30 April 2020
EMA/270155/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sovaldi

International non-proprietary name: sofosbuvir

Procedure No. EMEA/H/C/002798/X/0059/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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Table of contents

List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AUC	area under the concentration versus time curve
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
C_{max}	maximum observed concentration of drug
CSR	clinical study report
DAA	direct-acting antiviral
EC	European Commission
eGFR	estimated glomerular filtration rate
EMEA	European Medicines Evaluation Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gilead	Gilead Sciences
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDPE	High density polyethylene
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IFN	interferon
IL28B	IL28B gene
IND	investigational new drug (application)
INR	international normalized ratio
IPC	In-process control
LLOQ	lower limit of quantitation
N or n	number of subjects in a population (N) or subset (n)
NDA	new drug application
NF	National formulary
NI	nucleoside inhibitor
NOR	Normal operating range
NS (3/4A/5A/5B)	nonstructural protein (3/4A/5A/5B)
PAR	Proven acceptable range
PBRER	Periodic Benefit-Risk Evaluation Report
PDCO	Pediatric Development Committee
PDE	Permitted daily exposure
PE	Polyethylene
Peg-IFN	pegylated interferon
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia

PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update Report
QC	Quality control
RAV	resistance-associated variant
RBV	ribavirin
RH	Relative humidity
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of product characteristics
SOF	sofosbuvir (Sovaldi®)
SVR, SVRxx	sustained virologic response, sustained virologic response at "xx" weeks following completion of all treatment
TSE	Transmissible Spongiform Encephalopathy
UK	United Kingdom
US, USA	United States, United States of America
USP	United States Pharmacopoeia
UV	Ultraviolet
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 30 May 2019 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 strength (200 mg film-coated tablets) and a new pharmaceutical form (granules) associated with new strengths (150 and 200 mg). The new presentations are indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in patients aged 3 to <12 years.

The extension application is grouped with a type II variation (C.I.6.a) to include paediatric use in patients aged 3 to < 12 years who weigh greater than or equal to 35 kg to the existing presentations of 400 mg film-coated tablets. Sections 4.2, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated to support the extended indication. The RMP (version 8.3) is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial updates and linguistic corrections throughout the Product Information.

The legal basis for this application refers to:

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

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0172/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0172/2018 was completed.

The PDCO issued an opinion on compliance for the PIP P/0172/2018.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Filip Josephson

The application was received by the EMA on	30 May 2019
The procedure started on	20 June 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	10 September 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	16 September 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting o	3 October 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	17 October 2019
The MAH submitted the responses to the CHMP consolidated List of Questions on	18 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	29 January 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2020
The CHMP agreed on a list of outstanding issues to the MAH on	27 February 2020
The MAH submitted the responses to the CHMP List of Outstanding Issues on	1 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 April 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Sovaldi on	30 April 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

2.1.1.1. Epidemiology

Hepatitis C virus infection is a global health challenge with an estimated global prevalence of 1%, for a total of 71 million individuals worldwide chronically infected with HCV (The Polaris Observatory HCV Collaborators 2017), (World Health Organization (WHO) 2018b). In the US, over 3 million people are estimated to be chronically infected with HCV (Center for Disease Control and Prevention 2016), and in Europe an estimated 10 to 14 million people have chronic HCV infection (The Polaris Observatory HCV Collaborators 2017), (World Health Organization (WHO) 2018c). Up to 85% of individuals infected with HCV fail to clear the virus and progress to chronic infection; over the ensuing 20 years, as many as 20% of patients with chronic HCV infection are estimated to develop complications, including cirrhosis, end stage liver disease, and hepatocellular carcinoma (HCC). Curing HCV infection is associated with numerous health benefits, including more than 70% reduction in the risk of HCC and 90% reduction in the risk of liver-related mortality and liver transplantation (Morgan 2013), (van der Meer 2012), (Veldt 2007), (Poynard 2002).

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

2.1.1.2. Aetiology and pathogenesis

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

2.1.1.3. Clinical presentation

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

2.1.1.4. Management

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

In 2017, Sovaldi and Harvoni were approved in the US and EU for the treatment of patients 12 years of age and older or weighing ≥ 35 kg (in the US only). As such, per current international guidelines, pegylated interferon (Peg-IFN) and ribavirin (RBV) are no longer recommended for treatment of children 12 years of age and older (American Association for the Study of Liver Diseases (AASLD) 2018), (European Association for the Study of the Liver (EASL) 2018), (World Health Organization (WHO) 2018a), (Indolfi 2018). For patients younger than 12 years of age (and, in certain countries, weighing < 35 kg), however, there are no approved DAA treatments; currently, the only approved HCV treatment option is Peg-IFN and weight-based RBV for 24 or 48 weeks, depending on HCV genotype.

2.1.2. About the product

Sofosbuvir (Sovaldi, SOF) is a hepatitis C virus (HCV) nonstructural protein (NS) 5B polymerase inhibitor approved for use in combination with other agents for the treatment of chronic HCV infection. Sofosbuvir was first approved for commercial marketing in the United States on 6 December 2013 and in the European Union on 16 January 2014. Sofosbuvir is indicated for the treatment of genotypes 1 to 4 (US) and genotypes 1 to 6 (EU) HCV infection. In 2017, Sovaldi was approved in the US and EU for the treatment of patients 12 years of age and older, or weighing ≥ 35 kg (in the US only).

Type of Application and aspects on development

In the EU, a paediatric investigation plan (PIP) for SOF was agreed with the European Medicines Agency on 18 December 2012 (EMEA-001276-PIP01-12). Minor modifications to the original PIP have been agreed upon since this time, with the most recent European Medicines Agency Decision issued on 15 June 2018 (EMEA-001276-PIP01-12-M02). The design of Study GS-US-334-1112 reflected the advice received from the Paediatric Development Committee (PDCO) during agreement of the PIP.

2.2. Quality aspects

2.2.1. Introduction

This application concerns a line extension to add three paediatric formulations containing lower doses of the active substance, sofosbuvir, than the already authorised 400 mg film-coated tablets: 200 mg film-coated tablets and 150 mg and 200 mg coated granules in sachet.

Other ingredients in the film-coated tablets are:

Tablet core: mannitol, microcrystalline cellulose, croscarmellose sodium**,** colloidal anhydrous silica and magnesium stearate.

Film-coating: polyvinyl alcohol, titanium dioxide, macrogol, talc and iron oxide yellow.

Other ingredients in the granules are:

Granule cores: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, colloidal anhydrous silica and sodium stearyl fumarate

Film-coating: hypromellose, macrogol, amino methacrylate copolymer, talc, stearic acid, sodium lauryl sulfate, colloidal anhydrous silica

The film-coated tablets are available in high density polyethylene (HDPE) bottles with polypropylene child-resistant closures and the granules are available in sachets consisting of polyester/aluminium/polyethylene film as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

No new documentation has been provided for the active substance sofosbuvir. The same source of active substance is used as for the existing 400 mg film-coated tablets. This data was assessed in the original application and in subsequent variations and is considered sufficient to support the current line extension application without further review.

2.2.3. Finished Medicinal Product – 200 mg film-coated tablets

Description of the product and Pharmaceutical development

Sofosbuvir 200 mg film-coated tablets are yellow and oval-shaped, debossed with "GSI" on one side and "200" on the other side. The core composition and film-coating material for the 200 mg strength tablets are dose proportional to the already-commercialised 400 mg strength tablet. The only differences are tablet size, debossing and shape which provide sufficient distinction.

The aim of development was to identify a lower strength immediate release solid oral dosage form for use in paediatric patients. Development was based on the already approved 400 mg tablets.

The active substance is a crystalline solid, routinely manufactured as the most thermodynamically stable polymorphic form containing small quantities of an equivalent polymorphic form. The most thermodynamically stable polymorph is the third form used in product development and was used in phase III clinical trials and the already-approved 400 mg tablets. Sofosbuvir exhibits pH-independent solubility across the physiological pH range. Sofosbuvir is highly soluble but has low apparent intestinal permeability (BCS class III). Particle size was found to be critical for dissolution rate, so the active substance is sieved, or screen-milled and particle size is controlled in the active substance specification.

The excipients are the same as those used in the 400 mg tablets and their compatibility with the active substance was demonstrated. They 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 paragraph 2.2.1 of this report.

Two strength tablets were used in paediatric clinical trials – a 100 mg tablet used in phase 2 and the proposed commercial 200 mg tablet used in phase 3. Both are dose-proportional to the approved 400 mg tablets and used the same form of active substance. A waiver for *in vivo* bioequivalence studies was requested based on fulfilment of the criteria outlined in *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 rev 1./corr.). Comparative dissolution profiles of the 400 mg tablets were provided at pH 2, 4.5, 6.8 (the QC method, the same as was developed for the 400 mg tablets) and in simulated fed and fasted state intestinal fluids. Comparative dissolution profiles were also provided for 100, 200 and 400 mg tablets using the QC method. In all cases, >85% dissolution occurred in less than 15 minutes. Given the high solubility of sofosbuvir, the fact that all three strengths are dose proportional and manufactured by equivalent processes and the *in vitro* dissolution data, the strength biowaiver is considered justified.

The manufacturing process for the 200 mg tablets is equivalent to that for the 400 mg tablets, the only differences being in the compression and film-coating steps due to the change in tablet size and shape. A dry granulation approach is used and the same set-points, normal operating ranges (NORs) and proven acceptable ranges (PARs) are used for both tablet strengths.

The primary packaging is a high-density polyethylene (HDPE) bottle with a polypropylene child-resistant closure with a polyester coil. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: blending of sofosbuvir with intra-granular excipients and dry granulation, then milling; blending with extra-granular excipients; tabletting; film-coating; packaging. The process is considered to be a standard manufacturing process.

The robustness of the manufacturing procedure for the clinical and the proposed commercial formulation has been demonstrated by the successful manufacture of representative batches up to commercial scale. has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The set-points and ranges for unit operations have been set in line with the development data and are considered appropriate. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Process validation will be performed on a minimum of three consecutive production scale batches at each manufacturing site prior to commercial distribution. A process validation scheme including an expanded sampling plan has been submitted and is considered adequate.

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 (UV) and microbiological enumeration.

The specifications and tests are the same as those for the approved 400 mg tablets, including the limits for degradation products, several of which are also metabolites and are considered qualified.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Class 1, 2A and selected class 3 elements (based on the construction materials of the equipment) were considered and tested. Batch analysis

data from six production scale batches of the 400 mg tablets using a validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. This data can be considered representative of the 200 mg tablets since they use the same excipients and manufacturing process. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any controls for elemental impurities.

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 are provided for three production scale batches of the 200 mg tablets 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.

Stability of the product

Stability data from 3 production scale batches of the 200 mg tablets stored for up to 6 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. In addition, 60 months' long-term data was provided for 1 batch of the 100 mg tablets. Samples were tested for appearance, assay, degradation products, water content and dissolution. No significant changes were observed to any of the measured parameters under any conditions.

A further consideration is that the already-marketed 400 mg tablets have a 6-year shelf-life based on extensive stability data. Photostability data was generated for the 400 mg tablets indicating that sofosbuvir tablets are not photosensitive. Stressed studies were conducted, which indicate that the product is stable to heat and humidity if stored in the HDPE bottle. In an open dish study, the water content increased slightly without any significant impact on other measured parameters. The data from the 400 mg tablets is considered representative.

Based on available stability data, the proposed shelf-life of 6 years without any special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. The magnesium stearate is from vegetable sources.

2.2.4. Finished Medicinal Product – 150 and 200 mg coated granules in sachet

Description of the product and Pharmaceutical development

Sovaldi coated granules in sachet are an immediate-release taste-masked oral dosage form available in sachets for single use containing either 150 or 200 mg sofosbuvir as active substance.

The granules are white to off-white, approximately 2 mm in diameter and packaged into polyester/aluminum/polyethylene (PET/ALU/PE) heat-sealed sachets. The sachet has a length of 25 mm and a height of 70 mm. A 150 mg sachet contains 60 granules and a 200 mg sachet contains 80 granules.

The aim of development was to identify an immediate release dosage form for those paediatric patients unable to swallow the 200 mg tablet. The same active substance form is used as for the tablets and the choice of dosage form was influenced by sofosbuvir's physicochemical properties, i.e. highly soluble and pH dependent stability in aqueous solution. Therefore, a solid dosage form was selected.

Chosen excipients had to be suitable for use in paediatric patients. In addition, due to the bitter taste of sofosbuvir, the granules are formulated to provide sufficient taste-masking.

Compatibility of the active substance with the chosen excipients was demonstrated during formulation development. All excipients other than the film-coating agents are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. The film-coating agents are tested against in-house standards and their components meet compendial requirements. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

Chemical stability and dissolution were evaluated following mixing of the granules with non-acidic soft foods. The granules were demonstrated to be chemically stable with no observed degradation after 2 hours. In addition, the dissolution profile was not impacted by mixing with food. It is not considered likely that paediatric patients will require feeding tubes. Therefore, feeding tube administration was not investigated.

The QC dissolution method established for the tablets had to be amended for the granules.

Given the small size of the granules relative to the tablets, a different manufacturing principle was required. A fluid bed granulation process was developed and demonstrated to provide product with adequate quality attributes despite the water-sensitivity of the active substance. Initial risk assessments were conducted based on prior knowledge of the tablet product and other taste masked products, which guided development activities. As a result of these studies, target set-points and NORs were established for unit operations as part of control strategy for the manufacturing process.

The primary packaging is a unit dose PET/alu/PE sachet. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps, the first five of which result in a process intermediate: blending of sofosbuvir with intra-granular excipients followed by granulation, drying and milling; blending with extra-granular excipients; compression; sub-coating and screening; taste-mask coating and screening; packaging. The process is considered to be a standard manufacturing process.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner through the production of development, clinical and stability batches. The IPCs 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. Process validation will be conducted on 3 consecutive production scale batches prior to commercialisation. The process validation scheme provided is considered suitable.

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 examination(Ph. Eur.).

The specifications and tests are similar to those for the approved 400 mg tablets, including the degradation products, several of which are also metabolites and are considered qualified. The limits for these degradation products are slightly higher than in the tablets reflecting the different manufacturing process and are based on batch data gathered to date.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Class 1, 2A and selected class 3 elements (based on the construction materials of the equipment) were considered and tested. Batch analysis data from three production scale batches of the oral granules using a validated method was provided, demonstrating that each relevant elemental impurity was well below its control threshold.

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 degradation products testing has been presented.

Batch analysis results are provided for three 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.

Stability of the product

The two strengths of Sovaldi granules, 150 and 200 mg, differ only in the number of granules in each sachet. Therefore, a matrix approach was taken in line with ICH Q1D, with a one third reduction of testing of the three production scale batches of each strength at each time point. Long-term stability studies are being conducted at 30 °C/75% RH and 18 months' data is currently available. Accelerated stability studies were conducted at 40 °C/75% RH for a period of up to 6 months. Samples were tested for appearance, water content, assay, degradation products, dissolution and microbiological examination. All results were within the specifications and no trends were observed.

Further data was provided from a month-long study at -20 °C and a two-week study at 50 °C / 75% RH in both primary and bulk packaging indicating that the granules remain stable under those conditions. It is known from other formulations that sofosbuvir is not photosensitive so no additional studies on the granules were carried out.

Based on available stability data, the proposed shelf-life of 24 months with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

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.

2.2.5. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Satisfactory information has been provided in regard of both new presentations intended for treatment of paediatric patients.

2.2.6. 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.

2.2.7. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

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

2.3.1. Ecotoxicity/environmental risk assessment

Regarding the properties of SOF, it is a pro-drug with the active substance being the triphosphate GS-461203. Neither the pro-drug/SOF nor the active moiety/GS-461203 enter the environment at >10% of the administered dose. The focus of the environmental risk assessment of SOF is instead GS-331007, the only drug residue detected in total excreta at >10% of the applied radioactive dose (GS-331007 accounted for 79.6%).

The mean partition coefficient was 0.398, 0.286 and 0.0593, at pH 4, 7 and 9, respectively, (log Kow -0.417, -0.576 and -1.28, respectively) and GS-331007 is therefore not a PBT-substance. A refined market penetration of 3.5% (the highest relevant nationwide estimated prevalence) was used to calculate a refined PEC surface water value. The refined PEC surface water of 7.0µg/L is significantly higher than the action limit of 0.01 µg/L. A Phase IIA assessment has therefore been performed and since a partition to sediment was indicated (>10% AR shifted after 14 days) a further assessment with a sediment dweller in Phase IIB has also been initiated. Since results indicate that GS-331007 does not adsorb to soils or activated sludges, aquatic toxicity has been the focus of Phase IIA analysis.

None of the ratios between the predicted environmental concentrations and predicted no effect levels for the Sewage treatment plant-, Surface water- or Groundwater-compartment were above 1 and no further studies are therefore required. In the Phase IIB analysis on sediment dweller, the risk quotient was also found to be below 1. Based on the data presented it is concluded that the environmentally relevant residue of sofosbuvir, GS-331007, is not expected to pose a risk to the environment.

2.3.2. Discussion on non-clinical aspects

In line with the completed Sovaldi paediatric investigation plan (PIP) and as stated in the PDCO compliance report and decision document, EMEA-C-001276-PIP01-12-M02/P/0172/2018, no additional non-clinical safety pharmacology and pharmacokinetic (PK) studies were required as part of the Sovaldi PIP. It was determined that the non-clinical programme comprehensively evaluated and characterized the toxicity profile of SOF, and there is no expectation that the toxicity profile seen in adult animals will be different to that in juvenile animals. Therefore, no new additional non-clinical data has been included in this application to support use in the paediatric population.

2.3.3. Conclusion on the non-clinical aspects

No new non-clinical studies have been submitted for this procedure, which is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- ***Tabular overview of clinical studies***

Clinical Study Included in the Update to the SOF Marketing Application for Paediatric Subjects (3 to < 12 Years Old)

Study Number	Study Design	Subject Population[a]	Treatment Regimen[b,c]	N[a,d]	Location
GS-US-334-1112[a]	Phase 2, open-label, multi-cohort, 2-part study	Treatment-naive and treatment-experienced subjects 3 to < 12 years old with chronic genotype 2 or 3 HCV infection	Genotype 2: SOF+RBV for 12 weeks Genotype 3: SOF+RBV for 24 weeks	6 to < 12 years: Genotype 2: 13 Genotype 3: 28 3 to < 6 years: Genotype 2: 5 Genotype 3: 8	**CSR:** GS-US-334-1112 Final CSR **Narrative:** m2.7.3, Section 2.1

CSR = clinical study report; HCV = hepatitis C virus; RBV = ribavirin; SOF = sofosbuvir

a Only data for subjects 6 to < 12 years old and 3 to < 6 years old are discussed in this summary.

b The doses and formulations of SOF were based on age group and weight as follows:
- Subjects 6 to < 12 years old received SOF 200 mg orally once daily (2 × 100-mg tablets or 4 × 50-mg capsules containing granules) + weight-based RBV orally divided twice daily. The selection of the SOF formulation was based on a swallowability assessment using matching placebo tablet at screening or baseline.
- Subjects 3 to < 6 years old who weighed ≥ 17 kg received SOF 200 mg orally once daily (4 × 50-mg capsules containing granules) + weight-based RBV orally divided twice daily. Subjects 3 to < 6 years old who weighed < 17 kg received SOF 150 mg orally once daily (3 × 50-mg capsules containing granules) + weight-based RBV orally divided twice daily.

c The dose of RBV was a weight-based dose of 15 mg/kg/day (< 47 kg), 600 mg/day (47−49 kg), 800 mg/day (50−65 kg), 1000 mg/day (66−80 kg), 1200 mg/day (81−105 kg), or 1400 mg/day (> 105 kg), orally divided twice daily.

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

2.4.2. Clinical Pharmacology

2.4.2.1. Pharmacokinetics

Two new SOF formulations; SOF 200-mg tablet and SOF oral granules (150-mg or 200-mg) are introduced. A waiver for in vivo bioequivalence (BE) studies is accepted for sofosbuvir (SOF) tablets, 200 mg strength, based on fulfilment of criteria outlined in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 rev 1./corr). The formulation and manufacturing processes used for the SOF 200-mg tablet are the same as those used for the commercial Sovaldi (SOF 400 mg) tablet.

The oral granules formulation was investigated in healthy adult subjects in study GS-US-334-1111. In this study, the main objectives were to evaluate the relative bioavailability of SOF oral granules relative to the already approved 400 mg SOF tablet formulation in healthy subjects and to evaluate the effect of concomitant food intake on the PK of SOF oral granules.

Formulation effect: The AUC of sofosbuvir was similar in Treatments A (tablet formulation) and B (granule formulation) as were median Tmax and t1/2. Sofosbuvir Cmax was ~14% lower following administration of the granules compared to the tablet. (See Table below)

Food effect: Sofosbuvir AUC was ~70% higher in Treatment C (granule formulation under fed conditions) compared to Treatment B (granule formulation under fasted conditions), and Tmax being prolonged from 0.5 to 1.0 hours. Sofosbuvir Cmax was somewhat reduced (~10%) in the fed state. (See Table 1 below)

Table 1. Summary of sofosbuvir plasma pharmacokinetic parameters by treatment

SOF PK Parameter	Treatment A SOF 400 mg (1 × 400-mg tablet) fasted (N=18)	Treatment B SOF 400 mg (8 × 50-mg granule units) fasted (N=18)	Treatment C SOF 400 mg (8 × 50-mg granule units) fed (N=18)
AUC_{last} (ng*h/mL)	798.6 (37.9)	836.0 (42.5)	1300.8 (29.2)
AUC_{inf} (ng*h/mL)	804.8 (37.7)	842.9 (42.1)	1312.5 (28.8)
C_{max} (ng/mL)	963.8 (38.0)	829.7 (45.5)	799.5 (58.6)
C_{last} (ng/mL)	10.3 (59.6)	10.7 (84.8)	10.3 (49.4)
T_{max} (h)	0.75 (0.50, 0.75)	0.52 (0.50, 1.00)	1.00 (0.75, 1.68)
T_{last} (h)	3.52 (3.00, 4.50)	4.00 (3.00, 4.50)	6.00 (5.00, 8.00)
$t_{1/2}$ (h)	0.41 (0.34, 0.48)	0.41 (0.37, 0.51)	0.65 (0.60, 0.73)
CL/F (mL/h)	557,219.7 (32.0)	611,726.4 (71.1)	326,378.6 (25.2)

Note: All PK parameters are reported as mean (%CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are reported as median (Q1, Q3).

Overall PK conclusions from study GS-US-334-1111

Relative bioavailability between tablet and granules

Sofosbuvir passed the conventional BE limits for AUClast and AUCinf, whereas Cmax was somewhat reduced with a geometric mean ratio of 84% (90% CI: 65%, 108%). This small difference in Cmax has no clinical significance. In addition, bioequivalence was established for the two metabolites GS-331007 and GS-566500 after administration of sofosbuvir granules versus tablet formulation: i.e., the two metabolites passed the conventional BE limits of 80-125% for AUClast, AUCinf and Cmax.

Food effect on the sofosbuvir granules

The effects of food on the exposure to GS-331007, sofosbuvir, and GS-566500 after administration of sofosbuvir granules were similar compared to the effects observed on the previously approved tablet formulation (Sovaldi 400 mg):

- Sofosbuvir: AUClast and AUCinf increased by approximately 70%, whereas Cmax was somewhat reduced (10% decrease).
- GS-331007: The AUClast and AUCinf were somewhat reduced, but still passed the conventional BE limits. Cmax was reduced by 40% (ratio 60%; 90% CI: 54%, 67%).
- GS-566500: AUClast, AUCinf, and Cmax increased by approximately 66%, 65% and 28%.

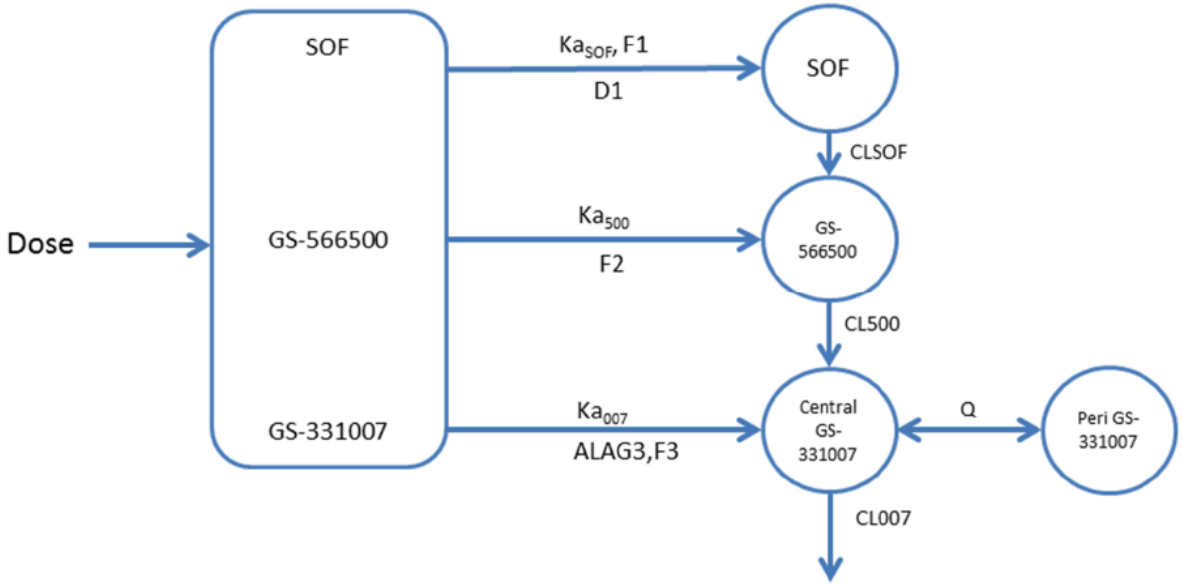
In summary, the granule formulation has similar exposure and food effect in healthy adults as the approved Sovaldi 400 mg tablet. In the SmPC it is stated that the granule (and the 200 mg tablet) should be administered with food. This is also the case for the approved 400 mg tablet (for practical reasons), as this product always is used together with Ribavirin that should be administered together with food.

Pharmacokinetics in Paediatric Subjects, 3-12 years

The PK of SOF and SOF's major circulating metabolite GS-331007, and intermediate metabolite GS-566500 were evaluated through population pharmacokinetic modelling. The population PK data included 226 subjects who received LDV/SOF±RBV in Study GS US 337-1116, and 105 subjects who received SOF+RBV in Study GS-US-334-1112. A total of 160 subjects in Study GS-US-337-1116 and 69 subjects in Study GS US-334-1112 had SOF samples included in the analysis population used for SOF joint model development (see

schematic diagram in Figure 1). A total of 197 and 198 subjects in Study GS-US-337-1116 had valid GS 566500 and GS-331007 samples, respectively, and a total of 70 and 85 subjects in Study GS US-334-1112 had valid GS-566500 and GS-331007 samples, respectively. In the analysis population, 11 subjects in Study GS US 337 1116 and 4 subjects in Study GS US 334 1112 had all BLQ concentrations for SOF, while 13 subjects in Study GS-US-337-1116 and 2 subjects in Study GS-US-334 1112 had all BLQ concentrations for GS-566500.

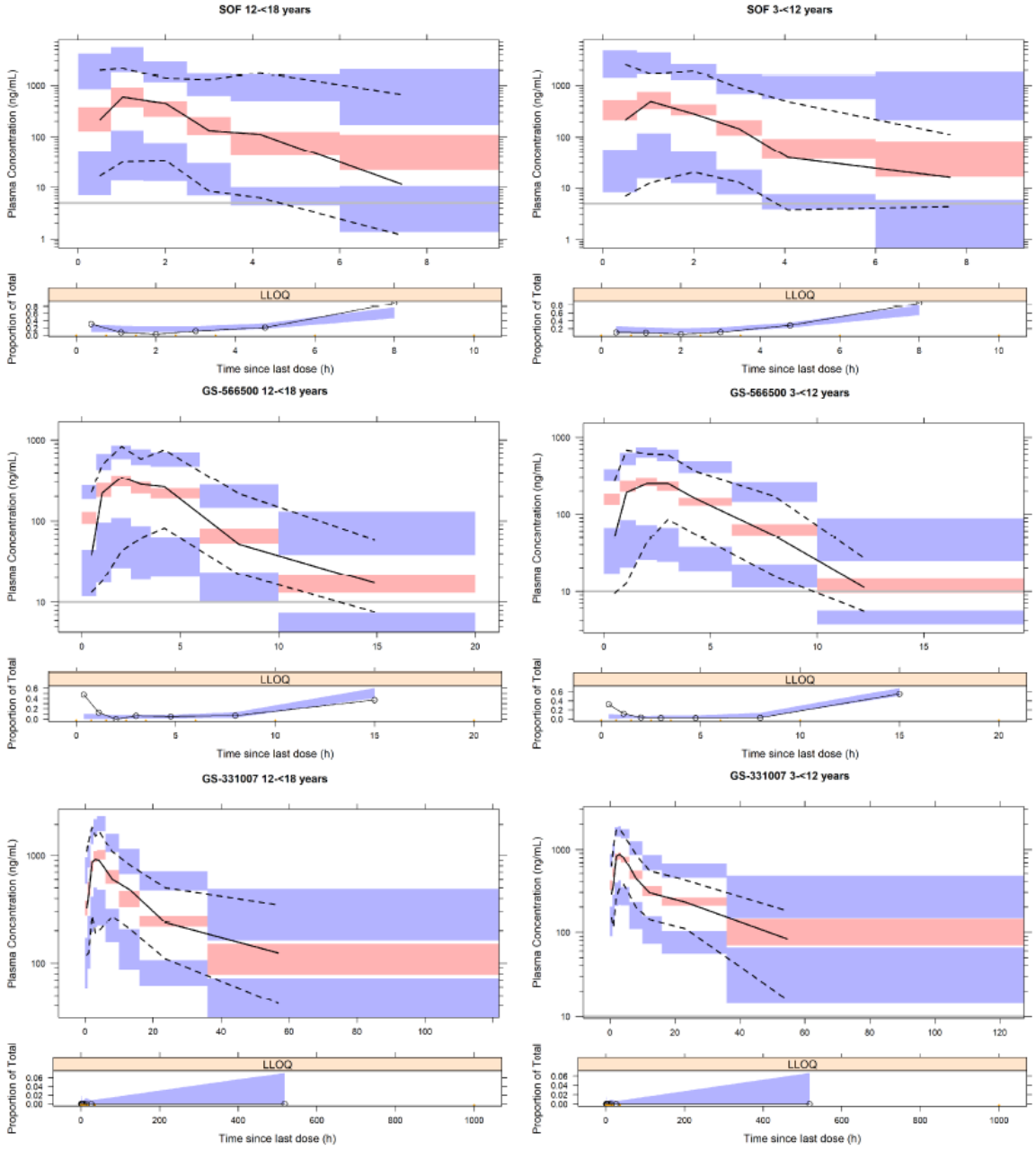
Figure 1 Population PK Model Diagram for SOF and SOF Metabolites.



Note: ALAG3 = absorption lag time of GS-331007; CL_{007} = apparent clearance of GS-331007; CL_{500} = apparent clearance of GS-566500; CLs_{OF} = apparent clearance of sofosbuvir (SOF); D1 = duration of absorption of SOF; F1 = relative bioavailability for SOF; F2 = relative bioavailability for GS-566500; F3 = relative bioavailability for GS-331007; Ka_{007} = absorption rate of GS-331007; Ka_{500} = absorption rate of GS-566500; Kas_{OF} = absorption rate of SOF; Q = apparent distribution clearance of GS-331007.

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 a lag-time for both SOF and GS-331007, followed by first-order elimination. The model included, a priori, the effect of weight (WT; allometric exponents fixed to 0.75 and 1 for clearances and volumes, respectively) on clearance and volume for SOF, GS-566500, and GS-331007; coadministration of LDV on the SOF relative fraction absorbed; and coadministration of RBV on clearance of the metabolites. In addition, the model included statistically significant covariates of age on on clearance of the metabolites and sex on clearance for GS-331007. The following covariates were tested in the analysis: baseline age, sex, race, ethnicity, creatinine clearance, food, and interleukin-28 status. The model performance is presented as prediction corrected visual predictive checks in Figure 2.

Figure 2 Prediction-corrected VPC of Plasma Concentration-Time Profiles for SOF and SOF Metabolites Stratified by Age (12 to < 18 Years and 3 to < 12 Years)



Note: BLQ = below limit of quantitation; LLOQ = lower limit of quantitation; SOF = sofosbuvir. pcVPC plots show median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the observed concentrations in all subjects. The red area is the 95% confidence interval of the simulated median and the blue area is the 95% confidence interval of the simulated 5th and 95th percentiles. pcVPC for adolescents (12 to < 18yr) is presented in left panels and pcVPC for subjects 3 to < 12yr is presented in right panels for SOF (top), GS-566500 (middle) and GS-331007 (bottom). LLOQ panels: open circles and black solid lines show observed proportion of BLQ samples, whereas the blue area shows the 95% confidence interval of the simulated BLQ samples.

Model Predicted Steady-State Exposure Parameters

Population PK analyses of all paediatric subjects 3 to < 12 years old in the PK lead-in and treatment phases confirmed that SOF and GS-331007 exposures were similar to exposures in HCV-infected adult subjects from Phase 2/3 studies. Sofosbuvir and GS-331007 AUCtau and Cmax were within the predefined PK equivalence boundaries of 50% to 200% (Table 2).

Table 2 GS-US-334-1112: Statistical Comparison of SOF and GS-331007 Exposures Between Paediatric Subjects 3 to < 12 Years Old and the Adult Phase 2/3 Population

Analyte	PK Parameter	6 to < 12 Years Old SOF 200 mg (N = 39 for SOF and N = 41 for GS-331007)[a]		3 to < 6 Years Old SOF 150 mg or 200 mg[b] (N = 12 for SOF and GS-331007)[c]	
		Mean (%CV)	% GMR (90% CI) Pediatric Subjects / Phase 2/3 Adult Population	Mean (%CV)	% GMR (90% CI) Pediatric Subjects / Phase 2/3 Adult Population
SOF	AUC_{tau} (h•ng/mL)	863.5 (66.6)	77.10 (70.13, 84.76)	1045.4 (52.3)	98.62 (83.67, 116.24)
	C_{max} (ng/mL)	453.9 (75.7)	78.24 (70.13, 87.29)	525.8 (51.1)	98.28 (81.28, 118.83)
GS-331007	AUC_{tau} (h•ng/mL)	9321.9 (32.7)	130.80 (120.56, 141.90)	12358.1 (31.2)	174.51 (150.30, 202.62)
	C_{max} (ng/mL)	866.3 (33.1)	152.29 (137.75, 168.36)	1084.3 (23.7)	195.03 (162.20, 234.51)

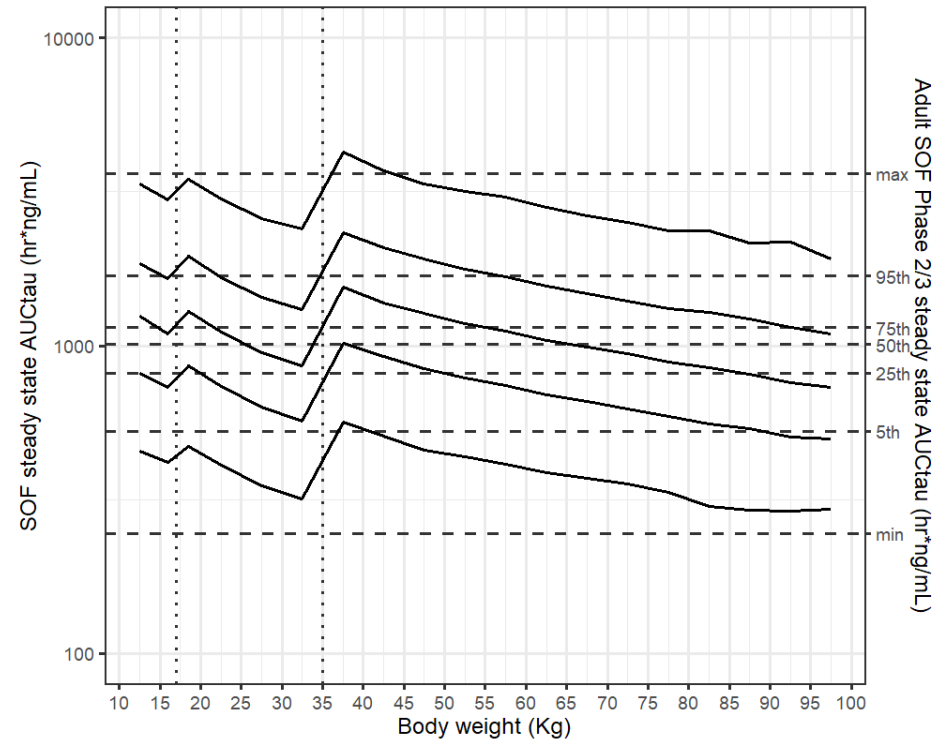
CI = confidence interval; CV = coefficient of variation; GMR = geometric mean ratio
a Sofosbuvir exposures were not determined for 2 subjects who did not have evaluable SOF plasma concentrations.
b Subjects weighing ≥ 17 kg received SOF 200 mg while subjects weighing < 17 kg received SOF 150 mg.
c Only 12 of 13 enrolled subjects 3 to < 6 years old were evaluated for PK due to 1 subject prematurely discontinuing study treatment due to AEs.
Source: Ad Hoc Tables 10170.4 and 10170.5

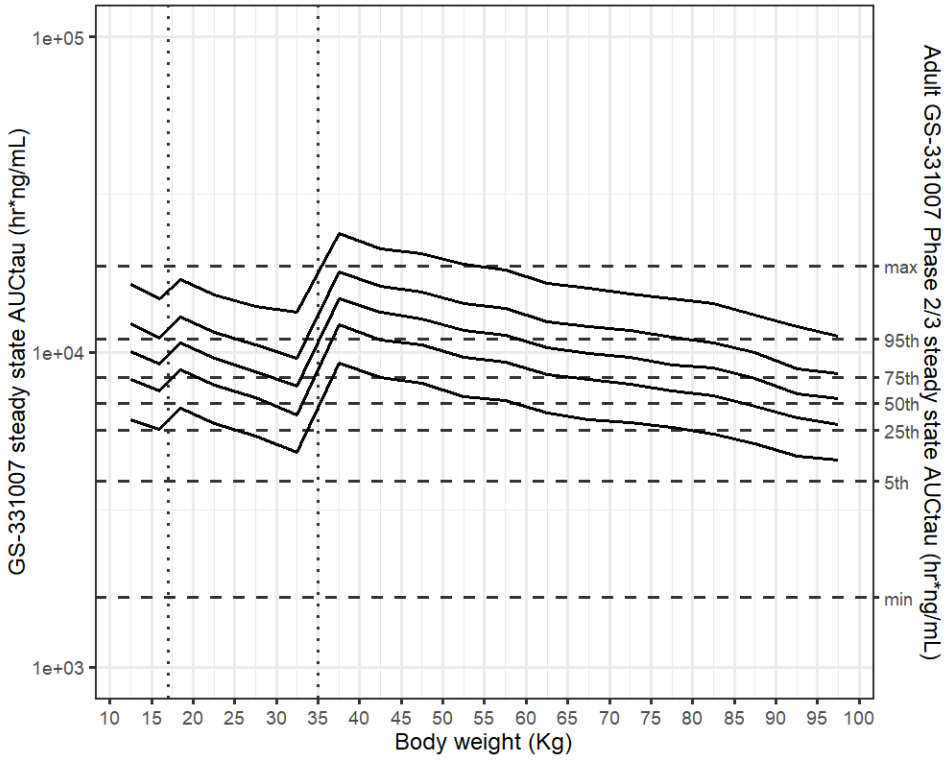
Population PK simulations were conducted to evaluate SOF and GS-331007 exposures (Figure 3) based on the proposed weight band-based dosing regimen (Table 3).

Table 3 Proposed SOF Weight Band-Based Doses

	Proposed SOF Dose for Pediatric Patients 3 to < 12 Years Old		
Weight (kg)	≥ 35	< 35 and ≥ 17	< 17
SOF Dose (mg)	400	200	150

Figure 3 Simulated SOF and GS-331007 Exposures by Proposed Weight Band-Based Dosing





WT = weight

Solid lines represent 5th, 25th, 50th, 75th, and 95th percentiles of simulated paediatric exposures. Horizontal dashed lines represent distribution of adult exposures. Vertical dashed lines indicate 17-kg and 35-kg cutoffs.

Simulated SOF exposures are largely contained within the range observed in the SOF+RBV adult Phase 2/3 population. In subjects with the lowest body weight within each identified weight band (ie, 13, 17, and 35 kg), approximately ≤ 6% are expected to achieve maximum overall exposures greater than those observed in the SOF+RBV adult Phase 2/3 population. However, < 1% of subjects is expected to exceed SOF exposures observed in the LDV/SOF adult Phase 2/3 population. Furthermore, < 3% of subjects, including those with the highest body weight, are expected to have exposures lower than the range of adult exposures.

Simulated GS-331007 exposures are largely contained within the range observed in the SOF+RBV adult Phase 2/3 population. In subjects with the lowest body weight within each identified weight band, approximately < 13% are expected to achieve maximum exposures greater than those observed in the SOF+RBV adult Phase 2/3 population. However, < 1% of subjects is expected to exceed GS-331007 exposures observed in the LDV/SOF adult Phase 2/3 population. Furthermore, no subjects, including those with the highest body weight, are expected to have exposures lower than the range of adult exposures.

2.4.2.2. Pharmacodynamics

Due to the high SVR rates in subjects 6 to < 12 years old (100.0%, 41 of 41 subjects) and subjects 3 to < 6 years old (92.3%, 12 of 13 subjects), with no virologic failures, exposure-response relationships for efficacy were not evaluated.

The PK/PD Analysis Set for PK-safety included all paediatric subjects 3 to < 12 years old with chronic HCV infection who received SOF and had evaluable population-based AUCtau estimates for SOF (N = 51) and GS-331007 (N = 53). Overall, SOF and GS-331007 exposures in paediatric subjects were similar regardless of the presence or absence of the evaluated AEs (vomiting, headache, fatigue, cough, diarrhea, or decreased appetite), both overall and by age group or treatment group strata. The exposure-response analyses are viewed as supportive evidence and hence the provided graphical analyses are accepted. No obvious trends with regards to exposure and safety could be detected.

2.4.3. Discussion on clinical pharmacology

Population PK analysis has been used to describe the sofosbuvir PK data in the paediatric population 3-18 years of age. A joint model has been developed where sofosbuvir and metabolites GS-566500 and GS-331007 have been simultaneously analysed. Furthermore, all sofosbuvir PK data, administered as Sovaldi or in the fixed-dose combination Harvoni (sofosbuvir+ledipasvir) have been pooled together to make use of all available data. This approach is highly encouraged. The following covariates were tested in the analysis: baseline age, sex, race, ethnicity, creatinine clearance, food, and interleukin-28 status. The only statistically significant covariates were age on clearance of both metabolites and sex on clearance for GS-331007. The effect of ledipasvir on sofosbuvir bioavailability, as well as the ribavirin effect on metabolite clearance was incorporated in the model. The joint model was able to describe the three analytes well and the model is considered adequate to be used for predicting the exposure (AUC and Cmax) in the paediatric population.

The population PK predicted exposures metrics have been compared with the corresponding observed exposure ranges in the adult population. The MAH had predefined PK equivalence boundaries of 50% to 200% and all the exposure metrics meet the criteria and the exposure comparisons are largely contained within the predefined boundaries. The CHMP noted that the AUC and Cmax for the metabolite GS-331007

were clearly higher than the adult exposures. However, given the safety profile of SOF and associated metabolites these exposure levels were considered acceptable.

The proposed body weight bands are endorsed. Although there is a peak at the 35 kg switch, it is considered that an additional weight band would not be of added value.

2.4.4. Conclusions on clinical pharmacology

Overall, the population PK analysis provided an adequate description of sofosbuvir and associated metabolites exposure in children 3-12 years of age. The CHMP concluded that the dosing recommendations can be endorsed.

2.4.5. Clinical efficacy

2.4.5.1. Main study

GS-US-334-1112

GS-US-334-1112 was a Phase 2 study evaluating the PK, safety, and antiviral activity of SOF+RBV in paediatric subjects aged 3 to < 18 years old with chronic genotype 2 or 3 HCV infection. This update to the marketing application presents data from all subjects 3 to < 12 years old who completed the posttreatment Week 24 visit or prematurely discontinued from the study.

2.4.5.2. Methods

- **Study Participants**

Subjects 6 to < 12 Years Old

Overall, 41 subjects aged 6 to < 12 years were enrolled into the study (18 subjects in the US, 8 subjects in the United Kingdom [UK], 6 subjects in Australia, 3 subjects in Germany, 3 subjects in Italy, 2 subjects in Belgium, and 1 subject in New Zealand). A total of 13 subjects had genotype 2 HCV infection, and 28 subjects had genotype 3 HCV infection.

Overall, the mean age of subjects was 8 years. The majority of subjects had been infected through vertical transmission (97.6%).

Subjects with host and viral factors that have been traditionally predictive of or associated with lower rates of SVR in Peg IFN+RBV containing regimens were included, such as non CC (CT or TT) IL28B alleles (65.9%), and high viral load (46.3% with HCV RNA ≥ 800,000 IU/mL). No subjects had known cirrhosis based on prior biopsy. The majority of subjects were treatment naive (97.6%).

Subjects 3 to < 6 Years Old

Overall, 13 subjects aged 3 to < 6 years were enrolled into the study (9 subjects in the US, 2 subjects in the UK, 1 subject in Australia, and 1 subject in Italy). A total of 5 subjects had genotype 2 HCV infection, and 8 subjects had genotype 3 HCV infection.

Overall, the mean age of subjects was 4 years. The majority of subjects had been infected through vertical transmission (84.6%).

Subjects with host and viral factors that have been traditionally predictive of or associated with lower rates of SVR in Peg IFN+RBV containing regimens were included, such as non-CC (CT or TT) IL28B alleles (76.9%), and high viral load (23.1% with HCV RNA ≥ 800,000 IU/mL). No subjects had known cirrhosis based on prior biopsy. All subjects were treatment-naive (100.0%).

Treatments

According to the study design, subjects received 1 of 2 different treatment regimens based on HCV genotype. Subjects with genotype 2 HCV infection received SOF+RBV for 12 weeks and subjects with genotype 3 HCV infection received SOF+RBV for 24 weeks.

The non-controlled study design, similar to the adult phase 3 studies, is endorsed as the primary endpoint (SVR12) is objective, the natural course of disease is well known and spontaneous clearance of HCV within the time frame in questions is very rare.

Outcomes/endpoints

The key efficacy endpoint for Study GS-US-334-1112 was SVR12, defined as HCV RNA < the lower limit of quantitation (LLOQ) 12 weeks following treatment completion. The choice of SVR12 as a primary endpoint is endorsed. In contrast to interferon-containing regimens, HCV relapses between week 12 and 24 has not been seen with DAA-only treatment.

2.4.5.3. Results

Baseline data

Subjects 6 to < 12 years old

The majority of subjects were female (73.2%), white (70.7%), and non-Hispanic/Latino (82.9%), with a mean age of 8 years. The mean (SD) baseline BMI value for subjects was 18.5 (4.65) kg/m2.
Table 4 presents a summary of the baseline disease characteristics for subjects 6 to < 12 years old.

Table 4 GS-US-334-1112: Baseline Disease Characteristics (6 to < 12 Years) (Safety Analysis Set)

Disease Characteristic	6 to < 12 Years Old SOF 200 mg + RBV		
	Total (N=41)	Genotype 2 12 Weeks (N=13)	Genotype 3 24 Weeks (N=28)
HCV Genotype			
Genotype 2	13 (31.7%)	13 (100.0%)	0
Genotype 2 (No Confirmed Subtype)	2 (4.9%)	2 (15.4%)	0
Genotype 2a/2c	4 (9.8%)	4 (30.8%)	0
Genotype 2b	7 (17.1%)	7 (53.8%)	0
Genotype 3	28 (68.3%)	0	28 (100.0%)
Genotype 3 (No Confirmed Subtype)	0	0	0
Genotype 3a	28 (68.3%)	0	28 (100.0%)
Cirrhosis			
No	5 (12.2%)	3 (23.1%)	2 (7.1%)
Unknown	36 (87.8%)	10 (76.9%)	26 (92.9%)
IL28B			
CC	14 (34.1%)	4 (30.8%)	10 (35.7%)
Non-CC	27 (65.9%)	9 (69.2%)	18 (64.3%)
CT	21 (51.2%)	7 (53.8%)	14 (50.0%)
TT	6 (14.6%)	2 (15.4%)	4 (14.3%)
Baseline HCV RNA Category			
< 800,000 IU/mL	22 (53.7%)	7 (53.8%)	15 (53.6%)
≥ 800,000 IU/mL	19 (46.3%)	6 (46.2%)	13 (46.4%)
Baseline HCV RNA (log_{10} IU/mL)			
Mean (SD)	5.7 (1.07)	5.8 (0.84)	5.7 (1.18)
Median	5.8	5.8	5.7
Q1, Q3	5.0, 6.6	5.1, 6.6	4.9, 6.5
Min, Max	2.2, 7.8	4.6, 6.7	2.2, 7.8
Baseline ALT (U/L)			
Mean (SD)	54 (87.7)	40 (29.5)	60 (104.3)
Median	34	33	37
Q1, Q3	25, 46	22, 37	28, 48
Min, Max	14, 583	14, 114	21, 583

Disease Characteristic	6 to < 12 Years Old SOF 200 mg + RBV		
	Total (N=41)	Genotype 2 12 Weeks (N=13)	Genotype 3 24 Weeks (N=28)
Baseline ALT Category			
≤ 1.5 × ULN	32 (78.0%)	10 (76.9%)	22 (78.6%)
> 1.5 × ULN	9 (22.0%)	3 (23.1%)	6 (21.4%)
Estimated Glomerular Filtration Rate Using Schwartz Formula (mL/min/1.73m^2)			
Mean (SD)	161.6 (30.82)	167.1 (27.08)	159.1 (32.56)
Median	157.6	169.5	157.5
Q1, Q3	146.6, 181.8	150.4, 176.0	143.5, 181.8
Min, Max	79.1, 241.3	123.1, 207.8	79.1, 241.3
Prior HCV Treatment Experience			
Treatment-Naive	40/41 (97.6%)	13/13 (100.0%)	27/28 (96.4%)
IFN-Eligible	39/40 (97.5%)	13/13 (100.0%)	26/27 (96.3%)
IFN-Ineligible	1/40 (2.5%)	0/13	1/27 (3.7%)
Treatment-Experienced	1/41 (2.4%)	0/13	1/28 (3.6%)
Most Recent HCV Treatment Response			
Non-Responder	1/1 (100.0%)	0/0	1/1 (100.0%)
Relapse/Breakthrough	0/1	0/0	0/1
IFN-Intolerant	0/1	0/0	0/1
Mode of HCV Infection			
Vertical Transmission	40 (97.6%)	13 (100.0%)	27 (96.4%)
Unknown	1 (2.4%)	0	1 (3.6%)

Baseline value is the last available value on or prior to first dose date of any study drug.
Source: Table 15.8.3.1

Subjects 3 to < 6 years old

The majority of subjects were female (76.9%), white (69.2%), and non-Hispanic/Latino (92.3%), with a mean age of 4 years. The mean (SD) baseline BMI value for subjects was 15.3 (1.13) kg/m2.

Table 5 presents a summary of the baseline disease characteristics for subjects 3 to < 6 years old.

Table 5 GS-US-334-1112: Baseline Disease Characteristics (3 to < 6 Years) (Safety Analysis Set)

Disease Characteristic	3 to < 6 Years Old SOF 200 mg or 150 mg + RBV		
	Total (N=13)	Genotype 2 12 Weeks (N=5)	Genotype 3 24 Weeks (N=8)
HCV Genotype			
Genotype 2	5 (38.5%)	5 (100.0%)	0
Genotype 2 (No Confirmed Subtype)	1 (7.7%)	1 (20.0%)	0
Genotype 2b	4 (30.8%)	4 (80.0%)	0
Genotype 3	8 (61.5%)	0	8 (100.0%)
Genotype 3a	8 (61.5%)	0	8 (100.0%)
Cirrhosis			
No	2 (15.4%)	1 (20.0%)	1 (12.5%)
Unknown	11 (84.6%)	4 (80.0%)	7 (87.5%)
IL28B			
CC	3 (23.1%)	2 (40.0%)	1 (12.5%)
Non-CC	10 (76.9%)	3 (60.0%)	7 (87.5%)
CT	9 (69.2%)	2 (40.0%)	7 (87.5%)
TT	1 (7.7%)	1 (20.0%)	0
Baseline HCV RNA Category			
< 800,000 IU/mL	10 (76.9%)	2 (40.0%)	8 (100.0%)
≥ 800,000 IU/mL	3 (23.1%)	3 (60.0%)	0
Baseline HCV RNA (log_{10} IU/mL)			
Mean (SD)	5.4 (0.81)	5.8 (1.09)	5.1 (0.45)
Median	5.4	5.9	5.3
Q1, Q3	4.8, 5.6	5.1, 6.5	4.7, 5.5
Min, Max	4.4, 7.2	4.5, 7.2	4.4, 5.6
Baseline ALT (U/L)			
Mean (SD)	31 (17.5)	28 (13.6)	33 (20.2)
Median	25	23	27
Q1, Q3	21, 33	20, 27	21, 39
Min, Max	11, 76	17, 51	11, 76
Baseline ALT Category			
≤ 1.5 × ULN	12 (92.3%)	5 (100.0%)	7 (87.5%)
> 1.5 × ULN	1 (7.7%)	0	1 (12.5%)
Estimated Glomerular Filtration Rate Using Schwartz Formula (mL/min/1.73m^2)			
Mean (SD)	155.7 (33.33)	165.1 (15.65)	149.8 (40.77)
Median	150.5	164.6	140.6
Q1, Q3	135.3, 172.5	150.5, 175.5	124.0, 169.3
Min, Max	99.0, 231.7	149.6, 185.5	99.0, 231.7

Disease Characteristic	3 to < 6 Years Old SOF 200 mg or 150 mg + RBV		
	Total (N=13)	Genotype 2 12 Weeks (N=5)	Genotype 3 24 Weeks (N=8)
Prior HCV Treatment Experience			
Treatment-Naive	13/13 (100.0%)	5/5 (100.0%)	8/8 (100.0%)
IFN-Eligible	13/13 (100.0%)	5/5 (100.0%)	8/8 (100.0%)
IFN-Ineligible	0/13	0/5	0/8
Treatment-Experienced	0/13	0/5	0/8
Mode of HCV Infection			
Vertical Transmission	11 (84.6%)	5 (100.0%)	6 (75.0%)
Unknown	2 (15.4%)	0	2 (25.0%)

Baseline value is the last available value on or prior to first dose date of any study drug.
Body Mass Index (BMI) = [weight (kg) / (height $(m)^2$)].
Source: Table 15.8.3.1

Outcomes and estimation

SVR12

Subjects 6 to < 12 Years Old

Table 6 presents the proportion of subjects 6 to < 12 years old who achieved SVR12 and virologic outcomes, overall and by treatment group. No subject had on treatment virologic failure (ie, breakthrough, rebound, or nonresponse) or relapsed.

Table 6. GS-US-334-1112: Virologic Outcomes (6 to < 12 Years Old) (Full Analysis Set)

	6 to < 12 Years Old SOF 200 mg + RBV		
	Total (N=41)	Genotype 2 12 Weeks (N=13)	Genotype 3 24 Weeks (N=28)
SVR12	41/41 (100.0%)	13/13 (100.0%)	28/28 (100.0%)
Overall Virologic Failure	0/41	0/13	0/28
Other	0/41	0/13	0/28

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.
Source: Ad Hoc Table 9900.1

Subjects 3 to < 6 Years Old

Table 7 presents the proportion of subjects 3 to < 6 years old who achieved SVR12 and virologic outcomes, overall and by treatment group. No subject had on treatment virologic failure (ie, breakthrough, rebound, or nonresponse) or relapsed. One of 5 subjects with genotype 2 HCV infection treated with SOF+RBV for 12 weeks (20.0%) did not achieve SVR12 due to premature discontinuation from the study due to AEs of

product use issue (the subject spit up the dose) and abnormal product taste, and was categorized as having "other" virologic outcome at posttreatment Week 12.

Table 7. GS-US-334-1112: Virologic Outcomes (3 to < 6 Years Old) (Full Analysis Set)

	3 to < 6 Years Old SOF 200 mg or 150 mg + RBV		
	Total (N=13)	Genotype 2 12 Weeks (N=5)	Genotype 3 24 Weeks (N=8)
SVR12	12/13 (92.3%)	4/5 (80.0%)	8/8 (100.0%)
Overall Virologic Failure	0/13	0/5	0/8
Other	1/13 (7.7%)	1/5 (20.0%)	0/8

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.

Source: Ad Hoc Table 9900.1

It is clear that LDV/SOF is highly effective in the patient population studied. Due to the close to 100% SVR12 rates in both study groups (100% and 92.3%, respectively), subgroup analyses are futile.

Ancillary analyses

Resistance Findings

Given the very few non-SVR12 patients, resistance analyses in relation to efficacy are of limited value.

Subjects 6 to < 12 Years Old

Among subjects 6 to < 12 years old, the prevalence of NS5B nucleoside inhibitor (NI) resistance associated variants (RAVs) at baseline was low (5.0%, 2 of 40 subjects with full sequencing data available). The presence of pretreatment NS5B NI RAVs did not impact treatment outcome, as both subjects with pretreatment NS5B NI RAVs achieved SVR12 and SVR24.

Subjects 3 to < 6 Years Old

No subjects 3 to < 6 years old had NS5B NI RAVs at baseline.

2.4.6. Discussion on clinical efficacy

The GS-US-334-1112 study has been designed and conducted in line with previous studies in the field of HCV treatment. The efficacy results in the age groups at question (3 to <6 and 6 to <12 years) were reassuring, with SVR12 rates close to 100%, but the size of the study groups, particularly 3 to <6 years old, was limited. Given that exposure is comparable, efficacy can be extrapolated from the adult phase 3 programme to support the proposed posology in these age groups.

2.4.7. Conclusions on clinical efficacy

The CHMP concluded that sofosbuvir is effective in the treatment of chronic HCV in children aged 3 to < 12 years of age.

2.4.8. Clinical safety

2.4.8.1. Patient exposure

Subjects 6 to < 12 years old

Overall, 41 subjects 6 to < 12 years old were enrolled and received at least 1 dose of SOF 200 mg + RBV. The mean (SD) duration of exposure to the study regimen for those with genotype 2 HCV infection treated for 12 weeks was 12.0 (0.18) weeks and for those with genotype 3 HCV infection treated for 24 weeks was 24.1 (0.13) weeks. All subjects in both treatment groups completed their assigned treatment duration (100.0%).

Subjects 3 to < 6 years old

Overall, 13 subjects 3 to < 6 years old were enrolled and received at least 1 dose of SOF 150 mg or 200 mg + RBV. The mean (SD) duration of exposure to the study regimen for those with genotype 2 HCV infection treated for 12 weeks was 9.8 (5.23) weeks and for those with genotype 3 HCV infection treated for 24 weeks was 24.0 (0.62) weeks. The majority of subjects completed their assigned treatment duration: 4 of 5 (80%) subjects with genotype 2 HCV treated for 12 weeks and 7 of 8 (87.5%) subjects with genotype 3 HCV infection treated for 24 weeks. One subject with genotype 2 HCV infection prematurely discontinued study treatment due to AEs of product use issue and abnormal product taste. One additional subject with genotype 3 HCV infection in the SOF+RBV 24-week treatment group was considered to have completed study treatment by the investigator; however, study drug administration data indicate that the subject took study drug until the last on-treatment study visit was performed.

The size of the study groups allows for a limited safety assessment which is, given that exposure is comparable, acceptable given the established safety profile of SOF in adults together with safety data from the LDV/SOF paediatric safety dataset.

2.4.8.2. Adverse events

Subjects 6 to < 12 Years Old

The majority of subjects (35 of 41, 85.4%) experienced at least 1 AE (9 of 13, [69.2%] subjects with genotype 2 HCV infection treated for 12 weeks and (26 of 28 [92.9%] subjects with genotype 3 HCV infection treated for 24 weeks).

All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. No subjects experienced SAEs. No deaths were reported. No subject prematurely discontinued SOF due to an AE. One subject with genotype 3 HCV infection treated for 24 weeks experienced a Grade 1 AE of vomiting that led to an interruption of SOF and RBV dosing for 1 day. There were no AEs consistent with progression of liver disease, such as AEs of HCC or hepatic decompensation.

No notable effects of study treatment on development or growth as assessed by changes from baseline through posttreatment Week 24 in Tanner pubertal stages, bone age, height, weight, and BMI percentiles

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

Table 8 GS-US-334-1112: Overall Summary of Adverse Events (6 to <12 Years Old) (Safety Analysis Set)

	6 to < 12 Years Old SOF 200 mg + RBV		
	Total (N=41)	Genotype 2 12 Weeks (N=13)	Genotype 3 24 Weeks (N=28)
Number (%) of Subjects Experiencing Any			
Treatment-Emergent Adverse Event	35 (85.4%)	9 (69.2%)	26 (92.9%)
Grade 3 or Above Treatment-Emergent Adverse Event	0	0	0
Treatment-Emergent Treatment-Related Adverse Event	13 (31.7%)	4 (30.8%)	9 (32.1%)
Grade 3 or Above Treatment-Emergent Treatment-Related Adverse Event	0	0	0
Treatment-Emergent Serious Adverse Event	0	0	0
Treatment-Emergent Treatment-Related Serious Adverse Event	0	0	0
Adverse Event Leading to Premature Discontinuation of Any Study Drug	0	0	0
Adverse Event Leading to Premature Discontinuation of SOF	0	0	0
Adverse Event Leading to Premature Discontinuation of RBV	0	0	0
Adverse Event Leading to Premature Discontinuation of All Study Drugs	0	0	0
Adverse Event Leading to Modification or Interruption of Any Study Drug	1 (2.4%)	0	1 (3.6%)
Adverse Event Leading to Interruption of SOF	1 (2.4%)	0	1 (3.6%)
Adverse Event Leading to Modification or Interruption of RBV	1 (2.4%)	0	1 (3.6%)
All Deaths	0	0	0

The denominator for percentages is based on the number of subjects in the safety analysis set.
Source: Table 15.11.2.1.1.1

Table 9 presents a summary of AEs reported for at least 10% of subjects 6 to < 12 years old in either treatment group by preferred term. Overall, the most commonly reported AEs across subjects with genotype 2 HCV infection treated for 12 weeks and subjects with genotype 3 HCV infection treated for 24 weeks were vomiting (15.4% and 39.3%, respectively), headache (30.8% and 28.6%, respectively), fatigue (23.1% and 17.9%, respectively), and cough (7.7% and 25.0%, respectively).

Table 9 GS-US-334-1112: Adverse Events Reported for at Least 10% of Subjects in Any Treatment Group by Preferred Term (6 to <12 Years old) (Safety Analysis Set)

	6 to < 12 Years Old SOF 200 mg + RBV	
	Genotype 2 12 Weeks (N=13)	Genotype 3 24 Weeks (N=28)
Number (%) of Subjects Experiencing Any Treatment-Emergent Adverse Event	9 (69.2%)	26 (92.9%)
Vomiting	2 (15.4%)	11 (39.3%)
Headache	4 (30.8%)	8 (28.6%)
Fatigue	3 (23.1%)	5 (17.9%)
Cough	1 (7.7%)	7 (25.0%)
Nasopharyngitis	1 (7.7%)	4 (14.3%)
Decreased appetite	2 (15.4%)	2 (7.1%)
Diarrhoea	1 (7.7%)	3 (10.7%)
Rhinorrhoea	1 (7.7%)	3 (10.7%)
Nausea	0	4 (14.3%)
Oropharyngeal pain	0	4 (14.3%)
Pyrexia	0	4 (14.3%)
Abdominal pain	0	3 (10.7%)
Contusion	0	3 (10.7%)
Gastroenteritis	0	3 (10.7%)

Adverse events are mapped according to MedDRA Version 20.1.
Subjects are counted once for each AE preferred term.
Data included to last dose date of any study drug + 30 days.
Source: Table 15.11.2.1.3.1

Subjects 3 to < 6 years old

Table 10 presents the overall summary of AEs for subjects 3 to < 6 years old by treatment group. All subjects with genotype 2 HCV infection treated for 12 weeks and subjects with genotype 3 HCV infection treated for 24 weeks (100.0%, respectively) experienced at least 1 AE. All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. One subject with genotype 3 HCV infection experienced an SAE (accidental RBV overdose) resulting in interruption of treatment with SOF and RBV for 8 days (Section 11.3.4). One subject with genotype 2 HCV infection prematurely discontinued SOF and RBV due to AEs (product use issue and abnormal product taste) (Section 11.3.5), and 2 subjects with genotype 2 HCV infection experienced Grade 1 AEs of vomiting that led to an interruption of SOF dosing for 1 day. No deaths were reported. There were no AEs consistent with progression of liver disease, such as AEs of HCC or hepatic decompensation.

No notable effects of study treatment on development or growth as assessed by changes from baseline through posttreatment Week 24 in Tanner pubertal stages, bone age, height, weight, and BMI percentiles were observed in either treatment group. No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during the study.

Table 10 GS-US-334-1112: Overall Summary of Adverse Events (3 to <6 Years old) (Safety Analysis Set)

	3 to < 6 Years Old SOF 200 mg or 150 mg + RBV		
	Total (N=13)	Genotype 2 12 Weeks (N=5)	Genotype 3 24 Weeks (N=8)
Number (%) of Subjects Experiencing Any			
Treatment-Emergent Adverse Event	13 (100.0%)	5 (100.0%)	8 (100.0%)
Grade 3 or Above Treatment-Emergent Adverse Event	0	0	0
Treatment-Emergent Treatment-Related Adverse Event	5 (38.5%)	4 (80.0%)	1 (12.5%)
Grade 3 or Above Treatment-Emergent Treatment-Related Adverse Event	0	0	0
Treatment-Emergent Serious Adverse Event	1 (7.7%)	0	1 (12.5%)
Treatment-Emergent Treatment-Related Serious Adverse Event	0	0	0
Adverse Event Leading to Premature Discontinuation of Any Study Drug	1 (7.7%)	1 (20.0%)	0
Adverse Event Leading to Premature Discontinuation of SOF	1 (7.7%)	1 (20.0%)	0
Adverse Event Leading to Premature Discontinuation of RBV	1 (7.7%)	1 (20.0%)	0
Adverse Event Leading to Premature Discontinuation of All Study Drugs	1 (7.7%)	1 (20.0%)	0
Adverse Event Leading to Modification or Interruption of Any Study Drug	3 (23.1%)	2 (40.0%)	1 (12.5%)
Adverse Event Leading to Interruption of SOF	3 (23.1%)	2 (40.0%)	1 (12.5%)
Adverse Event Leading to Modification or Interruption of RBV	2 (15.4%)	1 (20.0%)	1 (12.5%)
All Deaths	0	0	0

The denominator for percentages is based on the number of subjects in the safety analysis set.
Source: Table 15.11.2.1.1.1

Table 11 presents a summary of AEs reported for at least 2 subjects in any treatment group by preferred term.

Table 11 GS-US-334-1112: Adverse Events Reported for at Least 2 Subjects in Any Treatment Group by Preferred Term (3 to <6 Years old) (Safety Analysis Set)

	3 to < 6 Years Old SOF 200 mg or 150 mg + RBV	
	Genotype 2 12 Weeks (N=5)	Genotype 3 24 Weeks (N=8)
Number (%) of Subjects Experiencing Any Treatment-Emergent Adverse Event	5 (100.0%)	8 (100.0%)
Vomiting	3 (60.0%)	3 (37.5%)
Diarrhoea	2 (40.0%)	3 (37.5%)
Decreased appetite	0	3 (37.5%)
Arthropod bite	0	2 (25.0%)

Adverse events are mapped according to MedDRA Version 20.1.
Subjects are counted once for each AE preferred term.
Data included to last dose date of any study drug + 30 days.
Source: Table 15.11.2.1.3.1

Gastrointestinal AEs such as nausea, vomiting and diarrhoea are quite common. Nausea and decreased appetite are already listed in SmPC section 4.8, which is considered sufficient given that the baseline rate of these events are relatively high in a paediatric population and that these AEs resolved quickly without treatment interruption and there was no obvious pattern indicating a causal relation to SOF+RBV therapy.

2.4.8.3. Serious adverse events and deaths

No deaths, SAEs, or AEs leading to premature discontinuation of study drug were reported for subjects 6 to < 12 years old.

No deaths were reported for subjects 3 to < 6 years old. One subject (12.5%) with genotype 3 HCV infection treated for 24 weeks experienced an SAE (Grade 2) of accidental RBV overdose on study Day 83 that required hospitalization for monitoring. The subject remained asymptomatic, and the event was assessed as not related to study drug by the investigator. The SAE was considered resolved on Day 102.

2.4.8.4. Laboratory findings

Subjects 6 to < 12 years old

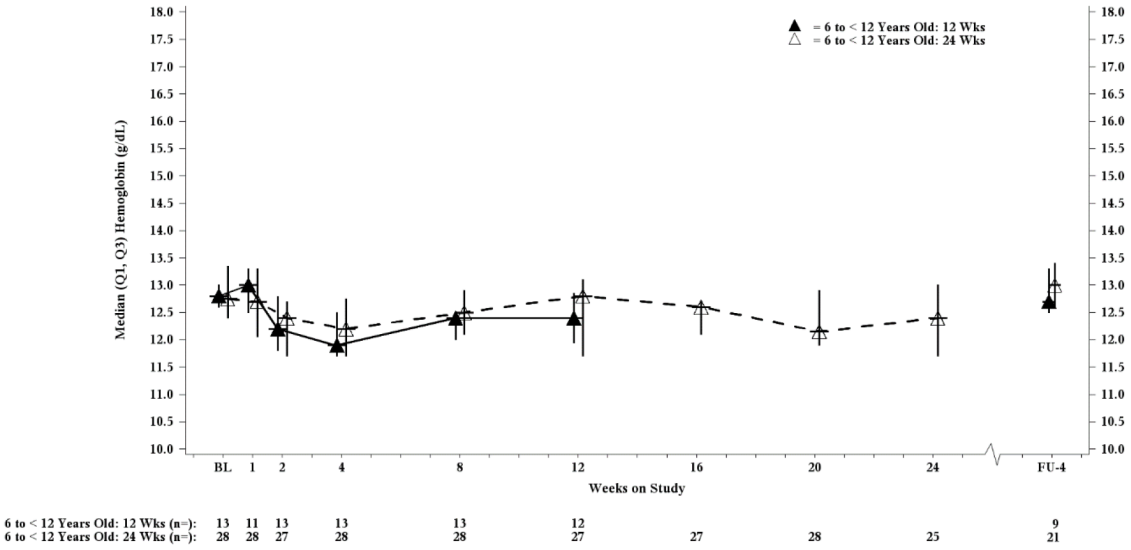
The majority of subjects 6 to < 12 years old (26 of 41, 63.4%) had at least 1 laboratory abnormality reported (subjects with genotype 2 HCV infection treated for 12 weeks [7 of 13 subjects], 53.8%; and subjects with genotype 3 HCV infection [19 of 28 subjects], 67.9%) (Table 15.11.6.2.1). For all subjects except one the maximum abnormality grade was Grade 1 or Grade 2 in severity. One subject with genotype 3 HCV infection treated for 24 weeks had a Grade 3 laboratory abnormality (increased INR), which was not associated with AEs. No subject had a Grade 4 laboratory abnormality.

Haematology

No subject with genotype 2 HCV infection treated for 12 weeks or with genotype 3 HCV infection treated for 24 weeks had Grade 3 or 4 haematology laboratory abnormalities. There was 1 subject with postbaseline

haemoglobin < 10 g/dL (protocol guideline for RBV dose reduction/modification) and no subject with postbaseline haemoglobin < 8.5 g/dL. One subject, with a baseline haemoglobin value of 12.7 g/dL had a Grade 2 decrease in haemoglobin to 9.9 g/dL at Week 4 followed by return to a normal haemoglobin level at Week 8 and for the remainder of the study, Figure 4.

Figure 4 GS-US-334-1112: Median (Q1, Q3) Hemoglobin (g/dL) by Visit (6 to<12 Years Old) (Safety Analysis Set)



Baseline value is the last available value on or prior to first dose date of any study drug.
Data included to last dose date of any study drug + 30 days.
Offsets have been applied to treatment groups.
Source: Figure 15.11.6.5.2

Decreased haemoglobin is a known effect of RBV therapy.

Chemistry

Table 12 presents a summary of subjects 6 to < 12 years old with Grade 3 or 4 coagulation or chemistry laboratory abnormalities by treatment group.

No subject with genotype 2 HCV infection treated for 12 weeks had Grade 3 or 4 chemistry laboratory abnormalities. One subject with genotype 3 HCV infection treated for 24 weeks had a Grade 3 laboratory abnormality of increased INR (1 of 28 subjects, 3.6%) at Study Weeks 2, 4, and 20. The INR was Grade 0 to Grade 1 at all other time points and was Grade 0 at Week 24. No AEs were associated with this laboratory abnormality.

Table 12 GS-US-334-1112: Grade 3 or 4 Coagulation or Chemistry Laboratory Abnormalities (6 to < 12 Years Old) (Safety Analysis Set)

	6 to < 12 Years Old SOF 200 mg + RBV	
	Genotype 2 12 Weeks (N=13)	Genotype 3 24 Weeks (N=28)
Coagulation		
INR		
Grade 3	0	1 (3.6%)

Laboratory abnormalities are graded using GSI Grading Scale, 1 April 2015 version.
Toxicity grade must increase at least one toxicity grade from baseline value (missing is considered grade 0) to be included.
Subjects counted once at maximum toxicity grade (hyper [+] and hypo [-] when applicable) for each laboratory test.
Data included to last dose date of any study drug + 30 days.
Toxicity grading of INR based on ULN = 1.2; ULN = upper limit of normal.
Source: Table 15.11.6.3.1

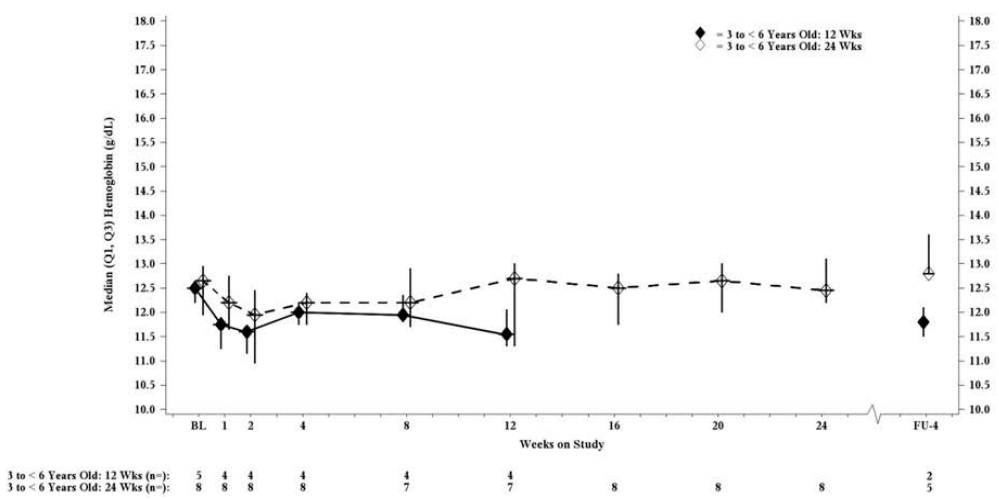
Subjects 3 to < 6 years old

The majority of subjects 3 to < 6 years old (10 of 12, 83.3%) had at least 1 laboratory abnormality reported (subjects with genotype 2 HCV infection treated for 12 weeks [2 of 4 subjects], 50.0%; and subjects with genotype 3 HCV infection [8 of 8 subjects], 100.0%). The maximum laboratory abnormality grades for all subjects were Grade 1 or Grade 2. No subject had Grade 3 or Grade 4 laboratory abnormality.

Haematology

No subject had Grade 3 or Grade 4 haematology laboratory abnormalities. There were no subjects with postbaseline haemoglobin < 10 g/dL (protocol guideline for RBV dose reduction/modification), Figure 5

Figure 5 GS-US-334-1112: Median (Q1, Q3) Hemoglobin (g/dL) by Visit (3 to <6 Years Old) (Safety Analysis Set)



Baseline value is the last available value on or prior to first dose date of any study drug.
Data included to last dose date of any study drug + 30 days.
Offsets have been applied to treatment groups.
Source: Figure 15.11.6.5.2

Chemistry

No subjects 3 to < 6 years old in either treatment group had Grade 3 or 4 coagulation or chemistry laboratory abnormalities.

Summary of haematology and chemistry in patients 3 to <12 years

Overall, the haematology and chemistry data appear to be in line with the currently established safety profile of SOF. However, when viewing the chemistry data in detail it seems that amylase abnormalities (without any concomitant lipase abnormalities) of grade 1-2 are relatively common.

Amylase abnormalities does not appear to be related to GI symptoms indicating pancreatitis and no such AEs were reported in the paediatric study. Given that similar numbers of patients normalised their pancreatic enzymes from baseline, compared to those who had abnormalities emerging on treatment, it is reasonable to assume that this reflects the underlying disease, and no update to SmPC section 4.8 is considered necessary.

2.4.9. Discussion on clinical safety

Overall, the SOF safety data set in patients aged 3-<6 and 6-<12 years is in line with the established favourable safety profile in adults. Section 4.8 of the SmPC was updated to indicate that decreased appetite was observed as a very common adverse drug reaction to Sovaldi when given in combination with ribavirin oral solution in paediatric patients aged 3 to < 12 years.

Given the available safety data in adults with severe and end-stage renal disease, where exposure of the metabolite GS-331007 was 20-fold increased without any apparent increase in GI symptoms, it is considered less likely that the 2-fold increase of this metabolite seen in paediatric patients would be a cause of specific toxicity.

The low level of treatment-emergent SAEs (1/54 study subjects aged 3-<12 years), no deaths and overall high adherence to treatment is in line with the established favourable safety profile of SOF.

Overall, the haematology and chemistry data did not provide cause of concern regarding any age-specific issues.

2.4.10. Conclusions on clinical safety

The safety profile of SOF is overall favourable in HCV patients between 3-<12 years of age.

2.5. Risk Management Plan

Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Important Identified Risks	Cardiac arrhythmia (bradycardia) when SOF-containing regimens are used concomitantly with amiodarone
	HBV reactivation in HBV/HCV coinfected patients
Important Potential Risks	Recurrence of HCC
	Emergence of HCC
Missing Information	Safety in patients with previous HCC
	~~Safety in patients with severe renal impairment or ESRD~~
	~~Safety in patients with previous HCC~~

The assessment below is in respect to that no changes to the summary of safety concerns has been proposed within this procedure.

The CHMP noted that the removal of *"Safety in patients with severe renal impairment or ESRD"* was assessed and endorsed in a parallel WS procedure (WS1518), which was adopted on 19 September 2019.

Having considered the data in the safety specification, it is agreed by the CHMP that the safety concerns listed by the applicant are appropriate.

Pharmacovigilance plan

The MAH did not propose any change to the summary table of additional pharmacovigilance activities below, which is endorsed by the CHMP.

Risk minimisation measures

The MAH did not propose any change to the summary table of pharmacovigilance and risk minimization activities by safety concern below, which is endorsed by the CHMP.

Conclusion

The CHMP and PRAC considered that the risk management plan version 10.0 is acceptable.

2.6. Pharmacovigilance

Periodic Safety Update Reports submission requirements

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

2.7. Product information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

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

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Harvoni (ledipasvir / sofosbuvir) 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 (The Polaris Observatory HCV Collaborators 2017), (World Health Organization (WHO) 2018b). In the US, over 3 million people are estimated to be chronically infected with HCV (Center for Disease Control and Prevention 2016), and in Europe an estimated 10 to 14 million people have chronic HCV infection (The Polaris Observatory HCV Collaborators 2017), (World

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

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

3.1.2. Available therapies and unmet medical need

In 2017, Sovaldi (SOF) and Harvoni were approved in the US and EU for the treatment of patients 12 years of age and older, or weighing ≥ 35 kg (in the US only). As such, per current international guidelines, pegylated interferon (Peg-IFN) and ribavirin (RBV) are no longer recommended for treatment of children 12 years of age and older (American Association for the Study of Liver Diseases (AASLD) 2018), (European Association for the Study of the Liver (EASL) 2018), (World Health Organization (WHO) 2018a), (Indolfi 2018). For patients younger than 12 years of age (and, in certain countries, weighing < 35 kg), however, there are no approved DAA treatments; currently, the only approved HCV treatment option is Peg-IFN and weight-based RBV for 24 or 48 weeks, depending on HCV genotype.

3.1.3. Main clinical studies

GS-US-334-1112 was a Phase 2 study evaluating the PK, safety and antiviral activity of SOF+RBV in paediatric subjects aged 3 to < 18 years old with chronic genotype 2 or 3 HCV infection. This update to the marketing application presents data from all subjects 3 to < 12 years old who completed the post-treatment Week 24 visit or prematurely discontinued from the study.

3.2. Favourable effects

Population PK analysis has been used to describe the sofosbuvir PK data in the paediatric population 3-18 years of age. A joint model has been developed where sofosbuvir and metabolites GS-566500 and GS-331007 have been simultaneously analysed. Furthermore, all sofosbuvir PK data, administered as Sovaldi or in the fixed-dose combination Harvoni (sofosbuvir+ledipasvir) have been pooled together to make use of all available data. The joint model was able to describe the three analytes well. The population PK predicted exposures metrics (AUC_{tau} and Cmax) have been compared with the corresponding observed exposure ranges in the adult population. The % geometric mean ratio between the paediatric patient population and the adult phase 2/3 population were largely contained within the predefined PK equivalence boundaries of 50% to 200%.

In the GS-US-334-1112 study, SVR12 was achieved in 12/13 (92.3%) patients in the group 3 to <6 years old and 41/41 (100%) in the group 6 to <12 years old. SVR12 is widely accepted as a surrogate endpoint for cure of HCV and halt of further progress of liver disease.

3.3. Uncertainties and limitations about favourable effects

The efficacy results in the age groups at question (3 to <6 and 6 to <12 years) are re-assuring, with SVR12 rates close to 100%, but the size of the study groups, particularly 3 to <6 years old, was limited. Given that exposure is comparable, efficacy can be extrapolated from the adult phase 3 programme to support the proposed posology in these age groups.

3.4. Unfavourable effects

Overall, the SOF safety data set in patients aged 3-<6 and 6-<12 years is in line with the established favourable safety profile in adults. Decreased appetite was observed as a very common adverse drug reaction to Sovaldi when given in combination with ribavirin oral solution in paediatric patients aged 3 to < 12 years.

Given the available safety data in adults with severe and end-stage renal disease, where exposure of the metabolite GS-331007 was 20-fold increased without any apparent increase in GI symptoms, it was considered less likely that the 2-fold increase of this metabolite seen in paediatric patients would be a cause of specific toxicity.

The low level of treatment-emergent SAEs (1/54 study subjects aged 3-<12 years), no deaths and overall high adherence to treatment is in line with the established favourable safety profile of SOF.

The haematology and chemistry data did not provide cause of concern regarding any age-specific issues.

3.5. Uncertainties and limitations about unfavourable effects

The paediatric data set is of limited size, particularly in patients aged 3 to <6 years (13 subjects). However, an additional number of patients in these age groups (34 aged 3 to <6 and 92 aged 6 to <12) have been treated with SOF in combination with ledipasvir in the GS-US-337-1116 study. Given the established safety profile of SOF and that exposure is comparable to what is seen in adults, the remaining uncertainty is acceptable.

3.6. Effects Table

Table 13. Favourable Effects (exposure) for Sovaldi in paediatric HCV positive patients 3-12 years:

Effect	Short description	Unit	Age 3-6 Years N=12	Age 6-12 Years N=39	Uncertainties / Strength of evidence	Ref
Sofosbuvir						
AUC_{tau} (h·ng/mL)	Steady-state daily exposure	%Geometric mean ratio[1]	98.62 (83.67,	77.10 (70.13,	Model predicted	Table 2

Effect	Short description	Unit	Age 3-6 Years N=12	Age 6-12 Years N=39	Uncertainties / Strength of evidence	Ref
		(90% CI)	116.24)	84.76)		
Cmax (ng/mL)	Maximum steady-state concentration	Geometric mean ratio[1] (90% CI)	98.28 (81.28, 118.83)	78.24 (70.13, 87.29)	Model predicted	Table 2
GS-331007						
AUC,ss (day·µg/mL)	Steady-state daily exposure	Geometric mean ratio[1] (90% CI)	174.51 (150.30, 202.62)	130.80 (120.56, 141.90)	Model predicted	Table 2
Cmax (ng/mL)	Maximum steady-state concentration	Geometric mean ratio[1] (90% CI)	195.03 (162.20, 234.51)	152.29 (137.75, 168.36)	Model predicted	Table 2

Abbreviations: CI = Confidence interval

Notes: 1. % Geometric mean ratio (90% CI) Paediatric patients / Phase 2/3 Adult Population

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

An adequate population PK analysis of sofosbuvir and selected metabolites has been performed and the model was considered adequate to provide predicted exposure metrics in the paediatric population. The model predicted sofosbuvir and GS-331007 plasma exposures display sufficiently similar levels between the adult and paediatric populations across all body weights. The proposed body weight band dosing is supported.

Overall, safety of the product in the paediatric population is in line with the established favourable safety profile in adults.

3.7.2. Balance of benefits and risks

The described similarity of sofosbuvir and selective metabolite PK in adults and children is considered sufficient to support the proposed posology and for extrapolation of the efficacy and safety results for Sovaldi in adults to the new paediatric population (3-12 years). The efficacy estimate (SVR12) showed a very high cure rate also in the paediatric setting and there were no indications of any age-specific safety concerns.

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

3.8. Conclusions

The overall B/R of Sovaldi in subjects 3 to <12 years of age is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Sovaldi 200 mg film-coated tablets, 200 mg coated granules and 150 mg coated granules is favourable in the following indication:

- Sovaldi is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adult and paediatric patients aged 3 years and above.

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

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Obligation to conduct post-authorisation measures

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

Description	Due date
In order to evaluate the recurrence of hepatocellular carcinoma associated with Harvoni, the MAH shall conduct and submit the results of a prospective safety study	**Q2 2023**

Description	Due date
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:	

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0172/2018 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, II and IIIB

Extension of indication to include paediatric use in patients aged 3 to < 12 years to the existing presentations of 400 mg film-coated tablets. Sections 4.2, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated to support the extended indication. The RMP (version 10.0) is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial updates and linguistic corrections throughout the Product Information.