11 November 2021
EMA/CHMP/603027/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on group of an extension of marketing authorisation and an extension of indication variation

Epclusa

International non-proprietary name: sofosbuvir / velpatasvir

Procedure No. EMEA/H/C/004210/X/0056/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

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration of drug versus time curve of the drug
AE	adverse event
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
BCS	Biopharmaceutics Classification System
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
CQA	critical quality attribute
CSR	clinical study report
C_{tau}	observed drug concentration at the end of the dosing interval
DAA	direct-acting antiviral
EM€A	European Medicines Evaluation Agency
EU	European Union
FDC	fixed-dose combination
FDC1	oral granule formulation #1
FDC2	oral granule formulation #2
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
HCV	hepatitis C virus
HPLC	High performance liquid chromatography
ICH	International Conference for Harmonisation
IPC	In-process control
LDV	ledipasvir
LLOQ	lower limit of quantitation
N	number of subjects
NI	nucleoside inhibitor
NMT	Not more than
NOAEL	no-observed-adverse-effect level
NS	nonstructural protein (5A, 5B)
PAR	Proven acceptable range

Peg-IFN	pegylated interferon
Ph. Eur.	European Pharmacopoeia
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
RAV	resistance-associated variant
rBA	relative bioavailability
RBV	ribavirin
RH	Relative humidity
RNA	ribonucleic acid
Rpm	Rotations per minute
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Medicinal Product characteristics
SOF	sofosbuvir (Sovaldi)
SOF/VEL	sofosbuvir/velpatasvir (coformulated; Epclusa)
SVR, SVRxx	sustained virologic response, sustained virologic response at "xx" weeks following completion of all treatment
US	United States
UV	ultraviolet
VEL	velpatasvir
VEL SDD	velpatasvir spray-dried dispersion
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 8 February 2021 a group of variation(s) consisting of extensions 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 pharmaceutical form (coated granules in sachet) associated with strengths 200mg/50mg and 150mg/37.5mg. The new presentations are indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients 3 years of age and older. The extension application is grouped with a type II variation (C.I.6.a) to include paediatric use in patients 3 years of age and older to the existing presentations of the 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 7.1) is updated in accordance.
In addition, the MAH took the opportunity to implement minor updates and corrections throughout the Product Information.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0150/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0150/2018 was completed.

The PDCO issued an opinion on compliance for the PIP P/0150/2018.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. 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 Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Ana Sofia Diniz Martins

The application was received by the EMA on	8 February 2021
The procedure started on	25 March 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 July 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	22 July 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	10 September 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	12 October 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 October 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Epclusa on	11 November 2021

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. Although less information is available about HCV in children, the global prevalence in 2018 of HCV infection in children from birth to 18 years has been estimated to be 0.13%, or 3.26 million children; over half (1.83 million) were aged 12 to 18 years {Schmelzer 2020}. Prevalence also varies by geographic location, with prevalence rates estimated to be 0.04% in Western Europe and 0.06% in the United States (US) compared with rates of 0.40% in Eastern Europe and up to 1.74% in Mongolia. Approximately 50% of the children with HCV infection were estimated to be living in Pakistan, China, India, and Nigeria.

2.1.1.2. 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 differs from that in adults since HCV infection in children is relatively benign. Most children chronically infected with HCV are asymptomatic or have mild nonspecific symptoms. However, cirrhosis has been reported in approximately 1% to 2% of adolescents and children with chronic HCV infection, and advanced liver disease and decompensated cirrhosis have been reported in children as young as 3 years of age and as early as 1 year after infection {Indolfi 2019}. Disease progression also may occur many years after the initial infection. At the time of a retrospective review of 1049 patients infected with HCV as children, cirrhosis developed in 32% of patients at a median of 33 years following diagnosis; 5% developed hepatocellular carcinoma (HCC), 4% had a liver transplant, and overall mortality was 3% {Modin 2019}.

2.1.1.4. Management

The goal of HCV treatment in both paediatric and adult populations is virus eradication, thereby preventing progressive hepatic inflammation, hepatic fibrosis, cirrhosis, and liver failure that result in the need for liver transplantation. The development and approval of safe and effective direct-acting antivirals (DAAs) have transformed the treatment and course of HCV infection. Several DAA therapies containing SOF, an HCV NS5B-directed inhibitor, have been approved for the treatment of adults with chronic HCV infection. Sovaldi and Harvoni (an FDC of ledipasvir [LDV] and SOF; LDV/SOF) also have been approved in the US and EU for

the treatment of patients 3 years of age and older, while Epclusa (an FDC of SOF and VEL) has been approved in the US and EU for children 6 years of age and older.

2.2. About the product

Epclusa combines SOF and VEL, inhibitors of NS5B and NS5A, respectively, to provide a 12-week treatment option for HCV-infected patients, regardless of HCV genotype, demographics and disease characteristics. Clinical studies of SOF/VEL in adults with chronic HCV infection demonstrated that the combination of SOF/VEL 400/100 mg administered for 12 weeks was well tolerated and resulted in high sustained virologic response (SVR) rates across HCV genotypes in adult subjects without cirrhosis or with compensated cirrhosis.

2.3. Type of Application and aspects on development

All studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP), applicable governmental regulatory requirements, and in compliance with the respective protocols. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312) and the European Community Directive 2001/20/EC.

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.

2.4. Quality aspects

2.4.1. Introduction

This application is a line extension to the already approved Epclusa 400 mg/100 mg and 200 mg/50 mg film-coated tablets. This line extension involves the addition of a new pharmaceutical form (coated granules in sachet) associated with strengths 200 mg/50 mg and 150 mg/37.5 mg. The new presentations are indicated for the treatment of chronic hepatitis C virus infection in patients 3 years of age and older. The extension application is grouped with a type II variation (C.I.6.a) to extend the indication of the already approved film-coated tablets to paediatric patients 3 years of age and older.

The finished product is presented as coated granules in sachet containing 150 mg/37.5 mg and 200 mg/50 mg of sofosbuvir and velpatasvir, respectively, as active substances.

Other ingredients are:

Granules core; copovidone (E1208), lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium (E468), colloidal anhydrous silica (E551) and magnesium stearate (E470b).

Film coating; hypromellose (E464), titanium dioxide (E171), macrogol (E1521), basic butylated methacrylate copolymer (E1205), talc (E553b), stearic acid (E570), colloidal anhydrous silica (E551) and L-tartaric acid (E334).

The product is available in unit-dose sachets comprised of polyester / aluminium / polyethylene film as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

This application is a line extension and contains the same active substances, sofosbuvir (SOF) and velpatasvir (VEL), 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.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Epclusa coated granules are an immediate-release taste-masked dosage form available as unit-dose sachets containing either 150 mg of SOF and 37.5 mg of VEL or 200 mg of SOF and 50 mg of VEL.

The granules are white to off-white, film-coated granules that are approximately 2 mm in diameter.

For the 150 mg/37.5 mg strength, unit-dose sachets contain 75 SOF/VEL coated granules.

For the 200 mg/50 mg strength, unit-dose sachets contain 100 SOF/VEL coated granules.

The PET/ALU/PE sachet has a length of 25 mm and a height of 70 mm.

The aim of pharmaceutical development was to develop an immediate release, multi-particulate, taste-masked oral granule formulation developed for paediatric patients 3 to < 6 years of age and patients that cannot swallow a tablet.

The sofosbuvir active substance in Epclusa coated granules is the same commercial active substance used in Sovaldi single-agent tablets and Harvoni, Epclusa, and Vosevi fixed-dose combination tablets. The velpatasvir active substance and velpatasvir spray-dried dispersion (VEL SDD) are the same as those used in Epclusa and Vosevi fixed-dose combination 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, but stability is pH-dependent. Sofosbuvir is most stable at pH 5 but is generally

susceptible to hydrolysis in aqueous media. Sofosbuvir is highly soluble but has low apparent intestinal permeability (BCS class III).

Design of the formulation approach and manufacturing process took into account the chemical and physical properties of both active ingredients. Commercial precedence for the co-formulation of sofosbuvir and velpatasvir has been established in Epclusa and Vosevi tablets.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. 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 this report.

Compatibility between the active substance and excipients was confirmed in stability studies.

The chosen excipients are suitable for use in paediatric patients. Due to the bitter taste of sofosbuvir, the granules are coated with a taste-masking film. The suitability of the proposed formulation in the proposed age group has been acceptably addressed. Palatability and acceptability of the SOF/VEL oral granule formulation was assessed in study GS-US-342-1143 throughout the duration of administration. The results of the study demonstrated that the SOF/VEL oral granules were palatable and the ease of taking the study drug was acceptable.

The impact of mixing the granules with soft foods prior to ingestion was also evaluated. Granules were mixed with various soft foods including chocolate pudding, chocolate syrup and vanilla ice cream. The granules were found to be chemically stable with no increase in degradation products after 1 hour. In addition, there was no impact on dissolution rate of either active substance.

A Ph. Eur. 2.9.3 Apparatus 2 (paddles) is used to perform dissolution testing. The dissolution medium was selected taking into account the physicochemical properties and stability of the two active substances.

The discriminatory power of the dissolution method was evaluated for key product attributes to discriminate clinically acceptable granules from meaningful variations to the manufacturing process and composition, such as non-bioequivalent granules (over-coated taste-mask layer), amorphous velpatasvir physically mixed with copovidone, and slowly dissolving granules without the disintegrant croscarmellose sodium. The discriminatory capability of the dissolution method was demonstrated for over-coated granules, use of amorphous velpatasvir and copovidone that were physically mixed in lieu of spray-dried and slowly disintegrating granules (oral granules manufactured without disintegrant). The data provided demonstrate that the dissolution method is appropriate as a quality control test that can discriminate between clinically relevant granules and granules with meaningful variations that would impact dissolution of sofosbuvir and velpatasvir.

Comparable dissolution performance is presented for sofosbuvir (SOF) and velpatasvir (VEL) from SOF/VEL oral granules (the test product) to SOF/VEL film-coated tablets (the reference product) in dissolution media at pH 2.0, 4.5, 6.8 and the dissolution media intended for finished product release (QC media). Similarity of drug dissolution was observed at all conditions, except at pH 6.8 where SOF release from oral granules is slower at earlier timepoints compared to SOF release from tablets. The slower dissolution of SOF from oral granules compared to tablets at pH 6.8 is by design and aligned with the target product profile of the oral granules.

The oral granules were shown to be bioequivalent to tablets in the relative bioavailability and food effect study GS-US-342-1142.

The formulation used during clinical studies is the same as that intended for marketing. The designated commercial SOF/VEL oral granule formulation was developed prior to initiating the Phase 2 clinical trial.

Development studies were conducted to define process parameter targets and proven acceptable ranges (PARs), and to establish the commercial SOF/VEL oral granule manufacturing process control strategy. The commercial process parameter targets identified in these evaluations were similar to those used to manufacture clinical, primary stability, and end-to-end lots of SOF/VEL oral granules. The VEL SDD commercial manufacturing process was defined for the adult strength Epclusa tablet and was not re-evaluated or modified during SOF/VEL oral granule development.

An initial risk assessment was performed to assess the likely impact of SOF/VEL oral granule manufacturing process unit operations on SOF/VEL oral granule critical quality attributes (CQAs). This assessment identified influential unit operations and led to the definition of process control strategies through targeted development studies.

This risk assessment identified dry granulation, compression, taste-mask coating, and the primary packaging processes as having the greatest potential influence on SOF/VEL oral granule CQAs.

The primary packaging is polyester / aluminium / polyethylene film. The material complies 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.

2.4.3.2. Manufacture of the product and process controls

The first part of the manufacturing process is production of the VEL-SDD. VEL SDD is produced and packaged according to the validated commercial manufacturing process initially developed, commercialized, and validated to support Epclusa SOF/VEL tablets, 400/100 mg, and is used to produce SOF/VEL coated granules without modification. Therefore, the process for manufacture of VEL SDD is not further discussed.

The subsequent steps of the manufacturing process comprise six main steps: blending of intra-granular excipients followed by roller compaction and milling; bending with extra-granular excipients and compression; sub-coating; taste-mask coating; addition of glidant; packaging. The process is considered to be a standard manufacturing process.

Process validation for the VEL-SDD step has already been completed in the context of the already approved Epclusa tablets. For the rest of the process, process validation will be conducted on 3 consecutive production scale batches prior to commercialisation, including the packaging step. The process validation scheme provided is considered suitable.

The in-process controls (IPC) are adequate for this type of manufacturing process and pharmaceutical form. Critical steps have been defined and the applied control strategy consisting of process controls, intermediate specifications as well as IPCs is suitable.

2.4.3.3. Product specification

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

The potential presence of class 1, 2A and select class 3 elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. No specific controls for elemental impurities are required in the finished product specification.

Acceptance limits for degradation products are established at release and during shelf-life for individual and total degradation products of sofosbuvir and velpatasvir. Selection of the specified degradation products was guided by release and stability data, development and forced degradation studies, as well as degradation products specified for other products containing sofosbuvir and velpatasvir. The acceptance limits were established based on safety data, batch release and stability data, and the acceptance limit in the respective active substance.

The acceptance limits during shelf-life were established taking into account the limits at release and the potential increase during storage. Since release and stability data are limited, the results from development studies of SOF/VEL oral granules stored in open containers and equilibrated to varying temperature and humidity conditions were used as guides for establishing the acceptance limits during storage.

The acceptance limits for each degradation product were established taking into consideration the limits applied and justified for velpatasvir, the limits for VEL SDD, the levels observed at release and on stability of the granules, and the levels qualified in toxicology studies.

The specified degradation products were qualified in toxicological studies TX-281-2042 and TX-281-2048, conducted in rats where exposure was ≥ 14 days. The qualified level was calculated from the NOAEL of 200 mg/kg/day, determined in the studies and the level of each degradation product present in the test article.

A nitrosamine risk assessment was performed according to principles outlined by EMA. The total potential nitrosamine content at the end of shelf-life was estimated by considering nitrosamine contaminants in the active substance, excipients, packaging components, and manufacturing facilities, as well as the potential formation of nitrosamine impurities during manufacturing and storage. No risk of nitrosamine contamination was identified. Additionally, no risk of nitrosamine formation was identified from the primary packaging components. This assessment indicates there is no risk of nitrosamine formation in SOF/VEL oral granules and therefore a test is not necessary.

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.

Batch analysis results were provided for 4 pilot to production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

2.4.3.4. Stability of the product

Stability data from three pilot scale batches of each strength of finished product stored for up to 12 months under long term conditions (30 ºC / 75% RH) and for up to six 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. In addition, data was generated for 1 batch of each strength of finished product manufactured with aged VEL SDD. The batches were tested according to a matrix design with 3 batches of each strength tested at each timepoint.

Samples were tested for appearance, water content, assay, degradation products, dissolution and microbiological examination. The analytical procedures used are stability indicating. No significant changes to any of the measured parameters were observed.

Stress studies have been carried out on SOF/VEL tablets at -20 °C for 4 weeks and 50 °C/ambient humidity for 2 weeks. The granules met the specification acceptance limits for all quality attributes evaluated.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. A small decrease in VEL assay and increase of a known VEL-related photodegradation product was observed in exposed samples. However, no changes to assay or degradation products were observed in packaged product, indicating that the primary packaging provides sufficient protection from light.

Based on available stability data, the proposed shelf-life of 2 years without specific storage conditions as stated in the SmPC (section 6.3 and 6.4) is acceptable.

2.4.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

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

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

This line extension concerns the addition of a new pharmaceutical form (coated granules in sachet) associated with strengths 200 mg/50 mg and 150 mg/37.5 mg, intended for patients 3 years of age and older.

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.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

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

2.5.1. Pharmacology

Epclusa is an all oral, once daily, fixed-dose combination (FDC) of sofosbuvir (SOF) and velpatasvir (VEL). SOF is an HCV non-structural protein (NS)5B polymerase nucleotide inhibitor that demonstrates potent in vitro inhibition of HCV replicon ribonucleic acid (RNA) replication. It is a nucleotide prodrug of 2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate that is converted to the active uridine analogue triphosphate form (GS 461203) within the hepatocyte. GS-461203 is incorporated by the HCV NS5B polymerase during HCV RNA replication, and acts to inhibit RNA replication via chain termination. SOF exhibits broad genotypic coverage in genotypes 1 to 6 replicon assays. VEL is an HCV NS5A inhibitor that has displayed potent in vitro inhibition of HCV RNA replication across genotypes 1 to 6 in replicon cell lines. The non-structural protein 5A (NS5A) protein of HCV is an essential viral protein that plays roles in both viral RNA replication and the assembly of HCV virions.

2.5.2. Toxicology

The toxicological dossier for SOF shows that exposure was well tolerated for up to 3 months in the mouse, 6 months in the rat, and 9 months in the dog with no likely relevant target organ toxicities for the clinical target population. The GI tract effects (emesis, soft faeces) and decrease in red cell indices/erythropoiesis observed in the dogs were minimal and not adverse. The GI tract is largely developed with major changes related to progressive adaptation to changes in diet by 2 years of age and the haematopoiesis mechanism fully active at birth (ICH S11). At the respective NOAELs, GS-331007 (nucleoside analogue metabolite) systemic exposure levels were 2/12- (male/female) fold higher, 5- (sexes combined) fold higher, and 6- (sexes combined) fold higher in mice, rats, and dogs, respectively, than those in adult subjects treated with the SOF/VEL. No adverse target organ toxicity has been identified with VEL in mice, rats, and dogs. Velpatasvir exposures at the NOEL/NOAELs from the 4-week mouse and chronic repeat dose toxicity studies in rats and dogs were approximately 74-, 5- and 10-fold higher (sexes combined) than clinical exposures in adult subjects treated with the SOF/VEL.

Sofosbuvir and VEL were negative for mutagenic potential in bacterial reverse mutation tests, negative in chromosome aberration tests using human peripheral blood lymphocytes, and negative in in vivo micronucleus assays. Thus, SOF and VEL can be considered nongenotoxic. The combination of both compounds is not expected to alter the genotoxicity profile compared to that of the individual agents. Sofosbuvir is not carcinogenic at exposure margins up to 15-fold and 9-fold in the 2-year mouse and rat studies, respectively. Velpatasvir was not carcinogenic in the 6-month rasH2 transgenic mouse and 2-year rat carcinogenicity studies at exposures at least 50-times and 5-times higher than human exposure, respectively. Thus, the combination of SOF and VEL is not expected to be carcinogenic.

Sofosbuvir and VEL did not have any adverse effects on fertility in rats. SOF has not shown significant adverse effects in reproductive and development studies. However, a possible teratogenic effect of VEL was indicated in rabbits where an increase in total visceral malformations was seen in exposed animals. The human relevance of this finding is not known. SOF and VEL had no adverse effects on behaviour, reproduction, or development of the juvenile offspring in the rat pre- and post-natal development study.

Sofosbuvir and VEL were considered non-irritants to skin and non-severe irritants to eyes; SOF and VEL were negative in delayed-type hypersensitivity studies. Velpatasvir is not phototoxic. The SOF and VEL combination is not expected to change the irritation potential of the agents. Identified impurities and degradants have been assessed as part of the routine toxicology or qualification studies with SOF or VEL.

2.5.3. Ecotoxicity/environmental risk assessment

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.

Velpatasvir accumulates in sediment in a persistent manner and additional evaluation is required on the effects of VEL on sediment-dwelling organisms. A study on bioaccumulation in sediment-dwelling benthic oligochaetes (OECD TG315) in procedure EMEA/H/C/004210/IB/0013 gave 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 regarding the risk for sediment-dwellers. The increase in environmental exposure based on the proposed change in lower age limit (from 6y to 3 y of age) is considered unlikely to change the conclusions in previous assessments.

Summary of main study results

Substance (INN/Invented Name): Velpatasvir			
CAS-number (if available): 1377049-84-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential log K_{ow}	OECD123	log D = 6.31 (at pH8)	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{OW}	log D = 6.31 (at pH8)	Possibly B
	BAF	0.13-0.23	Very unlikely B
Persistence	DT_{50} or ready biodegradability	Sediment: DT_{50} = 109–136 d (20C) ~ 120d DT_{50} = 233–291 d (12C) > 120d	P fulfilled
Toxicity	NOEC or CMR	6.56ug/L (Daphnia) < 10ug/L	T fulfilled
PBT-statement :	The compound is not considered PBT or vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{SW} , default or refined (i.e., max HCV prevalence from ECDC)	Prevalence : 2.60	µg/L	Prevalence PEC_{SW} > 0.01 ug/L threshold (Y)
Other concerns (e.g. chemical class)	NA	NA	(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD TG106	*K_d soil: 294-3062 L/kg* *K_d soil mean = 1009 L/kg* *K_{oc} soil > 10 000 L/kg* *K_d sludge : 1355-4387 L/kg* *K_d sludge mean = 2672 L/kg* *K_{oc} sludge: 3673 – 11 544 L/kg* *K_{oc} sludge mean = 7137 L/kg*	
Ready Biodegradability Test	OECD TG301	Not readily biodegradable	

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	$DT_{50, water}$ = 1.3-1.7 d $DT_{50, sediment}$ = 109–136 d (20C) $DT_{50, sediment}$ = 233–291 d (12C) $DT_{50, whole\ system}$ = 62.4 d % shifting to sediment = >10% AR at D14.			The DT50 for 12C was calculated based on the 20C value and using Arrhenius equation.
Phase IIA Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD TG201	NOEC	49	µg/L	*P. subcapitata*
Daphnia sp. Reproduction Test	OECD TG211	NOEC	6.56	µg/L	*D. magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG210	NOEC	200	µg/L	*P. promelas*
Activated Sludge, Respiration Inhibition Test	OECD TG209	NOEC	105	mg/L	*Sludge microorganisms*
Phase IIB Studies					
Bioaccumulation	OECD TG315	BAF	0.134-0.226	kg sediment /kg worm	*L. variegatus* %lipids: 1.76 %OC: 1.6
Sediment-dwelling organism	OECD TG218	NOEC $NOEC_{OC10}$	870 4142.9	mg/kg	*C. riparius*

2.5.4. Discussion and conclusion on non-clinical aspects

No new non-clinical studies have been submitted for this procedure. A discussion on the relevance of existing toxicological data for the intended patient population has been provided (3 years of age and above). No clear adverse effects on organs/tissues that may be developing in the paediatric population have been observed. The new clinical data did not indicate that the extended patient population would have a significant difference in ADME compared to present established populations and did not suggest any novel toxicities. As such, the non-clinical safety margin estimates established previously remain relevant.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trial was 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 Studies Included in the Update to the SOF/VEL Marketing Application for Paediatric Subjects (3 to < 6 years old)

Study Number	Study Design	Subject Population	Treatment Regimen[a]	N[b]
GS-US-342-1143	Phase 2, open-label, multicohort, 2-part, multicenter study	Treatment-naive and treatment-experienced subjects 3 to < 18 years old with chronic HCV infection	SOF/VEL for 12 weeks	3 to < 6 years: 41 Genotype 1: 32 Genotype 2: 6 Genotype 3: 2 Genotype 4: 1

CSR = clinical study report; HCV = hepatitis C virus; SOF/VEL = sofosbuvir/velpatasvir (coformulated; Epclusa)

a The doses of SOF/VEL were based on age group and weight as follows:
- Subjects 3 to < 6 years old who were ≥ 17 kg received SOF/VEL 200/50 mg orally, once daily.
- Subjects 3 to < 6 years old who were < 17 kg received SOF/VEL 150/37.5 mg orally, once daily.

b N = number of subjects in the Full Analysis Set, which included all subjects who received at least 1 dose of study drug.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

2.6.2.1.1. Introduction

This application is primarily based on extrapolation of efficacy and safety from adults to paediatric patients.

A PK lead-in phase in Study GS-US-342-1143 evaluated the SOF/VEL FDC doses. Pharmacokinetic parameters were estimated from the intensive PK samples for SOF, the predominant circulating metabolite GS-331007, and VEL. The lead-in phase exposure confirmed that the selected doses was adequate for continued evaluation in the treatment phase (**Table 6** below).

Table 2 GS-US-342-1143 Summary of PK Lead-in phase SOF, GS-331007 and VEL exposures in paediatric subjects 3 to <6 years old compared with population PK-based exposures in the adult Phase 2/3 SOF/VEL Population (Lead-in Phase PK analysis set)

Analyte	PK Parameter	Mean (%CV)		%GMR (90% CI)
		Pediatric Subjects 3 to < 6 Years Old SOF/VEL 200/50 mg or 150/37.5 mg (N = 18[a,b])	Adult Phase 2/3 Population SOF/VEL 400/100 mg (N = 982[c])	Pediatric Subjects vs Adult Phase 2/3 Population
SOF	AUC_{tau} (h•ng/mL)	3306.2 (105.8)	1261.6 (37.2)	192.01 (165.77, 222.39)
	C_{max} (ng/mL)	1207.8 (65.5)	566.3 (31.4)	190.20 (167.57, 215.89)
GS-331007	AUC_{tau} (h•ng/mL)	11604.0 (23.5)	13966.7 (28.0)	84.18 (75.77, 93.53)
	C_{max} (ng/mL)	1105.5 (23.0)	868.2 (27.6)	129.08 (115.93, 143.72)
VEL	AUC_{tau} (h•ng/mL)	4450.3 (73.8)	2967.3 (50.2)	122.93 (101.16, 149.40)
	C_{max} (ng/mL)	587.7 (66.3)	259.0 (53.9)	198.70 (160.24, 246.39)
	C_{tau} (ng/mL)	39.7 (74.0)	41.5 (65.0)	82.48 (65.87, 103.26)

%CV = percentage coefficient of variation; GMR = geometric mean ratio; N = number of subjects; PK = pharmacokinetic(s); SOF = sofosbuvir; VEL = velpatasvir

a Nineteen subjects were enrolled in the PK lead-in phase. One subject discontinued study at Day 1, therefore didn't complete PK Lead-in Phase. One subject was excluded from the comparison due to Covance PK label mix up issue.

b For SOF AUC_{tau}, N = 17

c For GS-331007 and VEL, N = 1428 and 1425, respectively

The applicant has provided a popPK analysis including the PK data from Study GS-US-342-1143 as well as previously available PK data for SOF/VEL. The popPK analysis was used to compare exposures in adults and paediatric patients 3 to <6 years. **Table 7** below summarizes the clinical studies conducted with SOF/VEL that contribute to the Clinical Pharmacology dossier of this application.

Table 3 Overview of Clinical Studies Contributing to the Characterization of the Clinical Pharmacology of SOF/VEL

Study Number/Location	Study Description	Test Treatment(s)		
		Dose and Formulation	Lot Number	n[a]
GS-US-342-1142 **CSR:** GS-US-342-1142 Final CSR **Narrative:** m2.7.1, Section 2.1	Phase 1 study to evaluate the relative bioavailability and food effect of SOF/VEL oral granules in healthy adult subjects	SOF/VEL (400/100 mg; 1 × 400/100-mg tablet or 8 × 50/12.5-mg packets containing granules)	SOF/VEL FDC (400/100-mg) tablet: DU1404B1 SOF/VEL FDC (50/12.5-mg) packets containing oral granules: FH1701B1 and FH1701C1	112
GS-US-342-1143[b] **CSR:** GS-US-342-1143 Final CSR **Narrative:** m2.7.3, Section 2.1	Phase 2 study to evaluate the PK, safety and efficacy of SOF/VEL in subjects 3 to < 18 years old with chronic HCV infection	3 to < 6 years weighing ≥ 17 kg: SOF/VEL (200/50 mg; 4 × 50/12.5-mg packets containing granules) 3 to < 6 years weighing < 17 kg: SOF/VEL (150/37.5 mg; 3 × 50/12.5-mg packets containing granules)	SOF/VEL FDC (50/12.5-mg) packets containing granules: FH1701C1 and FH1701C2	3 to < 6 years: n = 41

CSR = clinical study report; FDC = fixed-dose combination; HCV = hepatitis C virus; SOF = sofosbuvir; VEL = velpatasvir

a Safety Analysis Set (ie, all enrolled subjects who received at least 1 dose of study drug)

b Only information for pediatric subjects 3 to < 6 years old is presented. Data for adolescent subjects 12 to < 18 years old were previously presented in the GS-US-342-1143 Interim CSR and data for pediatric subjects 6 to < 12 years old were previously presented in the GS-US-342-1143 Interim 2 CSR.

2.6.2.1.2. Methods

- **Analytical methods**

Method validation has been assessed previously in the initial MA application (EMEA/H/C/4210). In brief, plasma concentrations of VEL were determined with an LC/MS/MS method with positive ionization using VEL-$^{13}C_6$ as internal standard. Sample preparation was based on liquid-liquid extraction. The validation results in plasma and clinical studies supported are given in **Table 8** . Long term stability in plasma was demonstrated for 1302 days at -20 °C and 1315 days at -70 °C. Interference from analyte(s) quantitated in the assay was tested and was found acceptable.

Table 4 Bioanalytical Method Validation for Determination of VEL in Human Plasma (QPS 60-1393)

	VEL
Calibrated Range (ng/mL)	1 to 1000
Inter-assay Precision Range (%CV)	1.6 to 3.8
Inter-assay Accuracy Range (%RE)	-2.0 to 4.5
Studies Supported	GS-US-342-1142, GS-US-342-1143

The SOF, GS-566500, and GS-331007 plasma methods were validated at two bioanalytical facilities (Tandem Labs and QPS). The method involved protein precipitation extraction of SOF, GS-566500, and GS-331007 and internal standards (SOF d_4, GS 566500 $^{13}C_1{}^2H_3$ and GS 331007 $^{13}C_1{}^2H_3$) from human plasma followed by LC/MS/MS with negative ionization. The validation results are given in **Table 9**. Long term stability in plasma

was demonstrated for 174 at −20°C and 813 at −70°C for SOF, 174 at −20°C and 747 at −70°C for GS-566500, and 174 at −20°C and 813 at −70°C for GS-331007.

Table 5 Bioanalytical Method Validation for SOF, GS 566500, and GS 331007 in Human Plasma (QPS 60-1323)

Parameter	SOF	GS-566500	GS-331007
Calibrated range (ng/mL)	5 to 2500	10 to 5000	10 to 5000
Inter-assay precision range (%CV)	2.4 to 9.7	5.1 to 7.7	2.5 to 7.2
Inter-assay accuracy range (%RE)	−5.1 to 3.4	−2.2 to 2.9	−1.0 to 2.5
Studies Supported	GS-US-342-1142, GS-US-342-1143		

- **Pharmacokinetic data analysis**

A popPK analysis (Population Pharmacokinetics of SOF, GS-331007, and VEL in HCV-Infected Pediatric Subjects) was provided in this application. Studies included in the popPK analysis dataset are shown **Table 10** below:

Table 6 Studies included in the popPK analysis

Studies Included in the PopPK Analysis

Study Number; Study Drug	Age Group (years)	Study Phase	Subjects with PK Sampling[a]	Dose Regimen (mg)[b]
GS-US-334-1112; SOF + RBV[c]	12 to < 18	PK lead-in	N = 10 (Int + Sparse)	400 SOF
		Treatment	N = 42 (Sparse only)	
	6 to < 12	PK lead-in	N = 12 (Int + Sparse)	200 SOF
		Treatment	N = 29 (Sparse only)	
	3 to < 6	PK lead-in	N = 11 (Int + Sparse)	≥ 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)	90/400 LDV/SOF
		Treatment	N = 90 (Sparse only)	
	6 to < 12	PK lead-in	N = 12 (Int + Sparse)	45/200 LDV/SOF
		Treatment	N = 80 (Sparse only)	
	3 to < 6	PK lead-in	N = 14 (Int + Sparse)	≥ 17 kg: 45/200 LDV/SOF < 17 kg: 33.75/150 LDV/SOF
		Treatment	N = 8 (Sparse only) N = 12[e] (Int + Sparse)	
GS-US-342-1143; SOF/VEL[f]	12 to < 18	PK lead-in	N = 17 (Int + Sparse)	400/100 SOF/VEL
		Treatment	N = 85 (Sparse only)	
	6 to < 12	PK lead-in	N = 20 (Int + Sparse)	200/50 SOF/VEL
		Treatment	N = 51 (Sparse only)	
	3 to < 6	PK lead-in	N = 19 (Int + Sparse)	≥ 17 kg: 200/50 SOF/VEL < 17 kg: 150/37.5 SOF/VEL
		Treatment	N = 17 (Sparse only)	
GS-US-367-1175; SOF/VEL/VOX[g]	12 to < 18	Treatment	N = 14 (Int + Sparse) N = 7 (Sparse only)	400/100/100 SOF/VEL/VOX

Int = intensive; LDV = ledipasvir; PK = pharmacokinetic; PopPK = population pharmacokinetic; QD = once daily; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir; WT = baseline body weight.

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

b Protocol-defined dose regimen based on defined age and WT cutoff. All listed regimens were given QD.

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 < 18 years 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 and 8 time points for pediatric subjects 3 to < 6 years old.
g Intensive PK sampling included 9 time points for pediatric subjects 12 to < 18 years old.

- **Evaluation and Qualification of Models**

SOF Joint Model

Dataset

SOF

After all exclusions, a total of 69 subjects in Study GS-US-334-1112, 160 subjects in Study GS-US-337-1116, 172 subjects in Study GS-US-342-1143, and 15 subjects in Study GS-US-367-1175 had at least 1 measurable SOF concentration value included in the SOF joint model population PK analysis.

GS-566500

A total of 70 subjects in Study GS-US-334-1112, 197 subjects in StudyGS-US-337-1116, 174 subjects in Study GS-US-342-1143, and 15 subjects in Study GS-US-367-1175 had at least 1 concentration value for GS-566500 included in the population PK analysis.

GS-331007

A total of 85 subjects in Study GS-US-334-1112, 198 subjects in Study GS-US-337-1116, 179 subjects in Study GS-US-342-1143, and 15 subjects in Study GS-US-367-1175 had at least 1 concentration value for GS-331007 included in the population PK analysis.

Plasma concentrations of SOF, GS-566500, and GS-331007 were best described by a joint 1- compartment (SOF and GS-566500) and a 2-compartment (GS-331007) model, including first-order absorption with zero-order input for SOF and an absorption lag time (ALAG) for both SOF and GS-331007, followed by first-order elimination. The model included the effect of WT (allometric exponents fixed to 0.75 and 1 for clearances and volumes, respectively) on apparent oral clearance of SOF (CLSOF), apparent volume of SOF (VSOF), apparent oral clearance of GS-566500 (CL500), apparent volume of GS-566500 (V500), apparent oral clearance of GS-331007 (CL007), and apparent central volume of GS-331007 (Vc007) .Additionally, the model included the separate effect of coadministration of LDV and VEL on relative fraction absorbed for SOF (F1) and coadministration of RBV CL500 and CL007. The model also included the effect of age on CL500 and CL007 and sex on CL007. Parameters for the final SOF Joint popPK model are shown in **Table 11**.

Table 7 Parameters for the final SOF Joint popPK model

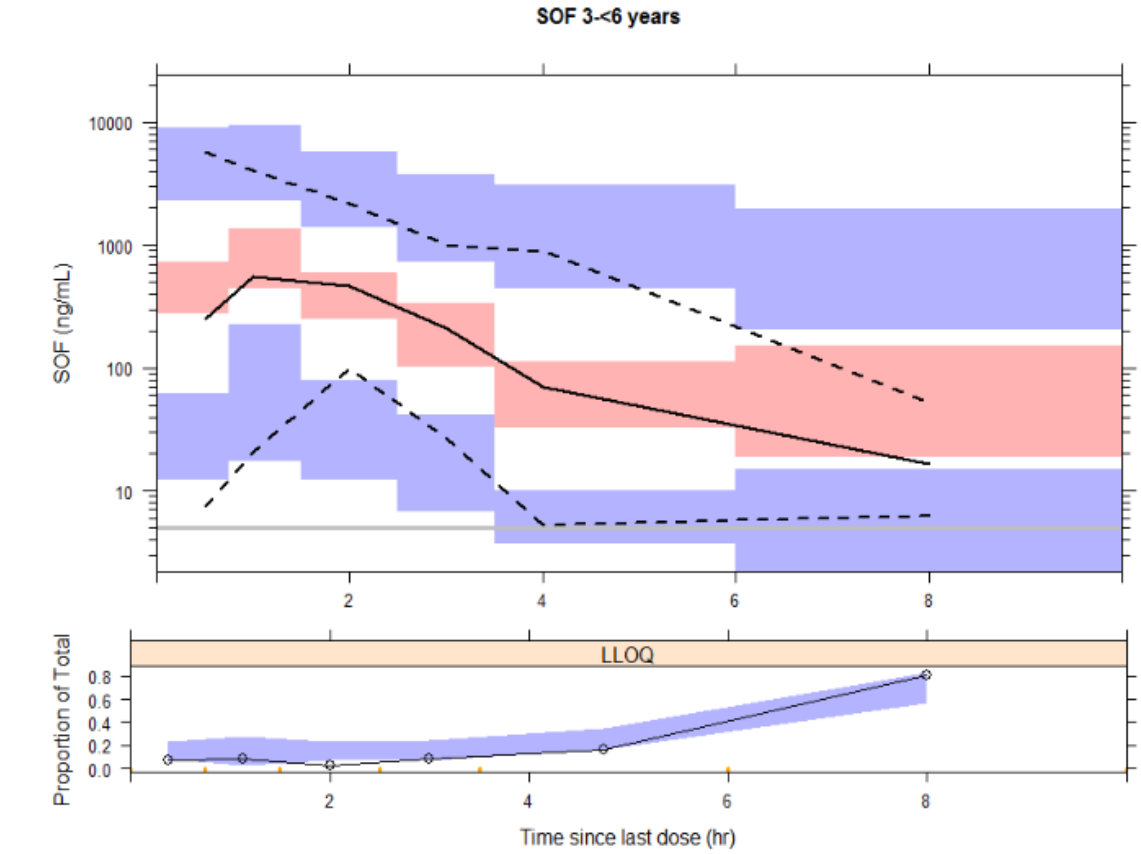
Parameter	Parameter Description		Population Estimate	Change from Typical (%)	IIV (%)
exp(θ1)	Absorption rate for SOF, k_{aSOF} (1/h)		1.22		
exp(θ2)	Absorption rate for GS-566500, k_{a500} (1/h)		0.286		
exp(θ3)	Absorption rate for GS-331007, k_{a007} (1/h)		0.022		
exp(θ4)	Apparent oral clearance of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

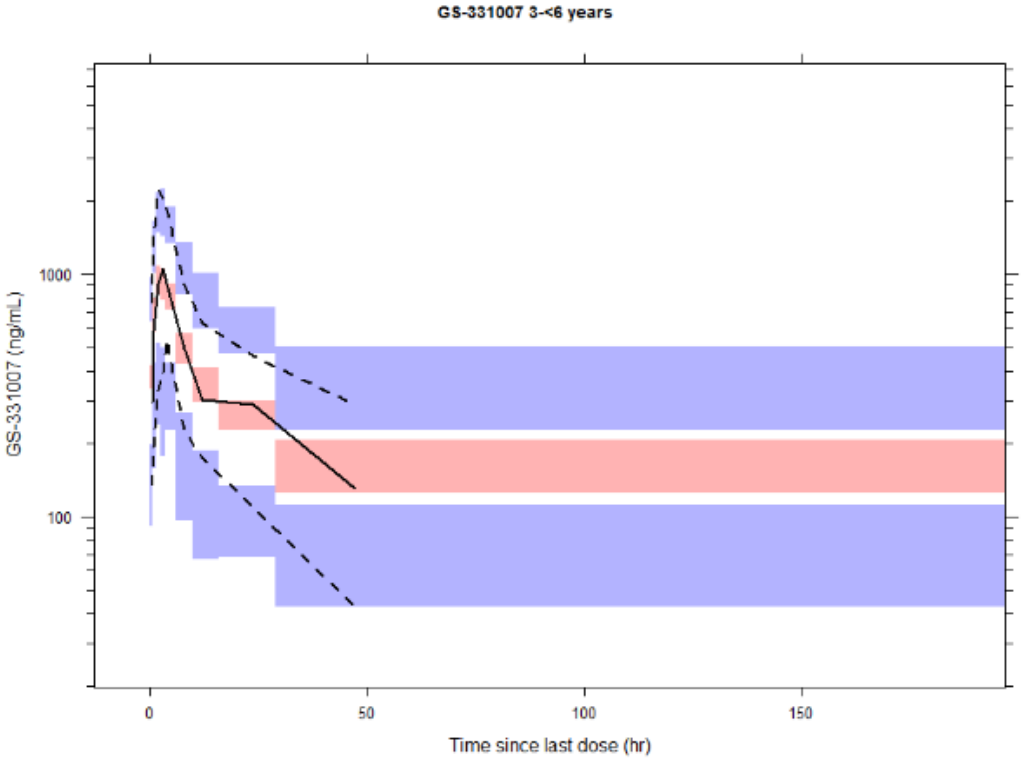
Parameter	Parameter Description		Population Estimate	Change from Typical (%)	IIV (%)
1 + θ14 [Fixed]	Relative fraction absorbed for SOF, F1	LDV/SOF FDC	1.77		
1 + θ23		SOF/VEL FDC	2.52		
θ13 [Fixed]	Relative fraction absorbed for GS-331007, F3		7.18		
θ15 [Fixed]	Relative fraction absorbed for GS-566500,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

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

Prediction-corrected VPC simulations were performed as a validation of the final PopPK model. A total of 1000 replicates of the studies were simulated using the final PopPK model parameter estimates, the estimated subject-specific ETA and the RV. The pcVPCs of SOF and GS3317007 plasma concentration-time profiles are shown in **Figure 1** below.

Figure 1 pcVPC for SOF and GS-331007, 3-<6 years





VEL popPK analysis

Dataset

The population PK data included 209 subjects from Study GS-US-342-1143 and 21 subjects from Study GS-US-367-1175. After all exclusions, a total of 179 subjects in Study GS-US-342-1143 and 15 subjects from Study GS-US-367-1175 had at least 1 measurable concentration value for VEL.

VEL popPK model

The final pediatric VEL model was described by a 2-compartment model with sequential zero-/first-order absorption and first-order elimination, with interindividual variability (IIV) on CL/F, Vc/F, and ka. The effect of WT on CL/F and Vc/F was included using fixed allometric exponents of 0.75 and 1, respectively. In the context of SOF/VEL/VOX administration, VOX was found to affect VEL CL/F (24.4% reduction). No additional covariates were found to significantly affect VEL exposure. The popPK parameters for the final VEL model are depicted in the **Table 12**.

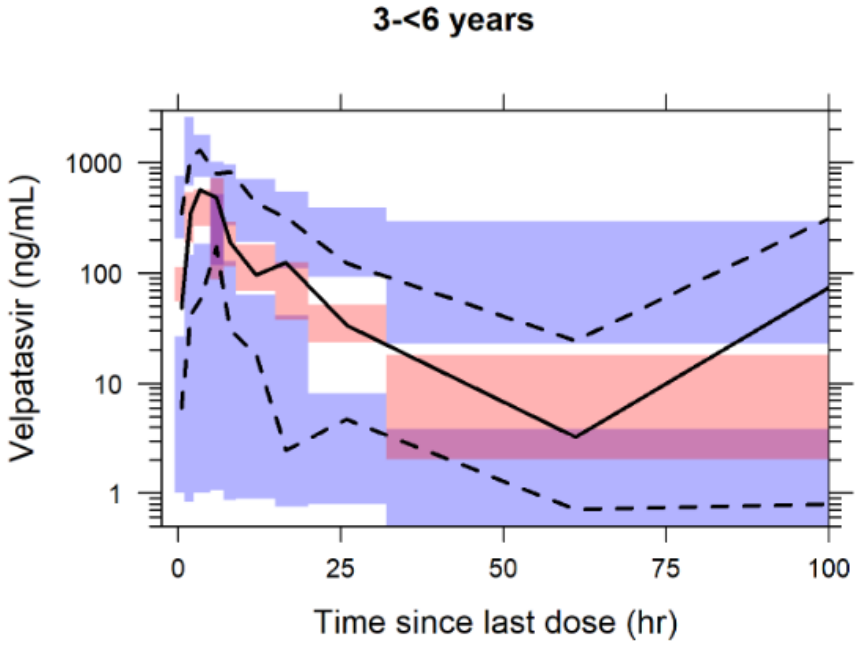
Table 8 Summary of Parameters for final VEL PopPK Model for Paediatric Subjects

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

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

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

Figure 2 pcVPC VEL 3-<6 years



2.6.2.1.3. Absorption

The pharmacokinetic properties of SOF, GS 331007 and VEL have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. Following oral administration of Epclusa, sofosbuvir was absorbed quickly and the peak median plasma concentration was observed 1-hour post dose. Median peak plasma concentration of GS 331007 was observed 3 hours post dose. VEL median peak concentrations were observed at 3 hours post dose.

SOF and GS 331007 are not inhibitors of drug transporters P gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3 and OCT1; VEL, in contrast to SOF, is an inhibitor of drug transporter P gp, BCRP, OATP1B1 and OATP1B3 and its involvement in drug interactions with these transporters is primarily limited to the process of absorption.

- **Bioavailability**

The absolute bioavailability of VEL has not been determined in humans.

- **Bioequivalence**

Study GS-US-342 -1142– relative bioavailability (BA) and food effect

The primary objectives of this study were (1) to evaluate the relative bioavailability of a paediatric oral granule formulation of sofosbuvir/velpatasvir (SOF/VEL) relative to the tablet formulation and (2) to evaluate the effect of concomitant food intake on the pharmacokinetics of a paediatric oral granule formulation of SOF/VEL. For the presentation of the results on the food effect and assessment thereof see section "Influence of food" below.

The applicant conducted a phase 1, randomized, open-label, single-centre, single-dose, multiple-period, crossover study and evaluated the bioequivalence of paediatric oral granule formulations of SOF/VEL (400/100mg; 8*50/12.5-mg packets) relative to the adult tablet formulation (400/100mg; 1 * 400/100-mg tablet) in healthy adult subjects.

Subjects were enrolled in 1 of 2 cohorts and randomized the treatment sequences within the cohort. The paediatric oral granule formulation used in cohort 1 is referred to as fixed dose combination 1 (FDC1) and the oral granule formulation in used in cohort 2 is referred to as FDC2. The active and inactive ingredients in FDC1 and FDC2 were identical; the only difference in the formulations was the amount of taste-mask coating, which was 20% for FDC1 and 5% for FDC2 (see quality report).

PK sampling was conducted relative to dosing at time 0 (pre-dose within ≤5 minutes of dosing), and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, 96, and 120 hours post-dose.

An analysis of variance (ANOVA) was performed for the natural logarithms of PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) for SOF and its metabolites (GS-331007and GS-566500), and VEL. The results for tablet of SOF/VEL400/100mg vs. FDC1 SOF/VEL oral granules OR vs. FDC1 SOF/VEL oral granules are presented in **Table 13**.

Table 9 Statistical comparison of PK parameters for VEL, GS-331007, SOF and GS-566500 following the administration of single oral doses of SOF/VEL as a tablet (1*400/100 mg tablet) and as oral granules (400/100mg; 8*50/12.5 mg packets) as FDC1 or FDC2.

Statistical Comparison	GLSM Ratio (90% CI) **AUClast** (h*ng/mL) (N=56)	GLSM Ratio (90% CI) **AUCinf** (h*ng/mL) (N=56)	GLSM Ratio (90% CI) **Cmax** (ng/mL) (N=56)
FDC1 Oral Granule Formulation versus Tablet Formulation, Fasted			
VEL	67.19 (60.23, 74.96)	67.47 (60.57, 75.16)	66.10 (59.23, 73.76)
GS-331007	94.80 (91.79, 97.91)	95.19 (92.24, 98.24)	118.00 (112.02, 124.30)
SOF	62.11 (55.98, 68.91)	62.97 (56.79, 69.82)	55.00 (48.19, 62.78)
GS-566500	71.63 (66.26, 77.44)	72.23 (66.95, 77.93)	70.13 (65.30, 75.31)
FDC2 Oral Granule Formulation versus Tablet Formulation, Fasted			
VEL	93.56 (82.00, 106.74)	94.01 (82.75, 106.81)	97.25 (85.83, 110.19)
GS-331007	102.26 (99.55, 105.05)	101.83 (99.29, 104.45)	109.43 (103.95, 115.20)
SOF	93.86 (86.41, 101.95)	94.01 (86.36, 102.33)	80.36 (71.91, 89.80)
GS-566500	97.46 (91.99, 103.27)	97.24 (91.92, 102.86)	95.61 (89.41, 102.23)

- **Influence of food**

Study GS-US-342 -1142–food effect

The effect of food on the SOF/VEL oral granule formulation was also evaluated in Study GS-US-342-1142, which compared SOF/VEL granule dosing with a high-fat meal with dosing under fasted conditions in healthy adults. For general study information and study design, see section on bioequivalence above.

The applicant concludes that, based on the results presented in study No GS-US-342 -1142, the effect of food on the PK of the SOF/VEL oral granule formulation was similar to what was observed with the approved tablet formulation. They further claim that these data support administration of SOF/VEL oral granules without regard to food. Dosing of SOF/VEL oral granule formulation in GS-US-342-1143 was thus administered without regard to food.

For assessment of the food effect, analyses were conducted for the primary PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) of VEL, SOF, GS-331007, and GS-566500, and is summarized in **Table 14**.

Table 10 Statistical comparison of PK parameters for VEL, GS-331007, SOF and GS-566500 following the administration of single oral granules of SOF/VEL as FDC2 (400/100mg; 8* 50/12.5-mg packets) under fasted conditions vs. single oral granules of SOF/VEL as FDC2 (400/100mg; 8*50/12.5 mg packets) following a high-fat meal.

Statistical Comparison	GLSM Ratio (90% CI) **AUC_{last}** (h*ng/mL) (N=56)	GLSM Ratio (90% CI) **AUC_{inf}** (h*ng/mL) (N=56)	GLSM Ratio (90% CI) **C_{max}** (ng/mL) (N=56)
FDC2 Oral Granule Formulation, Fasted, versus FDC2 Oral Granule Formulation, Fed			
VEL	122.33 (101.35, 147.65)	121.16 (101.06, 145.25)	100.88 (84.94, 119.81)
GS-331007	103.80 (100.23, 107.51)	103.82 (100.45, 107.31)	63.59 (60.57, 66.76)
SOF	167.69 (150.62, 186.70)	164.11 (147.95, 182.03)	105.26 (91.41, 121.20)
GS-566500	154.39 (142.37, 167.43)	153.19 (141.65, 165.68)	118.91 (109.19, 129.49)

2.6.2.1.4. Pharmacokinetics in target population

To facilitate the safe and efficacious use of SOF/VEL FDC in the paediatric clinical setting, a simplified weight band-based dosing regimen is presented in **Table 15**, as recommended by the World Health Organization for other paediatric antiviral medicines {World Health Organization 2008}.

Table 11 Proposed SOF/VEL weight band doses

	Proposed SOF/VEL Dose for Patients 3 to < 18 Years Old		
Weight (kg)	≥ 30	17 to < 30	< 17
SOF/VEL dose (mg)	400/100	200/50	150/37.5

SOF = sofosbuvir; VEL = velpatasvir

SOF, GS-331007, and VEL model predicted exposure metrics in HCV-Infected Pediatric Subjects 3 to <6 Years Old and adults are presented in **Table 16** below.

Table 12 GS-US-342-1143: Statistical Comparison of SOF, GS-331007 and VEL exposures between paediatric subjects 3 to <6 years old and the adult Phase 2/3 SOF/VEL population (PK Analysis Set)

Analyte	PK Parameter	Mean (%CV)		% GMR (90% CI)
		Pediatric Subjects 3 to < 6 Years Old SOF/VEL 200/50 mg or 150/37.5 mg (N = 36[a])	Adult Phase 2/3 Population SOF/VEL 400/100 mg (N = 1428[b])	Pediatric Subjects vs Adult Phase 2/3 Population
SOF	AUC_{tau} (h•ng/mL)	2537.0 (57.4)	1261.6 (37.2)	183.36 (165.28, 203.43)
	C_{max} (ng/mL)	1406.4 (69.2)	566.3 (31.4)	199.60 (180.82, 220.33)
GS-331007	AUC_{tau} (h•ng/mL)	12544.6 (48.6)	13966.7 (28.0)	87.36 (81.01, 94.21)
	C_{max} (ng/mL)	1132.4 (28.9)	868.2 (27.6)	131.37 (121.71, 141.80)
VEL	AUC_{tau} (h•ng/mL)	4480.5 (48.8)	2967.3 (50.2)	149.85 (130.64, 171.89)
	C_{max} (ng/mL)	494.1 (46.0)	259.0 (53.9)	192.46 (165.32, 224.06)
	C_{tau} (ng/mL)	54.6 (75.5)	41.5 (65.0)	116.98 (99.63, 137.36)

%CV = percentage coefficient of variation; GMR = geometric mean ratio; PK = pharmacokinetic(s); SOF = sofosbuvir; VEL = velpatasvir
SOF/VEL Adult Population = HCV-infected adult subjects administered SOF 400 mg and VEL 100 mg as either single agents or FDC in Phase 2 and 3 Study GS-US-337-0122, GS-US-342-0102, GS-US-342-0109, GS-US-342-1138, GS-US-342-1139, or GS-US-342-1140.
a For SOF, N = 34
b For SOF and VEL, N = 982 and 1425, respectively

SOF exposure - impact of weight

The relationship between WT and SOF exposure for subjects 3 to < 6 years old in Study GS-US-342 -1143 is presented in **Table 17**.

Table 13 Impact of WT on mean (%CV) steady-state SOF exposure in paediatric subjects 3 to <6 years old who received SOF/VEL in study GS-US-342-1143

Characteristics	WT Quartiles				Median Q4 – Q1 %Difference
	Q1	Q2	Q3	Q4	
WT (kg: min, median, max)	12.9, 15.1, 15.6	16.0, 17.9, 18.6	18.8, 19.7, 20.3	20.5, 23.3, 35.0	--
Number of subjects	9	7	9	9	--
SOF AUCtau (h*ng/mL)	2547.7 (72.8)	2877.6 (52.7)	2144.7 (43.9)	2653.9 (58.3)	16.4
SOF Cmax (ng/mL)	1260.3 (65.3)	1721.9 (88.7)	1031.8 (59.6)	1681.6 (51.3)	59.0

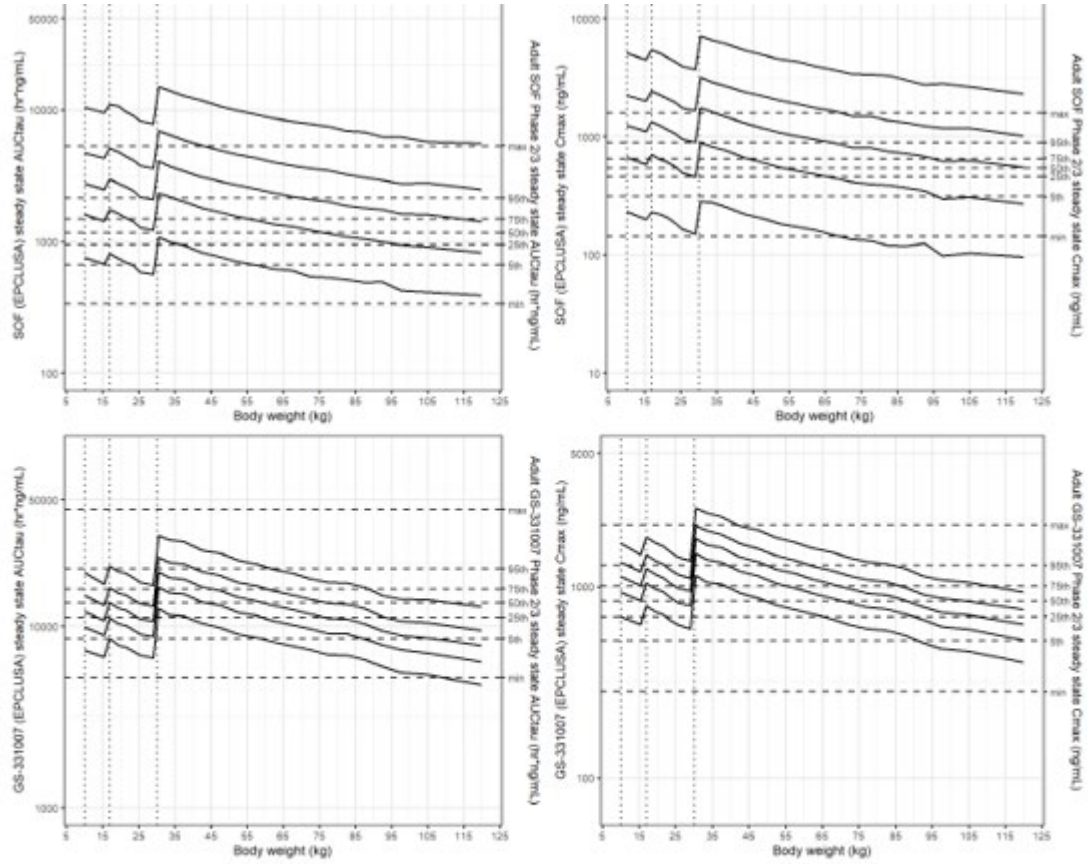
%CV = percentage coefficient of variation; AUC_{tau} = area under the concentration-time curve over the dosing interval; CI = confidence interval; C_{max} = maximum concentration; max = maximum; min = minimum; Q = quartile; SOF = sofosbuvir; VEL = velpatasvir; WT = baseline body weight.
Median Q4 – Q1 %Difference = (Median Q4 – Median Q1) / Median Q1 × 100%.

Simulated exposure SOF and GS-331007

The proposed weight band-based dosing regimen is supported by population PK simulations resulting in SOF and GS-331007 exposures that are comparable with exposures shown to be safe and effective in either HCV-infected subjects in the adult Phase2/3 program or HCV-infected pediatric subjects in Study GS-US-342-1143.

Population PK simulations for SOF and GS-331007 were conducted based on the weight band-based dosing regimen (**Figure 3** below).

Figure 3 Simulated steady-state SOF and GS-331007 AUCtau and Cmax following WT-band-based dosing in paediatric subjects who received SOF/VEL (updated)



AUC_{tau} = area under the concentration-time curve over the dosing interval; C_{max} = maximum concentration; PopPK = population pharmacokinetic; SOF = sofosbuvir; VEL = velpatasvir; WT = baseline body weight.
Solid lines represent 5th, 25th, 50th, 75th, and 95th percentiles of simulated pediatric exposures; horizontal dashed lines represent distribution of adult exposures; vertical dashed lines indicate 10-, 17-, and 30-kg cutoffs. Adult exposures are the PopPK-predicted exposures from SOF/VEL (Epclusa) Phase 2/3 studies (Report# QP 15-0002 Sofosbuvir PopPK); minimum, 5th, 25th, 50th, 75th, and 95th percentiles, and maximum are shown. Top and bottom panels show SOF and GS-331007 data, respectively. Left and right panels show AUC_{tau} and C_{max}, respectively.

VEL exposure – impact of body weight

The relationship between WT and VEL exposure for subjects 3 to < 6 years old in Study GS-US-342- 1143 is presented in **Table 18** below.

Table 14 Impact of WT on mean (%CV) steady-state VEL exposure in paediatric subjects 3 to <6 years old who received SOF/VEL in study GS-US-342-1143

Characteristics	WT Quartiles				Median Q4 – Q1 %Difference
	Q1	Q2	Q3	Q4	
WT (kg: min, median, max)	12.9, 15.1, 15.6	16.0, 17.9, 18.6	18.8, 19.7, 20.3	20.5, 23.3, 35.0	--
Number of subjects	9	9	9	9	--
VEL AUCtau (h*ng/mL)	3901.9 (46.9)	5505.7 (43.1)	4006.7 (66.0)	4507.9 (39.6)	-0.8
VEL Cmax (ng/mL)	435.3 (43.0)	597.3 (40.9)	438.8 (60.2)	505.1 (40.8)	24.4
VEL Ctau (ng/mL)	45.9 (73.4)	70.6 (66.0)	46.3 (106.8)	55.6 (63.4)	42.6

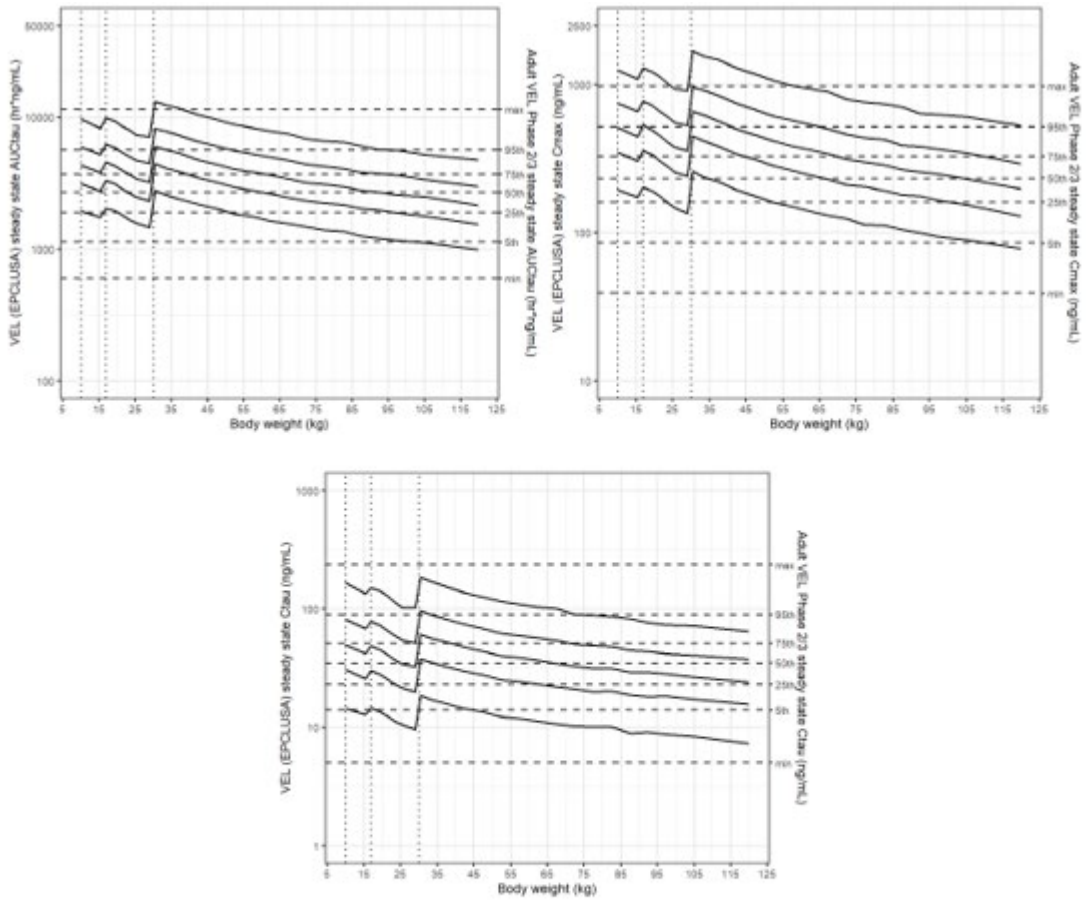
%CV = percentage coefficient of variation; AUC_{tau} = area under the concentration-time curve over the dosing interval; CI = confidence interval; C_{max} = maximum concentration; C_{tau} = concentration at the end of the dosing interval; max = maximum; min = minimum; Q = quartile; SOF = sofosbuvir; VEL = velpatasvir; WT = baseline body weight.
Median Q4 – Q1 %Difference = (Median Q4 – Median Q1) / Median Q1 × 100%.

Simulated exposure VEL

The proposed weight band-based dosing regimen is supported by population PK simulations resulting in VEL exposures that are comparable with exposures shown to be safe and effective in either HCV-infected subjects in the adult Phase2/3 program or HCV-infected paediatric subjects in Study GS-US-342-1143.

Population PK simulations for VEL were conducted based on the weight band-based dosing regimen (**Figure 4** below).

Figure 4 Simulated steady-state VEL AUCtau, Cmax and Ctau following WT-band-based dosing in paediatric subjects who received SOF/VEL (updated)



AUC_{tau} = area under the concentration-time curve over the dosing interval; C_{max} = maximum concentration; C_{tau} = concentration at the end of the dosing interval; PopPK = population pharmacokinetic; SOF = sofosbuvir; VEL = velpatasvir; WT = baseline body weight.
Solid lines represent 5th, 25th, 50th, 75th, and 95th percentiles of simulated pediatric exposures; horizontal dashed lines represent distribution of adult exposures; vertical dashed lines indicate 10-, 17-, and 30-kg cutoffs. Adult exposures are the PopPK-predicted exposures from SOF/VEL (Epclusa) Phase 2/3 studies (Report# QP 15-0001 GS-5816 PopPK); minimum, 5th, 25th, 50th, 75th, and 95th percentiles, and maximum are shown. Top left, top right, and bottom panels show AUC_{tau}, C_{max}, and C_{tau}, respectively.

2.6.2.2. Pharmacodynamics

No new data on pharmacodynamics were included in this submission.

2.6.3. Discussion on clinical pharmacology

An extrapolation approach of efficacy from adults to paediatric patients is considered suitable for hepatitis-C because the PD target is expected to respond similarly to similar plasma concentrations of SOF/VEL in both adult and paediatric patients.

Sofosbuvir is a nucleotide prodrug that is extensively metabolised. The active metabolite is formed in hepatocytes and not observed in plasma. The predominant (>90%) metabolite, GS-331007, is inactive. Focusing on sofosbuvir and the predominant circulating metabolite GS-331007 (not focusing on GS-566500) is considered adequate.

A population PK analysis was performed where all sofosbuvir data has been pooled and a joint model of SOF and metabolites were developed and a separate popPK model for VEL was developed. Adequate non-linear mixed effects modelling methods have been used. The model diagnostics indicate that the sofosbuvir join model as well as the VEL model adequately represents the observed data in the paediatric population and the models are considered adequate to use in simulations to support dose selection.

AUC and Cmax for SOF are higher than the adult exposures. The metabolite exposure is more similar to adults. Model predicted velpatasvir exposures were slightly higher in paediatric patients 3-<6 years compared to adults.

Under exposure (potential lack of efficacy) would have been of concern, here we see higher exposure. Given the favourable safety profile of SOF, GS-331007 and VEL, the exposure levels in the paediatric population 3-<6 years are considered acceptable.

The proposed dosing in the SmPC does not include a lower weight cut-off. In the popPK dataset the lowest weight patient had a weight of 12,9 kg. The 5th percentile for a 3-year-old is around 11,5 kg (CDC) which is close to 12,9 kg. Therefore, the CHMP considered that not having a lower weight cut of in the SmPC is acceptable.

The new paediatric oral granule formulation was compared to the approved tablets in terms of bioequivalence. The study design, including wash-out period, was adequate to compare pharmacokinetic parameters between oral granules and tablets and for investigation of potential food effect. The bioanalytical methods for the determination of total plasma concentrations of VEL, SOF and metabolites were adequately validated. Stability data covers the sample maximum transpired time.

During development, two different formulations of the oral granules (FDC1 and FDC2) were compared with the approved tablets in terms of bioequivalence. The active and inactive ingredients in FDC1 and FDC2 were identical; the only difference in the formulations was the amount of taste-mask coating, which was 20% for FDC1 and 5% for FDC2. Sufficient equivalence in exposure could not be demonstrated between FDC1 oral granules vs. the tablets. However, FDC2 oral granules showed similar AUC and Cmax as compared to single dose tablet of SOF/VEL. The only deviation was the 90% CI around SOF Cmax that fell outside the standard bioequivalence criteria (80.00-125.00) following exposure to FDC2 vs. tablets (lower Cmax). As a strict BE is not a requirement in this type of application, it is agreed that FDC2 oral granules 400/100mg give sufficiently similar exposure compared to tablets of SOF/VEL 400/100mg. Furthermore, as younger paediatric patients already show a slightly higher exposure to SOF compared to adults, the small decrease in Cmax for SOF following administration to granules compared to tablet will not result in any safety or efficiency concerns. Thus, SOF/VEL FDC2 oral granules give sufficiently similar exposure compared to tablets of SOF/VEL and is the granule formulation for which it has been applied for.

The effect of food on the SOF/VEL oral granule formulation (FDC2) was also evaluated in, which compared SOF/VEL granule dosing with a high-fat meal with dosing under fasted conditions in healthy adults. Although simultaneous food intake has a noticeable effect on AUC of both SOF and VEL, this effect was similar to that previously observed for the tablets. In line with what was previously decided, the changes in exposure due to food intake are not considered clinically relevant, thus these data support administration of SOF/VEL FDC2

oral granules without regard to food. This is in line with the wording in the current SmPC. The CHMP also considered that that dosing in study GS-US-342-1143 took place without regard to food.

2.6.4. Conclusions on clinical pharmacology

An extrapolation approach of efficacy from adults to paediatric patients is considered suitable for hepatitis C, because the PD target is expected to respond similarly to similar plasma concentrations of SOF/VEL in both adult and paediatric patients.

With a favourable safety profile for SOF and VEL, the CHMP considered that it is preferred to have a slight over exposure compared to under exposure, as under exposure could lead to potential lack of efficacy.

The CHMP considered that the oral granules give sufficiently similar exposure compared to tablets of SOF/VEL. The observed changes in exposure due to food intake were very similar to those previously observed for tablets and were not considered clinically relevant. Thus, these data supported administration of oral granules without regard to food.

Overall, the oral granules gave sufficiently similar exposure compared to tablets and the popPK analysis supported the indication and proposed dosing in paediatric patients 3 to <6 years old.

2.6.5. Clinical efficacy

2.6.5.1. Main study

Study GS US 342-1143

Phase 2, open-label, multicohort, 2-part study evaluated the PK, safety, and antiviral activity of SOF/VEL in paediatric subjects with chronic HCV infection.

This study consisted of a PK lead-in phase (Cohorts 1, 2, and 3) and a treatment phase (Groups 1 and 2) within each age group.

- Group 1 (including Cohort 1):
    - Adolescent subjects 12 to < 18 years old
- Group 2 (including Cohorts 2 and 3):
    - Pediatric subjects 6 to < 12 years old
    - Pediatric subjects 3 to < 6 years old

In the following sections, only the new data regarding subjects aged 3 to <6 years are presented and assessed.

Methods

- **Study participants**

A total of 41 subjects 3 to < 6 years old were enrolled into the study. Overall, the mean age of subjects was 4 years. The majority of subjects had been infected through vertical transmission (97.6%). The proportions of subjects with genotype 1, 2, 3, or 4 HCV infection were 78.0%, 14.6%, 4.9%, and 2.4%, respectively. The majority of the subjects (73.2%) had IL28B non-CC genotype (CT = 48.8%, TT = 24.4%). All subjects were treatment naive (100.0%) and no subjects had known cirrhosis based on prior biopsy or clinical history.

- **Treatments**

This was a single-arm trial. After a 7-day PK lead-in phase in a sentinel cohort, SOF/VEL was given once daily for 12 weeks to all patients, according to age group and weight as follows:

- Subjects 3 to < 6 years old who were ≥ 17 kg received SOF/VEL 200/50 mg orally, once daily.
- Subjects 3 to < 6 years old who were < 17 kg received SOF/VEL 150/37.5 mg orally, once daily.

- **Outcomes/endpoints**

The key efficacy endpoint for Study GS US 342-1143 was SVR12, defined as HCV RNA below the lower limit of quantitation (LLOQ) 12 weeks following treatment completion. Historically, SVR has been defined at 24

weeks following completion of treatment. More recently, analyses of datasets have demonstrated a high concordance between SVR12 and SVR24 (Florian 2011, Lawitz 2012, Luo 2012).

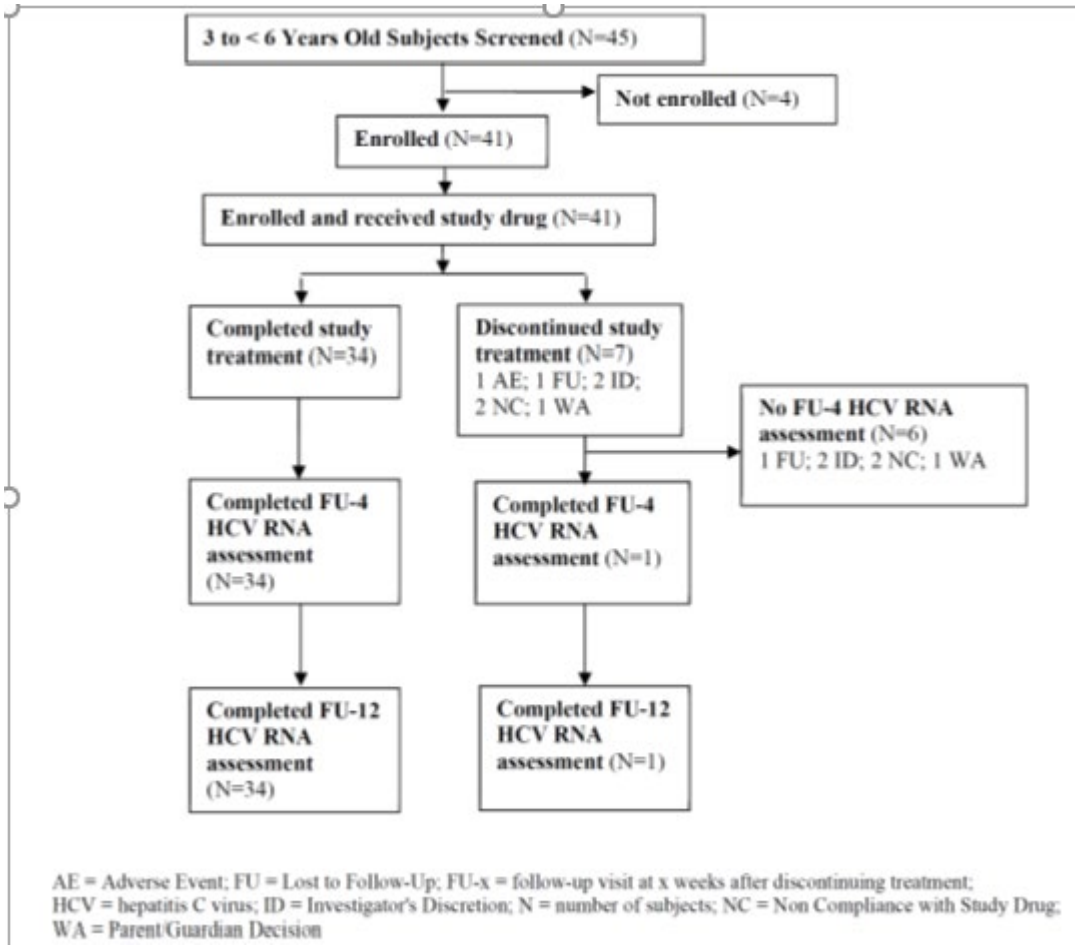
Using SVR12 as primary efficacy endpoint is in line with EMA HCV guidelines.

Results

- **Participant flow**

Study Participant flow

Below is the patient flow for subjects between 3 and <6 years.



- **Conduct of the study**

The original protocol (20 June 2016) was amended 4 times. None of the study protocol amendments was expected to affect the study integrity.

- **Baseline data**

The **Table 19** below presents a summary of demographic and baseline characteristics for paediatric subjects 3 to < 6 years old. Subjects were mainly white and treatment-naïve with HCV of GT1a and ALT levels close to the normal range.

Table 15 GS-US-342-1143: Demographic and Baseline Characteristics (3 to < 6 Years Old) (Safety Analysis Set)

	SOF/VEL (200/50 or 150/37.5 mg) 12 Weeks (N = 41)
Age at Baseline (Years)	
N	41
Mean (SD)	4 (0.8)
Median	4
Q1, Q3	4, 5
Min, Max	3, 5
Sex at Birth	
Male	17 (41.5%)
Female	24 (58.5%)
Race	
White	32 (78.0%)
Black or African American	3 (7.3%)
Asian	0
Other	5 (12.2%)
American Indian or Alaska Native	0
Not Permitted	1 (2.4%)
Native Hawaiian or Pacific Islander	0
Ethnicity	
Hispanic or Latino	4 (9.8%)
Not Hispanic or Latino	36 (87.8%)
Not Permitted	1 (2.4%)
Region	
US	38 (92.7%)
Non-US	3 (7.3%)
Baseline Weight (kg)	
N	41
Mean (SD)	19.3 (4.18)
Median	19.2
Q1, Q3	16.0, 20.7
Min, Max	12.9, 35.0
Baseline Height (cm)	
N	41
Mean (SD)	106.0 (8.33)
Median	107.2
Q1, Q3	101.5, 111.8
Min, Max	85.9, 126.0

	SOF/VEL (200/50 mg or 150/37.5 mg) 12 Weeks (N = 41)
HCV Genotype	
Genotype 1	32 (78.0%)
Genotype 1a	29 (70.7%)
Genotype 1b	2 (4.9%)
Genotype 1c	1 (2.4%)
Genotype 2	6 (14.6%)
Genotype 2 (No Confirmed Subtype)	1 (2.4%)
Genotype 2a	1 (2.4%)
Genotype 2b	4 (9.8%)
Genotype 3	2 (4.9%)
Genotype 3a	2 (4.9%)
Genotype 4	1 (2.4%)
Genotype 4a	1 (2.4%)
Cirrhosis	
Yes	0
No	10 (24.4%)
Not Determined	31 (75.6%)
IL28B	
CC	10 (24.4%)
Non-CC	30 (73.2%)
CT	20 (48.8%)
TT	10 (24.4%)
Missing	1 (2.4%)
Baseline HCV RNA Category	
< 800,000 IU/mL	21 (51.2%)
≥ 800,000 IU/mL	20 (48.8%)
Baseline HCV RNA (log_{10} IU/mL)	
N	41
Mean (SD)	5.9 (1.06)
Median	5.9
Q1, Q3	5.6, 6.3
Min, Max	1.1, 7.3
Baseline ALT (U/L)	
N	41
Mean (SD)	60 (42.2)
Median	47
Q1, Q3	37, 71
Min, Max	12, 245

	SOF/VEL (200/50 mg or 150/37.5 mg) 12 Weeks (N = 41)
Baseline ALT Category	
≤ 1.5 × ULN	24 (58.5%)
> 1.5 × ULN	17 (41.5%)
Estimated Glomerular Filtration Rate Using Schwartz Formula (mL/min/1.73 m^2)	
N	41
Mean (SD)	152.1 (29.70)
Median	152.7
Q1, Q3	132.9, 170.5
Min, Max	95.5, 212.4
Prior HCV Treatment Experience	
Treatment-Naive	41/41 (100.0%)
Treatment-Experienced	0/41
Most Recent HCV Treatment Response	
Non-Responder	0/0
Relapse/Breakthrough	0/0
Mode of HCV Infection	
Vertical Transmission	40 (97.6%)
Blood Product Transfusion + Vertical Transmission	1 (2.4%)

ALT = alanine aminotransferase; HCV = hepatitis C virus; IL28B = IL28B gene; Q1 = first quartile; Q3 = third quartile; SOF = sofosbuvir; ULN = upper limit of normal; VEL = velpatasvir
Baseline value was the last available value on or prior to first dose date of study drug.
HCV genotype was determined by sequencing or, if sequencing is not available, by LiPA 2.0.

- **Numbers analysed**

Of 216 patients in the study, 41 were 3 to <6 years of age.

- **Outcomes and estimation**

The SVR12 rate for subjects 3 to < 6 years old treated with SOF/VEL for 12 weeks was 82.9% (34 of 41 subjects), as presented in **Table 20**. For final analyses, the genotype determined by sequencing was used if available. In subjects with genotype 1 HCV infection, a total of 28 of 32 subjects (87.5%) who received SOF/VEL 200/50 mg or 150/37.5 mg achieved SVR12. In subjects with genotype 2 HCV infection, 3 of 6 subjects (50.0%) who received SOF/VEL 200/50 mg or 150/37.5 mg achieved SVR12. All subjects with genotype 3 (n = 2) and 4 (n = 1) HCV infection who received SOF/VEL 200/50 mg or 150/37.5 mg achieved SVR12.

A total of 7 of 41 subjects (17.1%) did not achieve SVR12 and were categorized as "Other." Of these, 2 subjects discontinued study drug due to noncompliance with study drug, 2 subjects discontinued study drug due to investigator discretion, 1 subject was lost to follow up, and 1 subject discontinued study drug due to withdrawal of parent/guardian assent; none of these subjects had any follow-up assessments. One subject discontinued study drug on Day 20 due to AEs of decreased appetite, irritability, psychomotor hyperactivity, and product use issue (reported term: spitting up study drug). No subject had virologic failure (i.e.

breakthrough, rebound, nonresponse, or relapse).

Table 16 GS-US-342-1143: Virologic Outcomes for Subjects 3 to < 6 Years Old (Full Analysis Set)

	SOF/VEL (200/50 or 150/37.5 mg) 12 Weeks (N = 41)
SVR12	34/41 (82.9%)
Overall Virologic Failure	0/41
Relapse	0/34
Completed Study Treatment	0/34
Discontinued Study Treatment	0/0
On-Treatment Virologic Failure	0/41
Other	7/41 (17.1%)

HCV = hepatitis C virus; LLOQ = lower limit of quantitation; N = number of subjects; SOF = sofosbuvir; SVR12 = sustained virologic response at 12 weeks following completion of all treatment; VEL = velpatasvir
HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, v2.0 with limit of quantitation 15 IU/mL.
Relapse = confirmed HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA <LLOQ at last on-treatment visit.
On-Treatment Virologic Failure = Breakthrough (confirmed HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while on treatment), Rebound (confirmed >1 $\log_{10}$ IU/mL increase in HCV RNA from nadir while on treatment), or Nonresponse (HCV RNA persistently ≥ LLOQ through 8 weeks of treatment).
Other = subject who did not achieve SVR12 and did not meet virologic failure criteria.

SVR12 rate was slightly lower than what is seen in adults and older children. However, as there were no cases of virologic failure, this reflects the general difficulties in treating younger children with an oral regimen rather than raises concerns on the efficacy of Epclusa.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Study GS-US-342-1143 followed the principles established for paediatric development of HCV drugs.

Efficacy data and additional analyses

Efficacy is bridged from the adult pivotal trials of Epclusa. Furthermore, the SVR12 rate in children aged 3 to <6 years and the lack of virologic failure among the 41 subjects treated in study GS-US-342-1143 also supports efficacy of Epclusa in the treatment of HCV in this age group.

2.6.7. Conclusions on the clinical efficacy

The CHMP concluded that SOF/VEL is effective in the treatment of chronic HCV in children aged 3 years and older.

2.6.8. Clinical safety

Patient exposure

The mean (SD) duration of exposure to SOF/VEL for subjects 3 to < 6 years old was 10.1 (4.32) weeks, and 80.5% of subjects (33 of 41) received SOF/VEL for 12 weeks.

Adverse events

The majority of subjects (78.0%, 32 of 41 subjects) had at least 1 AE, and 39.0% (16 of 41 subjects) had a treatment-related AE, as presented in **Table 21** below. All AEs were Grade 1 or 2 in severity. No subjects experienced Grade 3 or Grade 4 AEs. No subjects had any serious adverse events (SAEs). One subject (2.4%) had an AE that led to premature discontinuation of study drug. No subjects had AEs that led to interruption of study drug. No deaths were reported.

Table 17 GS-US-342-1143: Overall Summary of Adverse Events for Subjects 3 to < 6 Years Old (Safety Analysis Set)

Number (%) of Subjects Experiencing Any	SOF/VEL (200/50 mg or 150/37.5 mg) 12 Weeks (N = 41)
Adverse Event	32 (78.0%)
Grade 3 or Above Adverse Event	0
Treatment-Related Adverse Event	16 (39.0%)
Grade 3 or Above Treatment-Related Adverse Event	0
Serious Adverse Event	0
Treatment-Related Serious Adverse Event	0
Adverse Event Leading to Premature Discontinuation of SOF/VEL	1 (2.4%)
Adverse Event Leading to Interruption of SOF/VEL	0
All Deaths	0

SOF = sofosbuvir; VEL = velpatasvir
The denominator for percentages was based on the number of subjects in the Safety Analysis Set.

The most commonly reported AEs were vomiting (26.8%, 11 subjects), and cough, pyrexia, and rhinorrhea (14.6%, 6 subjects each) (**Table 22**).

Table 18 GS-US-342-1143: Adverse Events Reported for ≥ 5% of Subjects 3 to < 6 Years Old (Safety Analysis Set)

	SOF/VEL (200/50 mg or 150/37.5 mg) 12 Weeks (N = 41)
Number (%) of Subjects Experiencing Any Adverse Event	32 (78.0%)
Vomiting	11 (26.8%)
Cough	6 (14.6%)
Pyrexia	6 (14.6%)
Rhinorrhoea	6 (14.6%)
Diarrhoea	5 (12.2%)
Fatigue	5 (12.2%)
Nasal congestion	5 (12.2%)
Product use issue	4 (9.8%)
Decreased appetite	3 (7.3%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SOF = sofosbuvir; VEL = velpatasvir
Adverse events were mapped according to MedDRA Version 22.1.
Subjects were counted once for each AE preferred term.
Data included were to last dose date of study drug + 30 days.

Serious adverse events and deaths

No SAEs or deaths were reported for subjects 3 to < 6 years old.

Laboratory findings

Haematology

No Grade 3 or 4 haematology laboratory abnormalities were reported for subjects 3 to < 6 years old. Two subjects (5.6%) had an isolated postbaseline haemoglobin value < 10 g/dL, and no subject had postbaseline haemoglobin values < 8.5 g/dL.

No clinically meaningful changes from baseline in haemoglobin, reticulocytes, neutrophils, lymphocytes, or platelets were observed for subjects 3 to < 6 years old in Study GS-US-342-1143. The median values for these parameters were within the central laboratory normal ranges during treatment and at posttreatment Week 4.

Chemistry

There were no Grade 4 chemistry laboratory abnormalities. A Grade 3 increase in alkaline phosphatase was reported in a 3 year old subject (2.8%) at Day 84, which was resolved by the posttreatment Week 4 visit; the subject was asymptomatic and the investigator attributed the result to hyperalkaline phosphatemia of infancy. No notable changes from baseline in total bilirubin values were observed. No subject 3 to < 6 years old met any of the criteria for on-treatment liver-related laboratory abnormalities.

Safety in special populations

For subjects 3 to < 6 years old, no clinically relevant effects of SOF/VEL treatment on development as assessed by changes from baseline in Tanner pubertal stages to end of treatment, and to posttreatment Week 24 were observed for males or females.

No clinically relevant effects of SOF/VEL treatment on growth as assessed by changes from baseline in body height, body height percentiles, body weight, or body weight percentiles to posttreatment Week 24 were observed. In addition, no clinically relevant changes from baseline in BMI, BMI percentiles, or radiographic bone age to posttreatment Week 24 were observed.

Immunological events

No dermatologic or other immunologic events were reported for subjects 3 to < 6 years old.

Safety related to drug-drug interactions and other interactions

No additional drug interaction studies of SOF/VEL were conducted for subjects 3 to < 6 years old. No new findings relevant to the coadministration of SOF/VEL with other drugs are submitted with this update to the marketing application.

Discontinuation due to AES

One subject assigned to receive SOF/VEL 150/37.5 mg experienced Grade 1 AEs of decreased appetite and psychomotor hyperactivity and a Grade 2 AE of irritability with onset on Day 1 and a Grade 1 AE of product use issue (reported term: spitting up study drug) on Day 8. These AEs were assessed as related to the study drug and resulted in discontinuation of study drug on Day 20. The AEs resolved and this case did not raise any new safety concerns.

Post marketing experience

No post-marketing data were submitted with this application.

2.6.9. Discussion on clinical safety

The CHMP considered that safety can be bridged from the adult pivotal trials of Epclusa. AEs presented above were expected to be common among children in the given age group and were not necessarily related to treatment. However, the rate of vomiting was considered higher than expected. Although it is acknowledged that there is an expected base rate of vomiting in the age group concerned, it was notable that investigators assessed the event as treatment related on several occasions. Given a reasonable possibility that vomiting is causally related to treatment with Epclusa, the term has been added to the Product Information. No other safety concerns were raised.

2.6.10. Conclusions on the clinical safety

The safety profile of Epclusa in patients 3 years of age and older is considered acceptable.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table SVIII.1. 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
	Safety in patients with previous HCC

2.7.2. Pharmacovigilance plan

Table Part III.2. 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 Ongoing	To evaluate the impact of DAA treatment on the incidence of HCC recurrence, relative to no DAA therapy	*Important potential risk*: Recurrence of HCC *Missing information:* Safety in patients with previous HCC	Submission of final report	Final study report Q4 2021
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
De Novo DAA PASS: A post-authorisation safety	To evaluate among compensated cirrhotic patients, whether DAA therapy for	*Important potential risk:* Emergence of HCC	Submission of updated joint protocol	02 April 2019

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct acting antivirals for chronic hepatitis C Ongoing	chronic HCV infection increases the risk of incident HCC compared to no treatment or treatment with IFN-based regimens		End of Data Collection	18 months after protocol approval by IRB and PRAC
			Final Report of Study Results	12 months after end of data collection

2.7.3. Risk minimisation measures

Table Part V.3. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important potential risk(s)		
Recurrence of HCC	Routine risk minimization measures: None Additional risk minimization measures: None The need for risk minimization measures will be reassessed following the availability of the results from a study for HCC recurrence.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: DAA-PASS Final study report due date: Q4 2021
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: De Novo DAA PASS Final study report due date: 12 months after end of data collection
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: None Additional pharmacovigilance activities: None
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: DAA-PASS Final study report due date: Q4 2021

2.7.4. Conclusion

The CHMP considered that the risk management plan version 8.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. 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

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. Although less information is available about HCV in children, the global prevalence in 2018 of HCV infection in children from birth to 18 years has been estimated to be 0.13%, or 3.26 million children; over half (1.83 million) were aged 12 to 18 years {Schmelzer 2020}. Prevalence also varies by geographic location, with prevalence rates estimated to be 0.04% in Western Europe and 0.06% in the United States (US) compared with rates of 0.40% in Eastern Europe and up to 1.74% in Mongolia. Approximately 50% of the children with HCV infection were estimated to be living in Pakistan, China, India, and Nigeria.

The natural history of chronic HCV infection in children differs from that in adults since HCV infection in children is relatively benign. Most children chronically infected with HCV are asymptomatic or have mild nonspecific symptoms. However, cirrhosis has been reported in approximately 1% to 2% of adolescents and children with chronic HCV infection, and advanced liver disease and decompensated cirrhosis have been reported in children as young as 3 years of age and as early as 1 year after infection {Indolfi 2019}. Disease progression also may occur many years after the initial infection. At the time of a retrospective review of 1049 patients infected with HCV as children, cirrhosis developed in 32% of patients at a median of 33 years following diagnosis; 5% developed hepatocellular carcinoma (HCC), 4% had a liver transplant, and overall mortality was 3% {Modin 2019}.

3.1.2. Available therapies and unmet medical need

The availability of oral DAA therapies for HCV-infected paediatric patients represents a major therapeutic advance, by eliminating the need for weekly pegylated interferon (Peg IFN) injections and the side effects associated with its use. However, SOF is given in combination with RBV; RBV is associated with significant toxicities, including hematologic, constitutional, and teratogenic side effects. In addition, treatment duration with either SOF or LDV/SOF is dependent on HCV genotype and cirrhosis status, which also may represent a limiting factor for some paediatric patients. Therefore, treatment options that do not include RBV, that have fixed durations regardless of HCV genotype, and that are effective across all HCV genotypes would be beneficial by decreasing the frequency of monitoring and blood tests, and increasing patient adherence. Moreover, the availability of a pangenotypic regimen is anticipated to be especially beneficial in areas where HCV genotype diversity is high and where genotyping may not be readily available or routinely performed.

3.1.3. Main clinical studies

Study GS US 342-1143 was an open-label, multicohort, 2-part study evaluated the PK, safety, and antiviral activity of SOF/VEL in pediatric subjects with chronic HCV infection. This study consisted of a PK lead-in phase (Cohorts 1, 2, and 3) and a treatment phase (Groups 1 and 2) within each age group.

- Group 1 (including Cohort 1):
    - Adolescent subjects 12 to < 18 years old
- Group 2 (including Cohorts 2 and 3):
    - Pediatric subjects 6 to < 12 years old
    - Pediatric subjects 3 to < 6 years old

The new data in this submission pertained to subjects aged 3 to <6 years.

3.2. Favourable effects

In line with EMA guidelines on direct-acting antiviral, efficacy is bridged based on similar PK from adult pivotal trials.

In the limited paediatric dataset of subjects between 3 and <6 years, 34 of 41 subjects (82.9%) who received SOF/VEL achieved SVR12 and no cases of virologic failure were seen.

3.3. Uncertainties and limitations about favourable effects

The CHMP considered there were no uncertainties relevant to the B/R assessment.

3.4. Unfavourable effects

The CHMP considered that safety can be bridged from the adult pivotal trials of Epclusa, where the safety profile of both SOF and VEL were established as favourable. No safety concerns arose in the paediatric population, which would indicate a major difference in the safety profile compared to adults.

3.5. Uncertainties and limitations about unfavourable effects

In subjects aged 3-5 years old, the exposure is somewhat higher than in adults. However, in light of the favourable safety profile of SOF and VEL and the lack of any clear exposure response for AEs, this uncertainty is considered minor.

3.6. Effects Table

SOF, GS-331007, and VEL model predicted exposure metrics in HCV-Infected Paediatric Subjects 3 to <6 Years Old and adults are presented in **Table 23** below.

Table 23 Favourable effects of Epclusa in paediatric patients 3<6 years old

Favourable effects					
SOF/VEL					
Analyte	**PK Parameter**	**Mean (%CV)**		**% GMR (90% CI)**	**Uncertainties / Strength of evidence**
		Pediatric Subjects 3 to < 6 Years Old SOF/VEL 200/50 mg or 150/37.5 mg (N = 36[a])	**Adult Phase 2/3 Population SOF/VEL 400/100 mg (N = 1428[b])**	**Pediatric Subjects vs Adult Phase 2/3 Population**	
SOF	AUC_{tau} (h•ng/mL)	2537.0 (57.4)	1261.6 (37.2)	183.36 (165.28, 203.43)	Model predicted
	C_{max} (ng/mL)	1406.4 (69.2)	566.3 (31.4)	199.60 (180.82, 220.33)	Model predicted
GS-331007	AUC_{tau} (h•ng/mL)	12544.6 (48.6)	13966.7 (28.0)	87.36 (81.01, 94.21)	Model predicted
	C_{max} (ng/mL)	1132.4 (28.9)	868.2 (27.6)	131.37 (121.71, 141.80)	Model predicted
VEL	AUC_{tau} (h•ng/mL)	4480.5 (48.8)	2967.3 (50.2)	149.85 (130.64, 171.89)	Model predicted
	C_{max} (ng/mL)	494.1 (46.0)	259.0 (53.9)	192.46 (165.32, 224.06)	Model predicted
	C_{tau} (ng/mL)	54.6 (75.5)	41.5 (65.0)	116.98 (99.63, 137.36)	Model predicted

%CV = percentage coefficient of variation; GMR = geometric mean ratio; PK = pharmacokinetic(s); SOF = sofosbuvir; VEL = velpatasvir
SOF/VEL Adult Population = HCV-infected adult subjects administered SOF 400 mg and VEL 100 mg as either single agents or FDC in Phase 2 and 3 Study GS-US-337-0122, GS-US-342-0102, GS-US-342-0109, GS-US-342-1138, GS-US-342-1139, or GS-US-342-1140.
a For SOF, N = 34
b For SOF and VEL, N = 982 and 1425, respectively

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Chronic hepatitis C is a disease with both somatic and social consequences. Although paediatric patients rarely suffer liver fibrosis and subsequent decompensation, the favourable effects of a curative therapy are substantial.

In children between 3 and <6 years, given the favourable safety profiles of SOF and VEL, the unfavourable effects of treatment are expected to be related more often to the practicalities of medicine intake rather than to adverse drug reactions.

3.7.2. Balance of benefits and risks

An extrapolation approach of efficacy from adults to paediatric patients is considered suitable for hepatitis C because the PD target is expected to respond similarly to similar plasma concentrations of SOF/VEL in both adult and paediatric patients.

Exposure of SOF and VEL in the paediatric patients 3 to <6 years is higher than the adult exposures. With a favourable safety profile for SOF and VEL, it is preferred to have slight over exposure compared to under exposure, as under exposure could lead to potential lack of efficacy. The population pharmacokinetic analysis supported the indication and the proposed dosing in paediatric patients 3 to <6 years old.

3.8. Conclusions

The overall benefit/risk balance of Epclusa for the treatment of chronic hepatitis C infection in patients 3 years of age and older is positive, subject to the conditions stated in section 'Recommendations'.

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 150 mg / 37.5 mg coated granules and 200 mg / 50 mg coated granules is favourable in the following indication:

- Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients 3 years of age and older.

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 Marketing authorisation holder (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:	Q4 2021

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 3 years and older. 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 8.0) is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial updates throughout the Product Information.