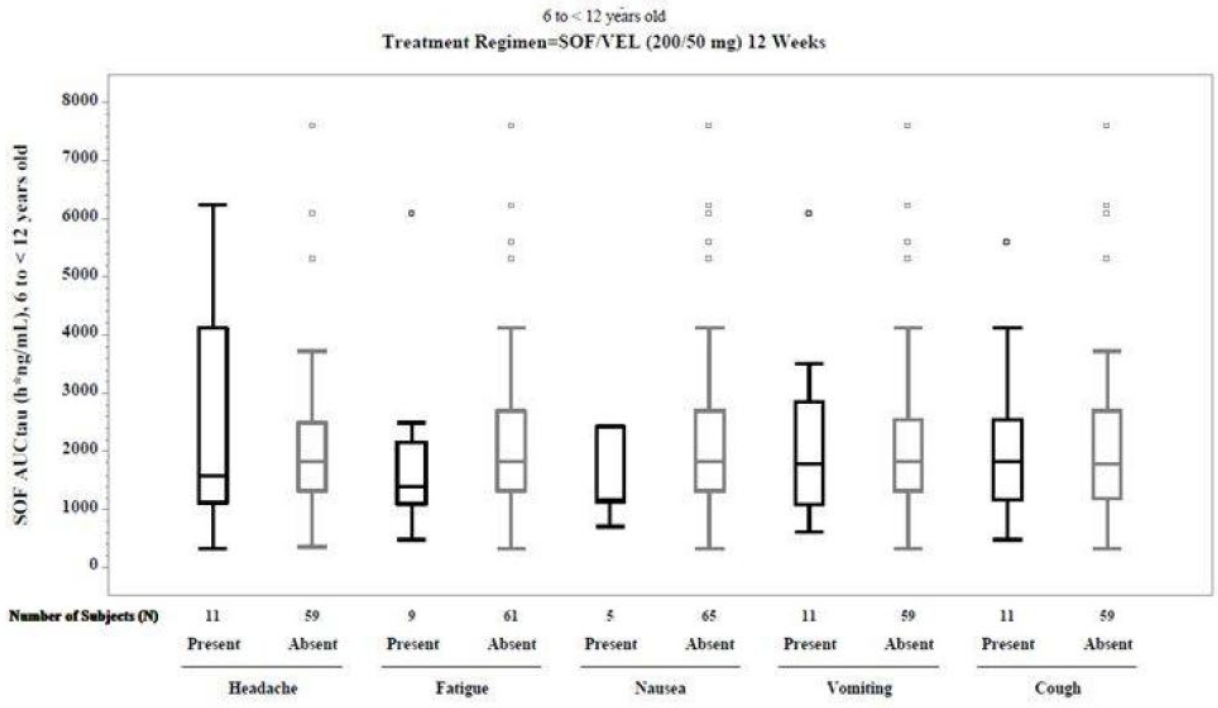


Figure 14 Summary statistics of VEL exposure by the presences of common AEs (group 1)

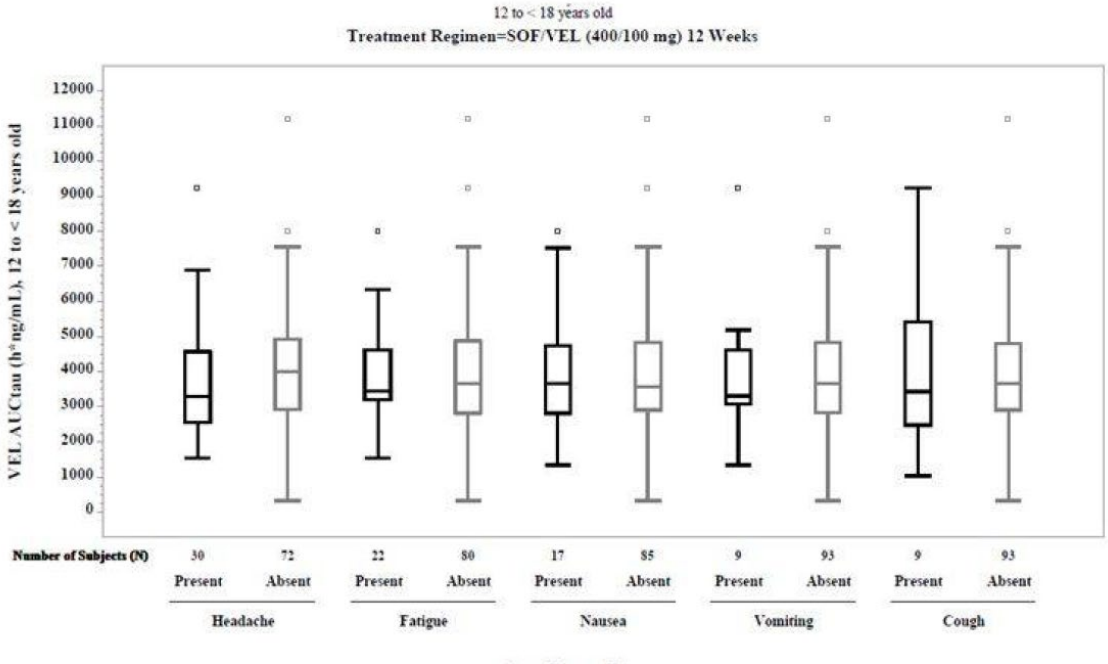
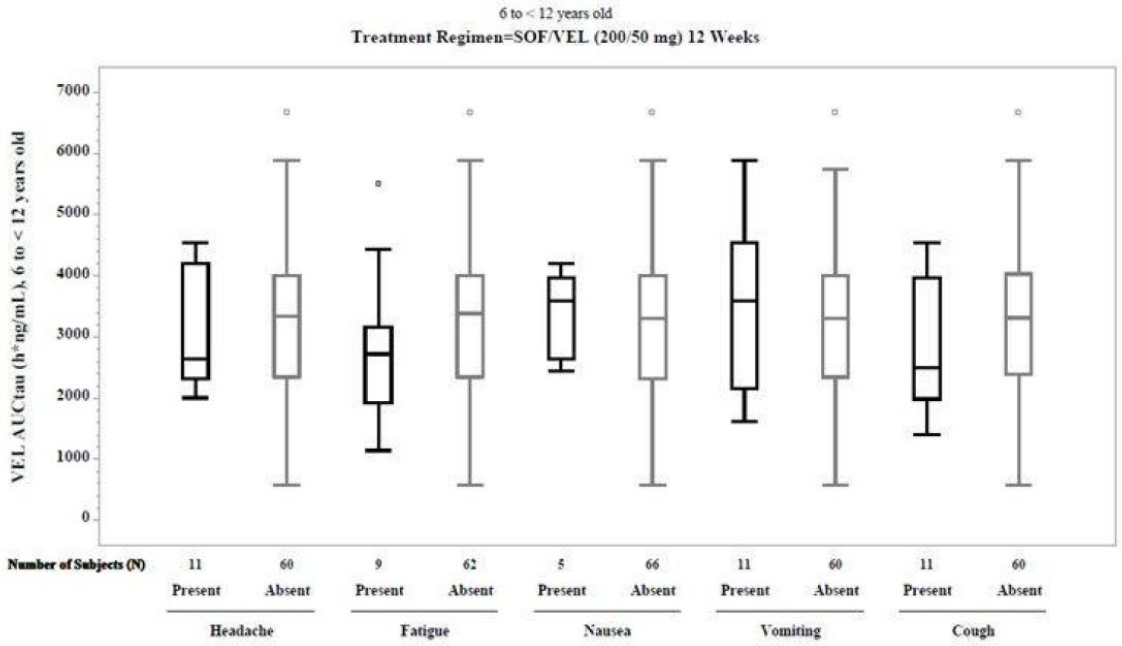


Figure 15 Summary statistics of VEL exposure by the presences of common AEs (group 2)



Psychiatric AEs and drug levels

Considering the more severe psychiatric events reported in a small number of subjects, details for subjects with reported Psychiatric Disorders are summarized in Table 16 and Table 17 below. With the exception of the cases already discussed, events are of grade 1, with a scattered pattern of terms, and without any indication for a disproportional proportion with markedly high VEL exposures.

Table 15 Subjects in group 1 (12-17 years) with AE reports of psychiatric disorders

age/gender	Problem	grade	Related/not related	days	AUC tau (1)	AUC TAU (2)
14/M	Sleep disorder	1	NR	?-63	-	2803.0
14/M	Sleep disorders	1	related	76-83	-	4838.0
13/F	Suicidal ideation (narrative previous page)	3	NR	55-57	-	4304.0
12/F	Emotional sensitivity	1	related	26-41	-	1396.0
13/M	ADHD	1	NR	44-	-	3228.0
14/F	Selective eating disorder	1	NR	29-	-	3435.0
17/F	Irritability	1	related	1-28	-	4725.0
15/F	Hearing voices	1	NR	?	-	1552.0
14/F	Narratives previous page	2/3			3237.0	3237.0

Also in group 2 psychiatric AEs were fairly infrequent, predominantly of grade 1.

Table 16 Details on all subjects in group 2 (6- <12 years) with AE reports of psychiatric disorder

age/ gender	Problem	grade	Related/not related	days	AUC tau (1)	AUC TAU (2)
8/M	worsening ADHD	grade 2	NR	29-	2603.2	2569.0
8/F	sleep disturbance	grade 1	related	19-22	-	1181.0
	Dizzy		related	49-57		
6/M	sleep walking	grade 1	NR	51-51	-	4202.0
8/M	worsening oppositional defiant	grade 1	related	4-6	-	2757.0
7/F	Irritability	grade 1	related	6-	2436.6	4195.0
11/F	worsening anxiety	grade 1	NR	18-	-	1413.0
8/F	increased emotions	grade 1	related	18-57	3135.2	3389.0
6/F	increased fear of being alone	grade 1	NR	?	-	4407.0
8/M	irritability	grade 1	related	3-28	-	5531
6/F	unpleasant thoughts	grade 2	related		7343.4	5743.0
	auditory hallucinations	grade 3	related			

2.6.4. Laboratory findings

When looking at maximum graded toxicity below, it should be noted that no clinically meaningful changes from baseline in hemoglobin, reticulocytes, neutrophils, lymphocytes, or platelets were observed for subjects 12 to < 18 years old (Table 18). The grade 3 Hemoglobin concerns a subject with thalassemia, the grade 3 neutrophils concern subjects with low neutrophils at baseline, grade 3 CK followed heavy exercise and grade 3 glucose a subject with diabetes.

Similarly, no clinically meaningful changes from baseline in hemoglobin, reticulocytes, neutrophils, lymphocytes, or platelets were observed for subjects 6 to < 12 years old, and no grade 3 or 4 max lab toxicity was seen in this group.

Table 17 Laboratory findings by toxicity grade

Parameter	Group 1 12-<18	Group 2 6-<12
Maximum Post dose Toxicity Grade	102	71
Grade 1	35 (34%)	24 (34%)
Grade 2	4 (4%)	3 (4%)
Grade 3	5 (5%)	0
Grade 4	0	0
Hemoglobin	102	71
Grade 1	4	1
Grade 2	1	0
Grade 3	1	0
Grade 4	0	0
Lymphocytes	70	Not provided
Grade 1	0	
Grade 2	0	
Grade 3	0	
Grade 4	0	
Neutrophils	102	71
Grade 1	2	4 (6%)
Grade 2	2	0
Grade 3	2	0

Grade 4	0	0
Platelets	102	71
Grade 1	2	0
Grade 2	1	0
Grade 3	0	0
Grade 4	0	0
ALT	102	71
Grade 1	1	0
Grade 2	0	1
Grade 3	0	0
Grade 4	0	0
ALP	102	71
Grade 1	1	0
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0
GGT	102	71
Grade 1	0	1
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0
BIL (total)	102	71
Grade 1	3	0
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0
CK	102	71
Grade 1	1	0
Grade 2	0	0
Grade 3	1	0
Grade 4	0	0
Creatinine	102	71
Grade 1	0	0
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0
Lipase	102	71
Grade 1	3	1
Grade 2	0	1
Grade 3	0	0
Grade 4	0	0
Glucose (Hyperglycemia)	102	71
Grade 1	14 (14%)	8 (11%)
Grade 2	2	1
Grade 3	1	0
Grade 4	0	0
Glucose (Hypoglycemia)	102	71
Grade 1	7	2
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0

Discontinuation due to adverse events

No adolescent subjects (group 1) discontinued or interrupted therapy due to AEs. Two subjects in group 2 discontinued due to AEs: one refused to take the treatment and the other case concerned the subject with auditory hallucinations, discussed above.

2.6.5. Discussion on clinical safety

SOF/VEL therapy was well tolerated in study GS-US-342-1143, despite the study design (dosing by age) which led to quite high exposures in some subjects (e.g. low weight for age, dosed 400/100 mg). Grade 3 or 4 AEs were very uncommon and only in one case (grade 3) considered related to therapy. Laboratory tests did not reveal any issues of concern.

In the 173 treated with the tablet formulation, serious adverse events were reported in 4 patients.

In age group 12-17 (n= 102) there were 1 case of suicidal ideation, not considered related to treatment by the investigator, which was endorsed by the CHMP, as there were alternative causes for the event. The other event concerned suicidal ideation and a suicide attempt. The investigator assessed these events as potentially triggered by starting hep C therapy and being part of the study, but not to the treatment per se. That conclusion was endorsed by the CHMP. In age group 6- <12 (n= 71 plus), an event of "negative thoughts (grade 2), followed by "auditory hallucinations" was reported in one patient, but the CHMP concluded that there was not sufficient evidence to conclude on a causal relationship. Update of the Product Information was not deemed necessary at this point.

With regards to psychiatric AEs overall, terms other than "headache" are uncommon, and with no distinct pattern.

2.6.6. Conclusions on the clinical safety

The safety assessment of Epclusa in paediatric patients aged 6 years and older is based on data from a phase 2, open-label clinical study that enrolled patients who were treated with sofosbuvir/velpatasvir for 12 weeks. The adverse reactions observed were consistent with those observed in clinical studies of Epclusa in adults.

The CHMP recommended that future PSURs of Epclusa should include a specific subsection on AEs reported in the paediatric population, with adequate narratives to allow for a meaningful assessment.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns

A new version of the RMP (version 6, dated 19 June 2020) was submitted as part of this application. The summary of safety concerns, below, is unchanged as compared to previous version and this is endorsed.

Summary of Safety Concerns

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
	Development of resistance
	Safety in patients with previous HCC

Pharmacovigilance plan

The MAH has updated the study title and milestones for HCC emergence post-authorisation safety study (PASS). In addition, the date of "submission of updated joint protocol" regarding De Novo DAA PASS was amended from 29 March 2019 (date of version 3 of the protocol) to 02 April 2019 (date of submission), in Table 2 1. Ongoing and Planned Additional Pharmacovigilance Activities and Table 3 1. Ongoing and Planned Additional Pharmacovigilance Activities.

The proposed changes are endorsed.

Summary table of additional pharmacovigilance activities:

Table 3-1. 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 interim and final reports	Interim study report Q3 2021 Final study report Q2 2023
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				
GS-US-248-0123 A Long Term Follow-up Registry Study of Subjects Who Did Not Achieve Sustained Virologic Response in Gilead-Sponsored Trials in Subjects with Chronic Hepatitis C Infection	To evaluate HCV viral sequences and the persistence or evolution of treatment-emergent viral mutations in subjects who fail to achieve an SVR after treatment with a Gilead oral antiviral containing regimen in a previous Gilead-sponsored hepatitis C study	*Missing information*: Development of resistance	Submission of final report	Final study report July 2020
De Novo DAA PASS: A study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated	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

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
with direct acting antivirals for chronic hepatitis C			Final Report of Study Results	12 months after end of data collection

Risk minimisation measures

The MAH has updated the study title for HCC emergence PASS for the important potential risk "Emergence of HCC", in line with changes made in Part III of the RMP. The Part VI, Annex 2 (Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program) and Annex 3 (Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan) were updated accordingly, in line with the updated Part III of the RMP.

Two minor improvements were also made in the RMP, addressing the following minor updates which were being requested for consistency purposes only:

- In Table 1 1 Planned and Ongoing Studies of Annex 2, the date of "submission of updated joint protocol" regarding De Novo DAA PASS was amended from 29 March 2019 (date of version 3 of the protocol) to 02 April 2019 (date of submission);

- In Annex 8 – Summary of changes to the risk management plan over time, the MAH has added the procedure number "EMEA/H/C/004210/X/0043/G" in the column "Approval date procedure" and the sentence "No changes to safety concerns." at the end of the subsection "Safety specification" of the column "Changes" of the update of the RMP (version 5.1).

This is endorsed.

Summary table of Pharmacovigilance and Risk Minimisation 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
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 of 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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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: Additional pharmacovigilance activities: None
Development of resistance	Routine risk minimization measures: None Additional risk minimization measures: None No risk minimization measures are considered necessary for the development of resistance at this time. Clinical data suggest that the presence of an NS5A RAV does not preclude successful retreatment.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Long term follow-up registry study of subjects who did not achieve sustained virologic response in Gilead-sponsored trials in subjects with chronic hepatitis C infection (GS-US-248-0123)
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

Conclusion

The CHMP and PRAC considered that the risk management plan version 6 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.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Epclusa (sofosbuvir / velpatasvir) 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

Around 70 million individuals worldwide are chronically infected with HCV. Around 3.5 million children aged 1 to 19 years has been estimated to be infected, mainly in low to middle income countries, including Pakistan, Egypt, Nigeria, China, and Russia (in order of decreasing prevalence).

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. In the general case, it takes decades to develop cirrhosis.

The HCV has significant genetic (RNA sequence) variability; 8 major genotypes have been identified: genotypes 1, 3 and 4 are the most prevalent globally.

3.1.2. Available therapies and unmet medical need

Highly effective DAA regimens and well tolerated DAA regimens have been available for adults for around 5 years. Some of them have recently been approved for the treatment of adolsecents and children. At present none of the regimens that are available have a pangenotypic effect; Epclusa is indicated for the treatment of HCV regardless of genotype.

3.1.3. Main clinical studies

GS-US-342-1143 is an ongoing study, evaluating SOF/VEL is adolescents (group 1), children aged 6 to <12 (group 2) and children aged 3 to <6 (group 3). The present application concerns group 1 and 2, where

adolescents were given the adult dose (400/100 mg qd) and those aged 6 to <12 half that dose (200/50 mg qd), provided by a new tablet. The treatment duration is the same as in adults, 12 weeks. A granule formulation has been developed for the very small ones (group 3); it was used by two subjects in group 2 who were not able to handle tablets, and those two subjects are not part of the efficacy evaluation.

Of note, since dosing was based on age rather than weight, low weight subjects in group 1 achieved high exposures, and high weight subjects in group 2 quite low exposures.

In line with the expected, the children/adolescents had mild HCV infection (no cirrhotic subjects, when this was evaluated); 80% of subjects in group 1, and two thirds in group 2 had a baseline ALT level < 1.5 x ULN.

3.2. Favourable effects

In practice all subjects achieved virological cure; SVR12 was achieved in 97/102 (95%) in group 1, and in 66/71 (93%) in group 2. The majority of those few not achieving SVR12 fulfilled treatment, had an adequate on-treatment response and undetectable HCV-RNA at end of treatment, but failed to come back for the week 12 follow-up visit. There was in practice no non-response or true relapse, despite the fact that some subjects achieved a low dose by weight (above).

3.3. Uncertainties and limitations about favourable effects

No uncertainties have been identified about favourable effects.

3.4. Unfavourable effects

The treatment was well tolerated. Reported AEs were mainly mild (grade 1 or 2). Grade 3 AEs were reported for 2/175 treated subjects (1 possibly related) and a grade 4 AE was reported for one subject (not deemed related). AEs leading to stopping therapy were reported for two subjects, both in group 2, related to 1) not accepting tablet and 2) a case defined as auditory hallucinations of questionable causality. There was no obvious difference in SOF or VEL exposures in cases with or without the most commonly reported potentially treatment related AEs (headache, fatigue, nausea), despite the fact that a substantial proportion of subjects achieved high exposures as a consequence of dosing by age. In summary, the safety profile in groups 1 and 2 was in line with that reported for adults.

3.5. Uncertainties and limitations about unfavourable effects

Adequate population PK analyses of SOF and selected metabolites, and VEL, respectively, has been performed and the models are considered adequate to provide predicted exposure metrics in the paediatric population. There is a slight overprediction of SOF trough concentration in the paediatric subjects, which would result in more conservative estimates of exposures with respect to safety.

Both SOF and VEL has a wide therapeutic index, both from an efficacy and safety perspective. A pragmatic approach has therefore been chosen on the basis of results obtained in groups 1 and 2 in study GS-US-342-1143, where the proposed dosing (200/50 mg qd for weights 17-30, and 400/100 mg (i.e. adult dose) for those above 30 kilo) results in higher exposures of SOF (but not major metabolite) and VEL in children at the lower end of the weight spans than that seen in adults. Having the well described efficacy and safety profiles

in mind, that is considered acceptable. Given the totality of knowledge on sofosbuvir and velpatasvir, this does not prompt any specific safety concerns.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

On basis of outcomes and PK in this fairly large paediatric study, and previous results in studies in adults, the proposed dosing schedule is supported. The higher exposures seen in children at low ends of the weight bands is not associated with any specific safety concerns. Of note, higher sofosbuvir exposures have been seen in studies of adults with severe renal insufficiency, for whom SOF/VEL is approved without dose adjustment.

The CHMP considered that there are no data on posology in patients weighing less than 17 kg. This has been reflected in section 4.1 of the SmPC.

3.6.2. Balance of benefits and risks

The described similarity of sofosbuvir, GS-331007, and velpatasvir PK in adults and children is considered sufficient to support the efficacy and safety results to the new paediatric population. The efficacy estimate (SVR12) showed a very high cure rate also in the paediatric setting and there were no indications of any age-specific safety concerns.

Given the natural course of chronic HCV infection in comparison to the high cure rate and favourable safety profile of SOF/VEL, the favourable effects outweigh the unfavourable effects.

3.7. Conclusions

The overall B/R of Epclusa is favourable.

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 Epclusa 200/50 mg film-coated tablets is favourable in the following indication:

- Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients aged 6 years and older and weighing at least 17 kg.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Epclusa 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 Epclusa, 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:	**Q2 2023**

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0150/2018 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 and IIIB

Extension of indication to include paediatric use in patients aged 6 years and older and weighing at least 17 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 6.0) is updated in accordance.

In addition, the MAH took the opportunity to implement minor editorial updates throughout the Product Information.