30 April 2020
EMA/270141/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Harvoni

International non-proprietary name: ledipasvir / sofosbuvir

Procedure No. EMEA/H/C/003850/X/0081/G

Note

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

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List of abbreviations

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

NA	not applicable
NDA	new drug application
NF	National formulary
NI	nucleoside inhibitor
NS (3/4A/5A/5B)	nonstructural protein (3/4A/5A/5B)
PAR	Proven acceptable range
PBRER	Periodic Benefit-Risk Evaluation Report
PDCO	Paediatric Development Committee
PE	Polyethylene
Peg-IFN	pegylated interferon
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PREA	Paediatric Research Equity Act
PSUR	Periodic Safety Update Report
QC	Quality control
RAV	resistance-associated variant
RBV	Ribavirin
RH	Relative humidity
RNA	ribonucleic acid
rpm	Revolutions per minute
SAE	serious adverse event
SD	standard deviation
SDD	spray-dried dispersion
SLS	Sodium lauryl sulfate
SmPC	Summary of product characteristics
SOF	sofosbuvir (Sovaldi)
SVR, SVRxx	sustained virologic response, sustained virologic response at “xx” weeks following completion of all treatment
TSE	Transmissible spongiform encephalopathy
UK	United Kingdom
ULN	upper limit of normal
US, USA	United States, United States of America
USP	United States Pharmacopoeia
UV	Ultraviolet
VEL	Velpatasvir
WHO	World Health Organization
WR	Written Request

1. Background information on the procedure

1.1. Submission of the dossier

Gilead Sciences Ireland UC submitted on 30 May 2019 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

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

Extension application to introduce a new strength (45/200 mg film-coated tablets) and a new pharmaceutical form (granules) associated with new strengths (33.75/150 and 45/200 mg). The new presentations are indicated 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 to the existing presentations of 90/400 mg film-coated tablets. Sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated to support the extended indication. The RMP (version 5.3) 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 P/0063/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0063/2017 was completed.

The PDCO issued an opinion on compliance for the PIP P/0063/2017.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur 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 on	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 in writing and/or in an oral explanation to be sent to the MAH on	27 February 2020
The MAH submitted the responses to the CHMP List of Outstanding Issues on	31 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 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 Harvoni 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

Harvoni (LDV/SOF) is an all oral, once-daily, fixed-dose combination (FDC) of LDV, a hepatitis C virus (HCV) non-structural protein (NS) 5A inhibitor, and SOF, an HCV NS5B polymerase inhibitor. Harvoni was first approved in the United States (US) on 10 October 2014 and in the European Union (EU) on 17 November 2014. Harvoni is indicated for the treatment of genotype 1, 3 (EU only), 4, 5 or 6 HCV infection. In 2017, Harvoni was approved in the US and EU for the treatment of patients 12 years of age and older, or weighing $\geqslant$ 35 kg (in the US only).

Type of Application and aspects on development

In the EU, a paediatric investigation plan (PIP) for LDV/SOF was agreed on 10 October 2013 (European Medicines Evaluation Agency [EMEA]-001411-PIP01-12). Minor modifications to the original PIP have been agreed since this time, with the most recent European Medicines Agency Decision received on 17 March 2017 (EMEA-001411-PIP01-12-M04). The design of GS-US-337-1116 reflected the PIP Decision agreed with the Paediatric Development Committee (PDCO) as part of the assessment of the PIP.

2.2. Quality aspects

2.2.1. Introduction

This application concerns a line extension to add two paediatric formulations containing lower doses of the active substances, ledipasvir and sofosbuvir, than the already authorised 90/400 mg film-coated tablets: 45/200 mg film-coated tablets and 33.75/150 mg and 45/200 mg coated granules in sachet.

Other ingredients in the film-coated tablets are:

Tablet core: copovidone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate.

Film-coating: partially hydrolysed polyvinyl alcohol, titanium dioxide, macrogol and talc.

Other ingredients in the granules are:

Granule cores: copovidone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate.

Film-coating: hypromellose, polyvinyl alcohol, titanium dioxide, macrogol, iron oxide yellow, iron oxide red, basic butylated methacrylate copolymer, talc and colloidal anhydrous silica**.**

The film-coated tablets are available in high density polyethylene (HDPE) bottles with polypropylene (PP) 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

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

2.2.3. Finished Medicinal Product – film-coated tablets

Description of the product and Pharmaceutical development

The new presentation of Harvoni film-coated tablets contain 45 mg ledipasvir and 200 mg sofosbuvir. They are white, capsule-shaped tablets debossed with GSI on one side and HRV on the other. The composition of the tablet core is dose-proportional to the already-commercialised 90/400 mg strength tablet. The only differences are the amount and colour of film-coating and the tablet size 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 90/400 mg tablets, including the use of the same manufacturing process, adapted to the smaller tablet size.

The active substances are the same as those used in the approved higher strength tablets. Sofosbuvir is a crystalline solid, routinely manufactured as the most stable polymorphic form containing small quantities of an equivalent polymorphic form. Sofosbuvir exhibits pH-independent solubility across the physiological pH range. Sofosbuvir is highly soluble but has low apparent intestinal permeability (BCS class III). Particle size was found to be critical for dissolution rate, so sofosbuvir is sieved, or screen-milled and particle size is controlled in the active substance specification.

Ledipasvir exhibits low, but pH-dependent, solubility and high apparent permeability (BCS class II). It is susceptible to the influence of gastrointestinal pH and fed state and so an amorphous spray-dried dispersion of ledipasvir and copovidone (LDV-SDD) was developed in order to mitigate these food effects. LDV-SDD is an amorphous solid powder. It is hygroscopic and photosensitive, but physically and chemically stable for up to 6 months if protected from light and moisture in a sealed container. The physicochemical properties of LDV-SDD are amenable to formulation in a solid oral tablet.

The excipients used in the 45/200 mg tablets are the same as those used in the 90/400 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.

The dissolution method is the same as used for the already-approved 90/400 mg tablets.

Two reduced strength tablets (45/200 mg and 22.5/100 mg) with dose-proportional compositions were developed for use in paediatric patients. Dissolution behaviour of both active substances was shown to be equivalent to the 90/400 mg table in the QC dissolution medium. A waiver for *in vivo* bioequivalence studies was requested for the 45/200 mg tablets based on fulfilment of criteria outlined in *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 rev 1./corr.). Dissolution profiles of 90/400 and

45/200 mg tablets were measured at pH 2, 4.5 and 6. The comparison of f2 factors indicated that they were >50 at all measured time-points. Therefore, the biowaiver is considered justified.

The primary packaging is HDPE bottles with a polypropylene child-resistant closure with a silica gel desiccant and 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 two parts: production of the LDV-SDD and then production of the film-coated tablets.

The manufacturing process for the LDV-SDD is identical to that used for the approved 90/400 mg tablets. The controls applied to the LDV-SDD intermediate have previously been assessed in the context of the original MAA and are considerde appropriate.

The tablet manufacturing process consists of 4 main steps: blending of LDV-SDD and sofosbuvir with intra-granular excipients followed by granulation; blending of granules with extra-granular excipients followed by compression to form tablet cores; film-coating; packaging. The process is considered to be a standard manufacturing process. IPCs are carried out to monitor the critical steps of the manufacturing process. The IPCs are adequate for this type of manufacturing process and pharmaceutical form.

Process validation was completed for the approved 90/400 mg tablets prior to commercialisation. The robustness of the process for the 45/200 mg tablets was demonstrated by manufacture of representative batches up to the planned 40 kg production scale. Formal process validation will be completed on at least three batches of 45/200 mg tablets prior to commercialisation and will include an extended sampling and testing plan. An adequate process validation scheme has been presented in the dossier.

Product specification

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

The potential presence of class 1, 2A and select class 3 elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 15 batches of the 90/400 mg demonstrate that the amount of each relevant elemental impurity was well below the respective control threshold. Therefore, no specific controls for elemental impurities are required in the finished product specification.

The limits for degradation products are aligned with those of the approved 90/400 mg tablets and are considered acceptable.

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

Batch analysis results were provided for three production scale batches 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 45/200 mg tablets stored for up to 12 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. 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 and the results were comparable to the data from the approved 90/400 mg tablets at each time-point.

A further consideration is that the already-marketed 90/400 mg tablets have a 72-month shelf-life based on extensive stability data which revealed little or no change in any of the measured quality attributes, and that the two strengths of tablet are manufactured from a common blend. Photostability data was generated for the 90/400 mg tablets indicating that Harvoni tablets are not photosensitive. Additional stability data reveals that the product is not impacted by freezing or temporary exposure to high temperature (60 ºC), which means that temperature excursions outside the normal temperature range which may be encountered during shipping will not have an adverse effect on product quality.

Based on available stability data, the proposed shelf-life of 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.

2.2.4. Finished Medicinal Product – coated granules in sachet

Description of the product and Pharmaceutical development

Harvoni coated granules in sachet are an immediate-release taste-masked oral dosage form available in sachets for single use containing either 33.75 mg ledipasvir and 150 mg sofosbuvir or 45 mg ledipasvir and 200 mg sofosbuvir and as active substances.

The granules are orange, 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 33.75/150 mg sachet contains 90 granules and a 45/200 mg sachet contains 120 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 sources of active substance form are used as for the tablets. Their relevant physicochemical properties are discussed in section 2.2.3. Ledipasvir is incorporated as an amorphous component of LDV-SDD to improve its solubility.

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. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel

excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

The impact of mixing the granules with soft foods prior to ingestion was also evaluated. Granules were mixed with various soft foods. The granules were found to be chemically stable with no increase in degradation products after 2 hours. In addition, there was no impact on dissolution rate of either active substance. It is not considered likely that paediatric patients in this indication will require feeding tubes. Therefore, feeding tube administration was not investigated.

The dissolution method was modified slightly from that used in the tablet formulation. The manufacturing process was developed using the same principles as for the tablet formulation.

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

Process validation for the LDV-SDD step has already been completed in the context of the already approved 90/400 mg tablets. For the rest of the process, process validation will be conducted on 3 consecutive production scale batches prior to commercialisation, including the packaging step. The process validation scheme provided is considered suitable.

The 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.

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.), residual ethanol (GC), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.) and microbiological enumeration (Ph. Eur.).

The potential presence of class 1, 2A and select class 3 elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on six bulk and four packaged batches of the coated granules demonstrate that the amount of each relevant elemental impurity was well below the respective control threshold. Therefore, no specific controls for elemental impurities are required in the finished product specification.

The release and shelf-life limits for degradation products, many of which are also metabolites, are set in line with batch data, stability data, and the approved 90/400 mg tablets. The limits for ethanol used in the production process are set acceptably given the intended paediatric patient population.

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 4 pilot to production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

Stability of the product

Stability data from three pilot scale batches of each strength of finished product stored for up to 12 months under long term conditions (30 ºC / 75% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

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

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

Based on available stability data, the proposed shelf-life of 24 months without specific 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 extension procedure.

2.3.1. Ecotoxicity/environmental risk assessment

2.3.1.1. Ledipasvir

In the original Harvoni ERA assessment from 2014, the worst case PECsurfacewater (Phase I estimation, based on the daily dose of 90mg) was estimated to 0.45µg/L and exceeds the action limit of 0.01 µg/L – making a Phase II assessment necessary. In the Phase II assessment, the risk quotients (RQ) for all compartments of concern (sludge/effluent, surface water, ground water and sediment) were RQ<0.10. Based on the risk assessment, it is considered unlikely that the extension of Harvoni in the present procedure will increase environmental exposure to LDV.

With regard to the PBT assessment, the CHMP concluded that ledipasvir is not a PBT substance. The NOEC of 0.74 µg/l for Daphnia magna is the highest concentration tested (mean measured conc.) and the NOEC is actually >0.74 µg/l. The real concentration where no effects are observed might be higher if higher concentrations had been tested. Hence, the NOEC of 0.74 µg/l might overestimate the toxicity due to the low water toxicity. Overall, ledipasvir is considered persistent and bioaccumulative but not toxic, based on the data provided. Sections 5.3 and 6.6 of the SmPC have been amended accordingly.

2.3.1.2. Sofosbuvir

It is considered unlikely that the extension of Harvoni will increase environmental exposure to SOF in relation to the previously accepted 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 Harvoni paediatric investigation plan (PIP) and as stated in Paediatric Committee (PDCO) compliance report and decision document EMEA-001411PIP01-12-P/0063/2017, no additional non-clinical safety pharmacology and pharmacokinetic (PK) studies were required as part of the Harvoni PIP. During this assessment, it was determined that the non-clinical programme comprehensively evaluated and characterized the toxicity profile of LDV/SOF, and there is no expectation that the toxicity profile seen in adult animals will be different to that in juvenile animals.

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***

Table 1 Clinical Study Included in the Update to the LDV/SOF Marketing Application for Paediatric Subjects (3 to < 12 Years Old)

Study Number	Study Design	Subject Population[a]	Treatment Regimen[b,c,d]	N[a,e]	Location
GS-US-337-1116[a]	Phase 2, open-label, multi-cohort, 2-part study	Treatment-naive and treatment-experienced subjects 3 to < 12 years old with chronic HCV infection without cirrhosis or with compensated cirrhosis	LDV/SOF for 12 weeks LDV/SOF for 24 weeks LDV/SOF+RBV for 24 weeks	6 to < 12 years: 92 • Genotype 1: 88 • Genotype 3: 2 • Genotype 4: 2 • Genotype 5: 0 • Genotype 6: 0 3 to < 6 years: 34 • Genotype 1: 33 • Genotype 3: 0 • Genotype 4: 1 • Genotype 5: 0 • Genotype 6: 0	**CSR:** GS-US-337-1116 Final CSR **Narrative:** m2.7.3, Section 2.1

a Only data for subjects 6 to < 12 years old and 3 to < 6 years old are discussed in this summary.
b According to the study design, subjects received 1 of 3 different treatment regimens based on country of enrollment, HCV genotype, prior HCV treatment experience, and cirrhosis status, as described in Table 6.
c The doses and formulations of LDV/SOF were based on age group and weight as follows:
- Subjects 6 to < 12 years old received LDV/SOF 45/200 mg orally once daily (2 × 22.5/100-mg tablets or 4 × 11.25/50-mg packets containing granules). The selection of the LDV/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 LDV/SOF 45/200 mg orally once daily (4 × 11.25/50-mg packets containing granules). Subjects 3 to < 6 years old who weighed < 17 kg received LDV/SOF 33.75/150 mg orally once daily (3 × 11.25/50-mg packets containing granules).

d RBV was administered orally with LDV/SOF in subjects with genotype 3 HCV infection. 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.
e 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

The pharmacokinetics part of this application is supported by one Phase 2 clinical study (GS-US-337-1116) that provides information relevant to the PK (steady state), efficacy, and safety of LDV/SOF in paediatric subjects (aged 3 to < 18 years) with Chronic HCV-Infection, and one Phase 1 relative bioavailability and food effect study (GS-US-337-2091) of the paediatric oral granule formulation of LED/SOF in healthy adult subjects, relative to the FDC 90/400-mg approved tablet.

The LDV/SOF FDC (45/200-mg) tablet is not bridged to the FDC 90/400-mg approved tablet in a bioequivalence study, as the formulation and manufacturing processes used for the 45/200-mg tablet are the same as those used for the approved LDV/SOF FDC (90/400-mg) tablet and the criteria for obtaining a Biowaiver outlined in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 rev 1./corr) are fulfilled.

The descriptive summary and statistical comparison of PK parameters for LDV, SOF, GS-566500, and GS-331007 following the administration of single oral doses of LDV/SOF as a tablet (90/400 mg; 1 x 90/400 mg tablet) and as oral granules (90/400 mg; 8 x 11.25/50 mg units) under fasted conditions are presented in the table below.

Table 2 Descriptive summary and statistical comparison of PK parameters (fasted conditions)

	Mean (%CV)		
	Treatment A	Treatment B	%GLSM Ratio (90% CI)
PK Parameter	LDV/SOF Tablet Formulation (1 × 90/400 mg) fasted (Reference)	LDV/SOF Oral Granule Formulation (8 × 11.25/50 mg units) fasted (Test)	LDV/SOF Oral Granules vs LDV/SOF FDC Tablet
LDV (N = 42 reference/N = 39 test)[a]			
AUC_{last} (ng*h/mL)	7362.3 (48.3)	6242.5 (40.7)	87.76 (77.94, 98.82)
AUC_{inf} (ng*h/mL)	8467.5 (54.4)	7088.4 (46.3)	88.36 (78.43, 99.54)
C_{max} (ng/mL)	261.3 (43.5)	214.8 (38.2)	84.59 (74.69, 95.81)
GS-331007 (N = 42 reference/N = 42 test)			
AUC_{last} (ng*h/mL)	11146.3 (26.9)	11525.8 (26.3)	103.14 (96.71, 110.00)
AUC_{inf} (ng*h/mL)	11720.0 (26.1)	12095.0 (24.4)	103.64 (98.48, 109.07)
C_{max} (ng/mL)	833.9 (23.6)	951.9 (27.0)	112.81 (104.12, 122.22)
SOF (N = 42 reference/N = 42 test)			
AUC_{last} (ng*h/mL)	1559.8 (40.5)	1676.9 (43.7)	102.13 (87.16, 119.67)
AUC_{inf} (ng*h/mL)	1580.8 (40.2)	1684.1 (43.5)	101.60 (86.67, 119.10)
C_{max} (ng/mL)	1221.0 (38.5)	1266.7 (46.6)	95.98 (78.00, 118.11)
GS-566500 (N = 42 reference/N = 42 test)			
AUC_{last} (ng*h/mL)	1846.6 (31.4)	1952.9 (33.5)	100.59 (88.89, 113.83)
AUC_{inf} (ng*h/mL)	1894.9 (30.8)	2009.7 (33.0)	101.37 (90.17, 113.96)
C_{max} (ng/mL)	475.1 (33.9)	511.3 (34.9)	103.04 (91.06, 116.60)

a Three subjects [patient identifiers removed] in Treatment B were excluded since their LDV predose plasma concentration was > 5% of C_{max}

GS-331007 exposure in the LDV/SOF oral granules was bioequivalent to the LDV/SOF tablets. Exploratory analyses showed that the AUC and Cmax of SOF and GS-566500 were also comparable between the 2 formulations, with the 90% CIs for the %GLSM ratios contained within the range of 78% to 120% and 89% to 117%, respectively.

The results demonstrated modestly lower LDV exposure (approximately 12%) in the LDV/SOF oral granules compared with the LDV/SOF tablet formulation, with the lower bounds of the 90% CI being approximately 75% to 78%. These modest decreases in exposure are not considered to be clinically relevant, as the exposure was within the predefined equivalence boundaries of 50 to 200% selected for extrapolation of adult safety and efficacy data to children as part of a previous Harvoni extension of indication to add adolescents aged 12 to < 18 years (EMA/CHMP/246998/2017).

Thus, the granule formulation gives similar systemic exposure in healthy volunteers in the fasted state as the already approved LDV/SOF tablet.

The descriptive summary and statistical comparison of PK parameters for LDV, SOF, GS-566500, and GS-331007 following the administration of single oral doses of LDV/SOF as oral granules (90/400 mg; 8 x 11.25/50 mg units) under fasted and fed conditions are presented in the Table 3.

Table 3 Descriptive summary and statistical comparison of PK parameters (fasted & fed conditions)

	Mean (%CV)		
	Treatment B	Treatment C	%GLSM Ratio (90% CI)
PK Parameter	LDV/SOF Oral Granule Formulation (8 × 11.25/50 mg units) fasted (Reference)	LDV/SOF Oral Granule Formulation (8 × 11.25/50 mg units) fed (Test)	LDV/SOF Oral Granules High-Fat Meal vs Fasted
LDV (N = 39 reference/N = 40 test)[a,b]			
AUC_{last} (ng*h/mL)	6242.5 (40.7)	5149.6 (26.2)	87.62 (79.65, 96.39)
AUC_{inf} (ng*h/mL)	7088.4 (46.3)	5748.3 (29.0)	87.06 (78.95, 96.00)
C_{max} (ng/mL)	214.8 (38.2)	159.8 (28.9)	78.15 (71.26, 85.71)
GS-331007 (N = 42 reference/N = 42 test)			
AUC_{last} (ng*h/mL)	11525.8 (26.3)	11653.6 (18.9)	103.12 (97.61, 108.94)
AUC_{inf} (ng*h/mL)	12095.0 (24.4)	12220.6 (18.3)	102.26 (98.18, 106.52)
C_{max} (ng/mL)	951.9 (27.0)	583.1 (24.2)	62.01 (56.90, 67.59)
SOF (N = 42 reference/N = 42 test)			
AUC_{last} (ng*h/mL)	1676.9 (43.7)	2577.2 (33.1)	166.11 (145.00, 190.30)
AUC_{inf} (ng*h/mL)	1684.1 (43.5)	2597.7 (32.9)	166.18 (145.56, 189.71)
C_{max} (ng/mL)	1266.7 (46.6)	1236.3 (49.0)	100.32 (84.83, 118.65)
GS-566500 (N = 42 reference/N = 42 test)			
AUC_{last} (ng*h/mL)	1952.9 (33.5)	2931.7 (19.1)	163.23 (144.62, 184.23)
AUC_{inf} (ng*h/mL)	2009.7 (33.0)	2988.8 (18.7)	160.65 (143.40, 179.99)
C_{max} (ng/mL)	511.3 (34.9)	593.9 (31.0)	122.12 (108.28, 137.73)

a Three subjects [patient identifiers removed] in Treatment B were excluded since their LDV predose plasma concentration was > 5% of C_{max}
b Two subjects [patient identifiers removed] in Treatment C were excluded since their LDV predose plasma concentration was >5% C_{max}

With regards to food effect, the primary analysis demonstrated that the prespecified equivalence criteria for AUC of LDV (70% to 143%) and GS-331007 (80% to 125%) after administration of LDV/SOF oral granules under fed conditions compared with fasted conditions were met. Exploratory analyses showed the administration of the oral granules formulation under fed conditions compared with fasted conditions resulted in < 2-fold increase in AUC of SOF, and AUC and Cmax of GS-566500, with no alteration in SOF Cmax. These observations are consistent with historical data (Study GS-US-337-0101) on the effect of a high-fat/high-calorie meal on the approved LDV/SOF tablet formulation, which can be administered without regard to food. In addition, the slight decrease (13%) of LDV exposure (AUC) with food, compared to fasted state, is still within the equivalence boundaries of 50 to 200% used for extrapolation of adult safety and efficacy data to children as part of a previous Harvoni extension of indication to add adolescents aged 12 to < 18 years (EMA/CHMP/246998/2017).

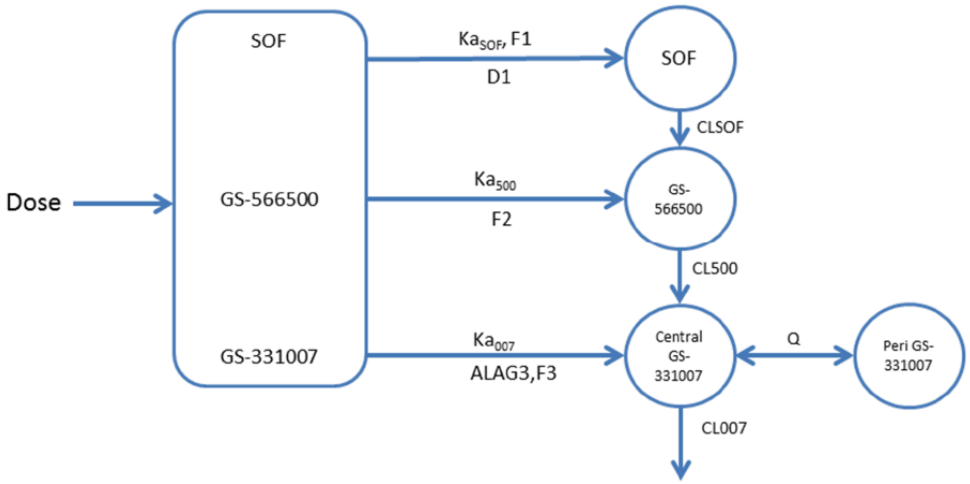
Taken together, the results from study GS-US-337-2091 indicate that the oral granule formulation of LDV/SOF gives similar systemic exposure as the approved LDV/SOF tablet and can be administered without regard to food.

Pharmacokinetics in Paediatric Subjects, 3-12 years

Sofosbuvir and metabolites

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.

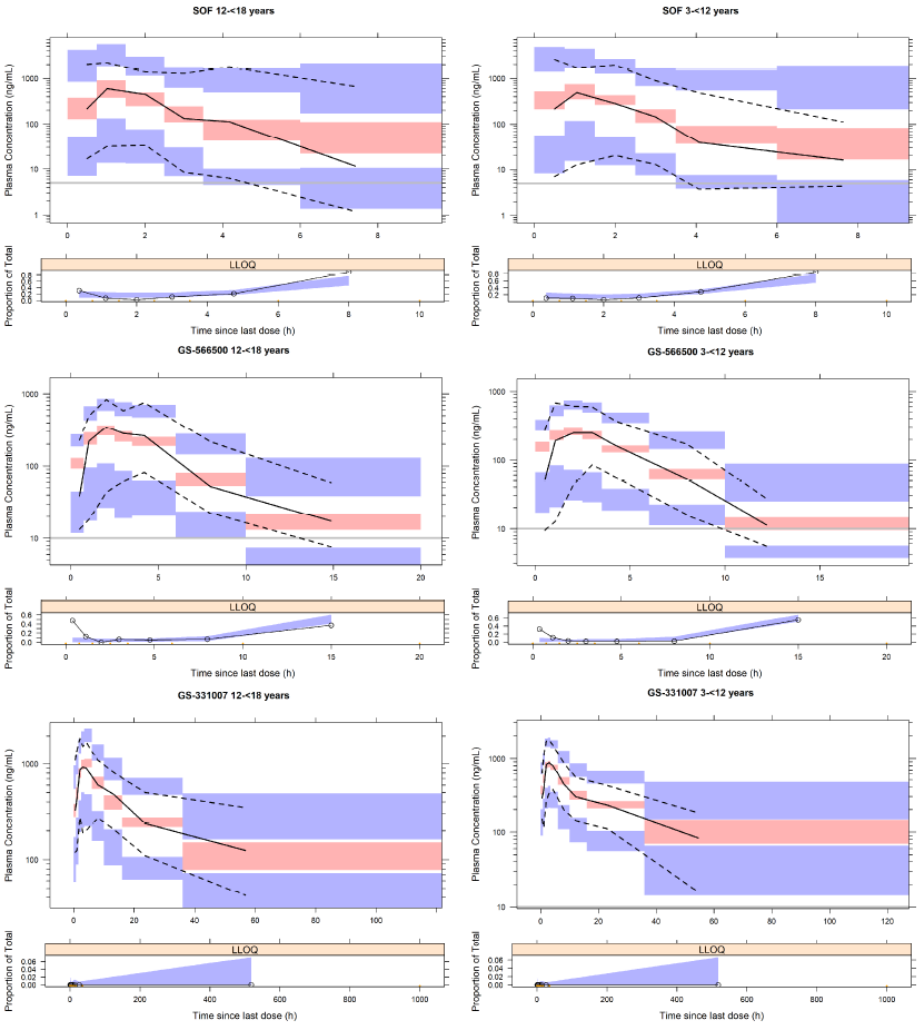
Figure 1 Population PK Model Diagram for SOF and SOF Metabolites.



Note: ALAG3 = absorption lag time of GS-331007; CL_{007} = apparent clearance of GS-331007; CL_{500} = apparent clearance of GS-566500; $CLsof$ = 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; $Kasof$ = 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)

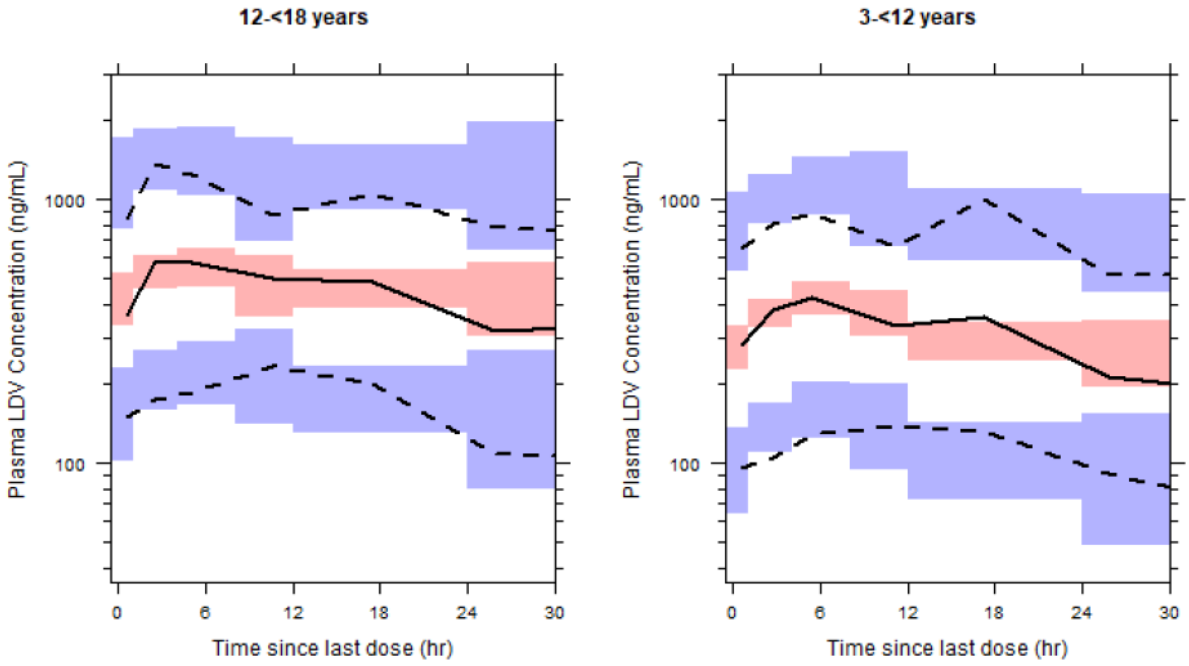


Note: BLQ = below limit of quantitation; LLOQ = lower limit of quantitation; SOF = sofosbuvir. pcVPC plots show median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the observed concentrations in all subjects. The red area is the 95% confidence interval of the simulated 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.

Ledipasvir

The ledipasvir PK was evaluated in a population PK analysis. The population PK dataset for LDV analysis included 1271 observations from 198 subjects. The final paediatric LDV model was described by a 2-compartment model including a zero-order input followed by a first-order absorption model, with interindividual variability on CL/F and Vc/F. Weight on CL/F and weight on Vc/F were included using fixed allometric exponents of 0.75 and 1, respectively. In addition, age and sex were found as statistically significant covariates on CL/F. 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 3.

Figure 3 Prediction Corrected Visual Predictive Check of Plasma Concentration-Time Profiles for LDV Stratified by Age (12 to < 18 years and 3 to < 12 years)



Note: LDV = ledipasvir; pcVPC = predicted corrected visual predictive check. The pcVPC plots show median (solid red line) and spread (5th to 95th percentile, dashed red lines) 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 fifth 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 LDV.
Source: LDV final PK model review – 20190401.R

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, GS-331007, and LDV exposures were similar to in HCV-infected adult subjects from Phase 2/3 studies. The AUCtau and Cmax for SOF, GS-331007, and LDV were within the predefined PK equivalence boundaries of 50% to 200% (***Table 4***).

Table 4 GS-US-337-1116: Statistical Comparison of SOF, GS-331007, and LDV Exposures Between Paediatric Subjects 3 to < 12 Years Old and the Adult Phase 2/3 Population

Analyte	PK Parameter	6 to < 12 Years Old LDV/SOF 45/200 mg (N = 62 for SOF and N = 91 for GS-331007 or LDV)[a]		3 to < 6 Years Old LDV/SOF 45/200 mg or 33.75/150 mg[b] (N = 33 for SOF, GS-331007, and LDV)[a]	
		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)	1483.0 (47.3)	101.41 (95.28, 107.94)	2482.0 (43.1)	173.80 (159.98, 188.82)
	C_{max} (ng/mL)	721.6 (47.8)	103.53 (95.28, 112.50)	1205.5 (55.1)	168.24 (150.36, 188.25)
GS-331007	AUC_{tau} (h•ng/mL)	9648.0 (33.8)	77.03 (73.23, 81.03)	11367.7 (16.9)	93.69 (86.28, 101.73)
	C_{max} (ng/mL)	879.5 (26.1)	120.38 (114.54, 126.52)	1054.2 (11.9)	147.96 (136.41, 160.50)
LDV	AUC_{tau} (h•ng/mL)	8726.7 (48.1)	107.95 (97.84, 119.11)	9077.7 (42.3)	116.23 (98.89, 136.60)
	C_{max} (ng/mL)	434.9 (47.3)	121.50 (111.50, 132.39)	483.2 (38.8)	140.76 (122.31, 161.99)
	C_{tau} (ng/mL)	284.3 (50.6)	120.37 (108.96, 132.97)	272.7 (48.7)	117.97 (100.18, 138.92)

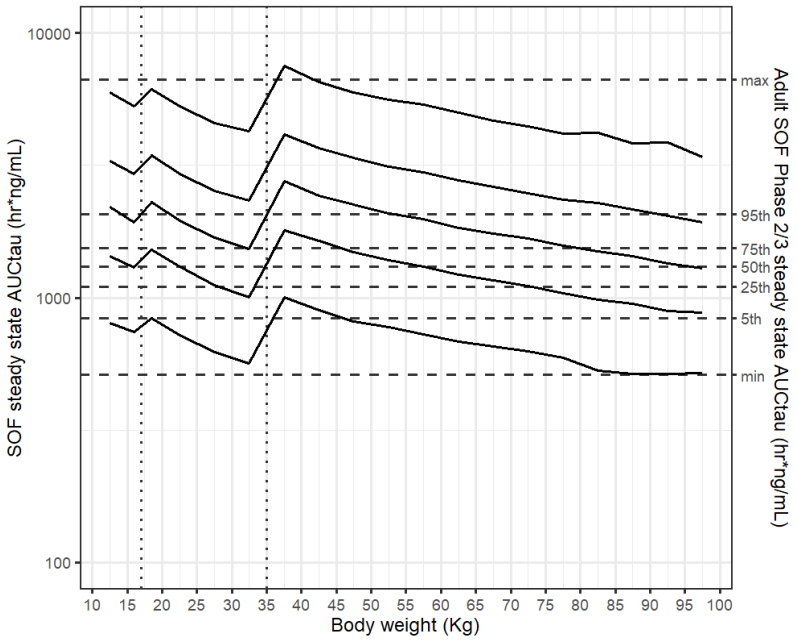
CI = confidence interval; CV = coefficient of variation; GMR = geometric mean ratio
a Exposures were not determined for 1 subject who did not have evaluable SOF, GS-331007, or LDV plasma concentrations.
b Subjects weighing ≥ 17 kg received LDV/SOF 45/200 mg, while subjects weighing < 17 kg received LDV/SOF 33.75/150 mg.
Source: Ad Hoc Tables 10170.6 and 10170.7

Further, population PK simulations were conducted to evaluate SOF, GS-331007, and LDV exposures (*Figure 4* to *Figure 6*) based on the proposed weight band-based dosing regimen (***Table 5***).

Table 5 Proposed LDV/SOF Weight Band-Based Doses

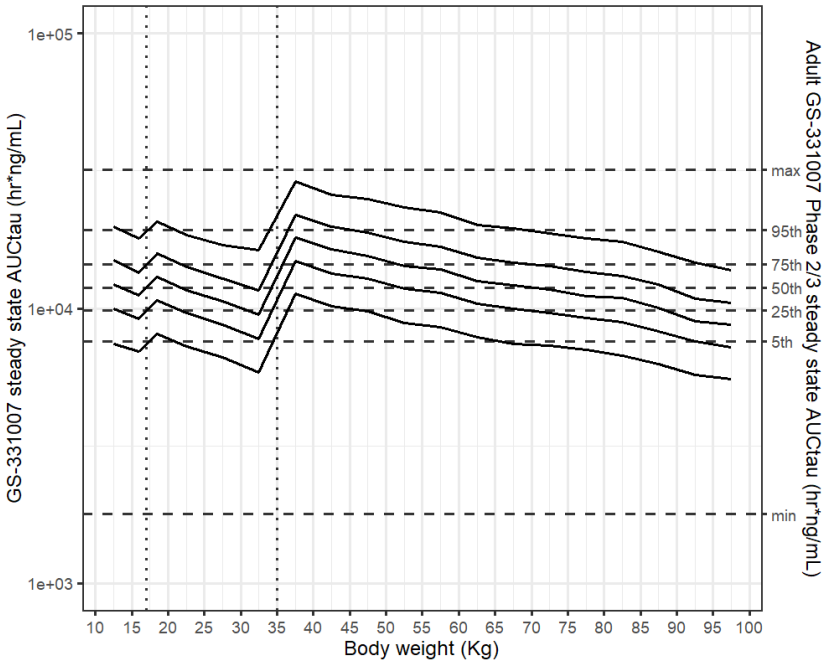
	Proposed LDV/SOF Dose for Pediatric Patients 3 to < 12 Years Old		
Weight (kg)	≥ 35	< 35 and ≥ 17	< 17
LDV/SOF Dose (mg)	90/400	45/200	33.75/150

Figure 4 Simulated SOF Exposures by Proposed Weight Band-Based Dosing



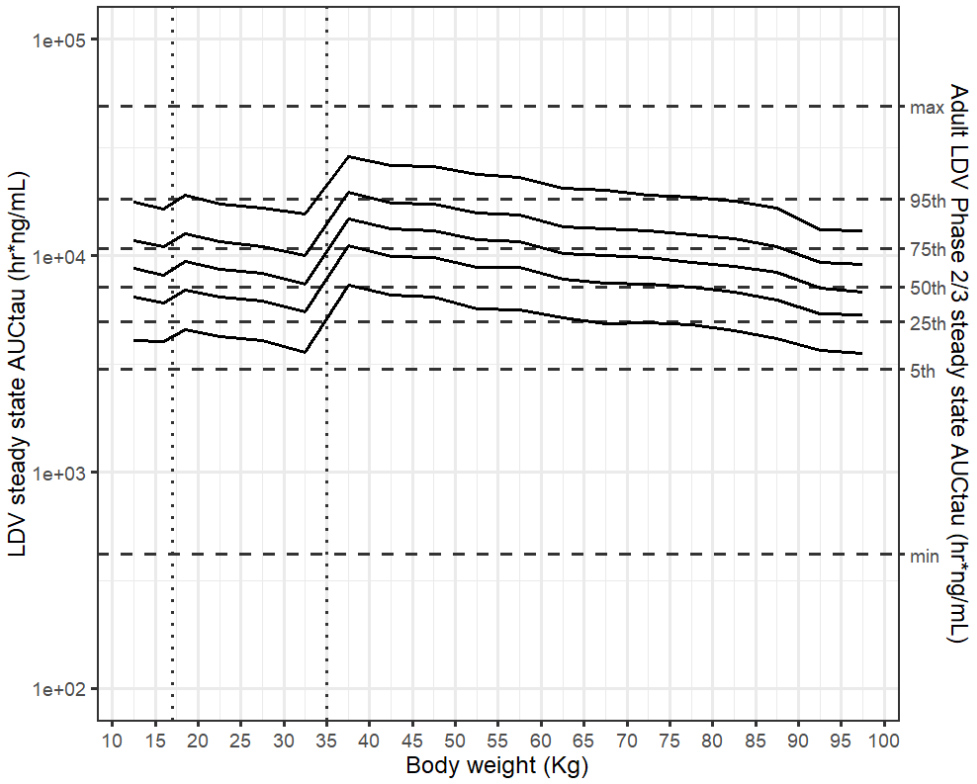
WT = weight
Solid lines represent 5th, 25th, 50th, 75th, and 95th percentiles of simulated paediatric exposures; horizontal dashed lines represent distribution of adult exposures; vertical dashed lines indicates 17 kg and 35 kg cutoffs.
Source: Population PK Report CTRA-2019-1031, Figure 30

Figure 5 Simulated 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 indicates 17 kg and 35 kg cutoffs.
Source: Population PK Report CTRA-2019-1031, Figure 30

Figure 6 Simulated LDV 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 indicates 17 kg and 35 kg cutoffs.
Source: Population PK Report CTRA-2019-1031, Figure 33

Simulated SOF exposures are largely contained within the range observed in the adult Phase 2/3 population. In subjects with the lowest body weight within each identified weight band (ie, 11, 17, and 35 kg), approximately ≤ 6% are expected to achieve maximum exposures greater than those observed in the adult Phase 2/3 population. In addition, < 5% 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 adult Phase 2/3 population. In subjects with the lowest body weight within each identified weight band, < 2% of subjects are expected to achieve maximum exposures greater than those observed in the 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.

Simulated LDV exposures are largely contained within the range observed in the adult Phase 2/3 population. In subjects with the lowest body weight within each identified weight band, < 1% of subjects are expected to achieve maximum exposures greater than those observed in the 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 3 to < 12 years old, 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 LDV/SOF and had evaluable population-based AUC_{tau} estimates for SOF (N = 95), GS-331007 (N = 124), and LDV (N = 124). Overall, SOF, GS-331007, and LDV exposures in paediatric subjects were similar regardless of the presence or absence of the evaluated AEs (headache, pyrexia, abdominal pain, fatigue, vomiting, cough, or rhinorrhoea), both overall and by age group treatment 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 ledipasvir PK model described the data well and is adequate for exposure predictions and dose selection.

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, and all analytes, 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 seem reasonable. 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 ledipasvir 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-337-1116

GS-US-337-1116 was a Phase 2 study evaluating the PK, safety, and antiviral activity of LDV/SOF±RBV in paediatric subjects aged 3 to < 18 years old. 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. Data for adolescent subjects 12 to < 18 years old were previously presented in the GS-US-337-1116 Interim CSR, and final data through posttreatment Week 24 are presented in the GS-US-337-1116 Final CSR. Only data for paediatric subjects 3 to < 12 years old are presented below.

2.4.5.2. Methods

- **Study participants**

Although the GS-US-337-1116 study allowed for inclusion of HCV multiple genotypes (1, 3, 4, 5, 6 and subsequently 2) the population studied was predominantly GT1 patients (121/126). In line with the pharmacokinetic bridging, this is acceptable given that the pharmacological targets of SOF and LDV are HCV-specific (NS5B and NS5A, respectively).

Subjects 6 to < 12 Years Old

A total of 92 subjects aged 6 to < 12 years were enrolled into the study (70 subjects in the US, 11 subjects in the United Kingdom (UK), 7 subjects in Australia, and 4 subjects in New Zealand).

Overall, the mean age of subjects was 9 years. The majority of subjects had been infected through vertical transmission (96.7%).

The majority of subjects had genotype 1 HCV infection (95.7%, 88 subjects [77 with the genotype 1a subtype, 10 with the genotype 1b subtype, and 1 with undetermined subtype]); 2 subjects (2.2%) had genotype 3 HCV infection; and 2 subjects (2.2%) had genotype 4 HCV infection. 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 (73.9%), and high viral load (58.7% with HCV RNA ≥ 800,000 IU/mL). Two subjects (2.2%) had known cirrhosis based on prior biopsy. The majority of subjects were treatment-naive (78.3%).

Subjects 3 to < 6 Years Old

A total of 34 subjects aged 3 to < 6 years were enrolled into the study (29 subjects in the US, 3 subjects in the UK, and 2 subjects in Australia).

Overall, the mean age of subjects was 4 years. All subjects had been infected through vertical transmission (100.0%).

The majority of subjects had genotype 1 HCV infection (97.1%, 33 subjects [28 with the genotype 1a subtype and 5 with the genotype 1b subtype]); 1 subject (2.9%) had genotype 4 HCV infection. 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 (64.7%), and high viral load (55.9% 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 3 different treatment regimens based on country of enrolment, HCV genotype, prior HCV treatment experience, and cirrhosis status, as described in Table 6.

Table 6. GS-US-337-1116: Treatment Regimens Based on Country of Enrollment, HCV Genotype, HCV Treatment Experience, and Cirrhosis Status

	United States/Australia/New Zealand	United Kingdom
Treatment Naive with or without Cirrhosis		
Genotype 1	LDV/SOF 12 weeks	LDV/SOF 12 weeks
Genotypes 4, 5, or 6	LDV/SOF 12 weeks	LDV/SOF 12 weeks
Treatment Experienced without Cirrhosis		
Genotype 1	LDV/SOF 12 weeks	LDV/SOF 12 weeks
Genotypes 4, 5, or 6	LDV/SOF 12 weeks	LDV/SOF 12 weeks
Genotype 3	NA	LDV/SOF+RBV 24 weeks
Treatment Experienced with Cirrhosis		
Genotype 1	LDV/SOF 24 weeks	LDV/SOF 24 weeks
Genotypes 4, 5, or 6	LDV/SOF 12 weeks	LDV/SOF 24 weeks
Genotype 3	NA	LDV/SOF+RBV 24 weeks

NA = not applicable

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-337-1116 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**

Patients in both age groups were predominantly vertically HCV infected, GT1 non-cirrhotic(or with unknown cirrhosis status). This is acceptable, given that the efficacy can be bridged from adult pivotal studies given that drug exposure is comparable.

Subjects 6 to < 12 years old

Overall, the majority of subjects were male (58.7%), white (79.3%), and non-Hispanic/Latino (84.8%), with a mean age of 9 years. The mean (SD) baseline BMI value for subjects was 18.2 (3.47) kg/m2. Table 7 presents a summary of the baseline disease characteristics for subjects 6 to < 12 years old overall and by treatment group.

Table 7 GS-US-337-1116: Baseline disease characteristics (6 to <12 Years old) (Safety Analysis Set)

	6 to < 12 Years Old					
		LDV/SOF FDC (45/200 mg) 12 Weeks			LDV/SOF FDC (45/200 mg) 24 Weeks	LDV/SOF FDC (45/200 mg) + RBV 24 Weeks
Disease Characteristic	**Total (N = 92)**	**LDV/SOF 12 Weeks Total (N = 89)**	**GT1 or GT4 TN With or Without Cirrhosis (N = 72)**	**GT1 TE Without Cirrhosis (N = 17)**	**GT1 TE With Cirrhosis (N = 1)**	**GT 3 TE With or Without Cirrhosis (N = 2)**
HCV Genotype						
Genotype 1	88 (95.7%)	87 (97.8%)	70 (97.2%)	17 (100.0%)	1 (100.0%)	0
Genotype 1 (No Confirmed Subtype)	1 (1.1%)	1 (1.1%)	1 (1.4%)	0	0	0
Genotype 1a	77 (83.7%)	76 (85.4%)	61 (84.7%)	15 (88.2%)	1 (100.0%)	0
Genotype 1b	10 (10.9%)	10 (11.2%)	8 (11.1%)	2 (11.8%)	0	0
Genotype 3	2 (2.2%)	0	0	0	0	2 (100.0%)
Genotype 4	2 (2.2%)	2 (2.2%)	2 (2.8%)	0	0	0
Cirrhosis						
Yes	2 (2.2%)	1 (1.1%)	1 (1.4%)	0	1 (100.0%)	0
No	35 (38.0%)	33 (37.1%)	16 (22.2%)	17 (100.0%)	0	2 (100.0%)
Unknown	55 (59.8%)	55 (61.8%)	55 (76.4%)	0	0	0
IL28B						
CC	23 (25.0%)	23 (25.8%)	22 (30.6%)	1 (5.9%)	0	0
Non-CC	68 (73.9%)	65 (73.0%)	50 (69.4%)	15 (88.2%)	1 (100.0%)	2 (100.0%)
CT	55 (59.8%)	53 (59.6%)	39 (54.2%)	14 (82.4%)	0	2 (100.0%)
TT	13 (14.1%)	12 (13.5%)	11 (15.3%)	1 (5.9%)	1 (100.0%)	0
Missing	1 (1.1%)	1 (1.1%)	0	1 (5.9%)	0	0
Baseline HCV RNA Category						
< 800,000 IU/mL	38 (41.3%)	37 (41.6%)	31 (43.1%)	6 (35.3%)	0	1 (50.0%)
≥ 800,000 IU/mL	54 (58.7%)	52 (58.4%)	41 (56.9%)	11 (64.7%)	1 (100.0%)	1 (50.0%)
Baseline HCV RNA (log_{10} IU/mL)						
Mean (SD)	6.0 (0.59)	6.0 (0.60)	6.0 (0.60)	6.2 (0.56)	6.2	5.7 (0.31)
Median	6.1	6.1	6.1	6.1	6.2	5.7
Q1, Q3	5.6, 6.5	5.6, 6.5	5.5, 6.5	5.8, 6.4	6.2, 6.2	5.5, 5.9
Min, Max	4.6, 7.3	4.6, 7.3	4.6, 7.1	5.3, 7.3	6.2, 6.2	5.5, 5.9
Baseline ALT (U/L)						
Mean (SD)	66 (41.1)	65 (41.6)	61 (38.4)	83 (50.5)	94	70 (17.0)
Median	57	55	54	71	94	70
Q1, Q3	41, 83	41, 82	40, 76	53, 96	94, 94	58, 82

Disease Characteristic	6 to < 12 Years Old					
	Total (N = 92)	LDV/SOF FDC (45/200 mg) 12 Weeks			LDV/SOF FDC (45/200 mg) 24 Weeks	LDV/SOF FDC (45/200 mg) + RBV 24 Weeks
		LDV/SOF 12 Weeks Total (N = 89)	GT1 or GT4 TN With or Without Cirrhosis (N = 72)	GT1 TE Without Cirrhosis (N = 17)	GT1 TE With Cirrhosis (N = 1)	GT 3 TE With or Without Cirrhosis (N = 2)
Min, Max	14, 255	14, 255	14, 247	37, 255	94, 94	58, 82
Baseline ALT Category						
≤ 1.5 × ULN	41 (44.6%)	40 (44.9%)	36 (50.0%)	4 (23.5%)	0	1 (50.0%)
> 1.5 × ULN	51 (55.4%)	49 (55.1%)	36 (50.0%)	13 (76.5%)	1 (100.0%)	1 (50.0%)
Estimated Glomerular Filtration Rate Using Schwartz Formula (mL/min/1.73m^2)						
Mean (SD)	156.4 (24.38)	156.2 (24.55)	157.2 (25.59)	151.7 (19.56)	181.0	153.3 (20.77)
Median	152.9	152.8	153.0	148.2	181.0	153.3
Q1, Q3	141.5, 172.3	141.9, 171.1	142.1, 174.1	141.1, 159.5	181.0, 181.0	138.6, 168.0
Min, Max	116.3, 249.5	116.3, 249.5	116.3, 249.5	123.3, 195.3	181.0, 181.0	138.6, 168.0
Prior HCV Treatment Experience						
Treatment-Naive	72/92 (78.3%)	72/89 (80.9%)	72/72 (100.0%)	0/17	0/1	0/2
IFN-Eligible	64/72 (88.9%)	64/72 (88.9%)	64/72 (88.9%)	0/0	0/0	0/0
IFN-Ineligible	8/72 (11.1%)	8/72 (11.1%)	8/72 (11.1%)	0/0	0/0	0/0
Treatment-Experienced	20/92 (21.7%)	17/89 (19.1%)	0/72	17/17 (100.0%)	1/1 (100.0%)	2/2 (100.0%)
Most Recent HCV Treatment Response						
Non-Responder	16/20 (80.0%)	14/17 (82.4%)	0/0	14/17 (82.4%)	1/1 (100.0%)	1/2 (50.0%)
Relapse/Breakthrough	3/20 (15.0%)	2/17 (11.8%)	0/0	2/17 (11.8%)	0/1	1/2 (50.0%)
IFN-Intolerant	1/20 (5.0%)	1/17 (5.9%)	0/0	1/17 (5.9%)	0/1	0/2
Mode of HCV Infection						
Vertical Transmission	89 (96.7%)	86 (96.6%)	69 (95.8%)	17 (100.0%)	1 (100.0%)	2 (100.0%)
Unknown	2 (2.2%)	2 (2.2%)	2 (2.8%)	0	0	0
Contaminated Needle or IV Drug Use	0	0	0	0	0	0
Blood Product Transfusion	1 (1.1%)	1 (1.1%)	1 (1.4%)	0	0	0
Contact with Infected Individual	0	0	0	0	0	0

Baseline value was 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 (70.6%), white (79.4%), and non-Hispanic/Latino (82.4%), with a mean age of 4 years. The mean (SD) baseline BMI value for subjects was 16.7 (2.35) kg/m2. Table 13 presents a summary of the baseline disease characteristics for subjects 3 to < 6 years old.

Table 8 GS-US-337-1116: Baseline disease characteristics (3 to <6 Years old) (Safety Analysis Set)

Disease Characteristic	3 to < 6 Years Old LDV/SOF FDC (45/200 mg or 33.75/150 mg) 12 Weeks GT1 or GT4 TN With or Without Cirrhosis (N = 34)
HCV Genotype	
Genotype 1	33 (97.1%)
Genotype 1 (No Confirmed Subtype)	0
Genotype 1a	28 (82.4%)
Genotype 1b	5 (14.7%)
Genotype 3	0
Genotype 4	1 (2.9%)
Cirrhosis	
Yes	0
No	14 (41.2%)
Unknown	20 (58.8%)
IL28B	
CC	10 (29.4%)
Non-CC	22 (64.7%)
CT	16 (47.1%)
TT	6 (17.6%)
Missing	2 (5.9%)
Baseline HCV RNA Category	
< 800,000 IU/mL	15 (44.1%)
≥ 800,000 IU/mL	19 (55.9%)
Baseline HCV RNA (log_{10} IU/mL)	
Mean (SD)	6.0 (0.62)
Median	6.0
Q1, Q3	5.6, 6.5
Min, Max	4.8, 7.3
Baseline ALT (U/L)	
Mean (SD)	62 (31.6)
Median	52
Q1, Q3	35, 90
Min, Max	25, 130

Disease Characteristic	3 to < 6 Years Old LDV/SOF FDC (45/200 mg or 33.75/150 mg) 12 Weeks GT1 or GT4 TN With or Without Cirrhosis (N = 34)
Baseline ALT Category	
≤ 1.5 × ULN	16 (47.1%)
> 1.5 × ULN	18 (52.9%)
Estimated Glomerular Filtration Rate Using Schwartz Formula (mL/min/1.73m^2)	
Mean (SD)	169.1 (28.04)
Median	170.5
Q1, Q3	148.6, 184.9
Min, Max	98.9, 220.2
Prior HCV Treatment Experience	
Treatment-Naive	34/34 (100.0%)
IFN-Eligible	33/34 (97.1%)
IFN-Ineligible	1/34 (2.9%)
Treatment-Experienced	0/34
Most Recent HCV Treatment Response	
Non-Responder	0/0
Relapse/Breakthrough	0/0
IFN-Intolerant	0/0
Mode of HCV Infection	
Vertical Transmission	34 (100.0%)
Unknown	0
Contaminated Needle or IV Drug Use	0
Blood Product Transfusion	0
Contact with Infected Individual	0

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

- **Outcomes and estimation**

SVR12

Subjects 6 to < 12 Years Old

Table 9 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). One treatment-naive subject with genotype 1a HCV infection and cirrhosis completed 12 weeks of LDV/SOF and relapsed at the posttreatment Week 4 visit; the subject was reported to have 97.6% study drug adherence.

Table 9. GS-US-337-1116: Virologic Outcomes (6 to < 12 Years Old) (Full Analysis Set)

	6 to < 12 Years Old					
		LDV/SOF FDC (45/200 mg) 12 Weeks			LDV/SOF FDC (45/200 mg) 24 Weeks	LDV/SOF FDC (45/200 mg) + RBV 24 Weeks
	Total (N = 92)	LDV/SOF 12 Weeks Total (N = 89)	GT1 or GT4 TN With or Without Cirrhosis (N = 72)	GT1 TE Without Cirrhosis (N = 17)	GT1 TE With Cirrhosis (N = 1)	GT3 TE With or Without Cirrhosis (N = 2)
SVR12	91/92 (98.9%)	88/89 (98.9%)	71/72 (98.6%)	17/17 (100.0%)	1/1 (100.0%)	2/2 (100.0%)
Overall Virologic Failure	1/92 (1.1%)	1/89 (1.1%)	1/72 (1.4%)	0/17	0/1	0/2
Relapse	1/92 (1.1%)	1/89 (1.1%)	1/72 (1.4%)	0/17	0/1	0/2
Completed Study Treatment	1/92 (1.1%)	1/89 (1.1%)	1/72 (1.4%)	0/17	0/1	0/2
Discontinued Study Treatment	0/0	0/0	0/0	0/0	0/0	0/0
On-Treatment Virologic Failure	0/92	0/89	0/72	0/17	0/1	0/2
Other	0/92	0/89	0/72	0/17	0/1	0/2

GT = genotype; TE = treatment-experienced; TN = treatment-naive
HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation of 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 9901.3

Subjects 3 to < 6 Years Old

Table 10 presents the proportion of subjects 3 to < 6 years old who achieved SVR12 and virologic outcomes. No subject had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse) or relapsed. One subject (2.9%) did not achieve SVR12 due to premature discontinuation of study drug due to an AE of product taste abnormal, and was categorized as having "other" virologic outcome at posttreatment Week 12.

Table 10. GS-US-337-1116: Virologic Outcomes (3 to < 6 Years Old) (Full Analysis Set)

	3 to < 6 Years Old
	LDV/SOF FDC (45/200 mg or 33.75/150 mg) 12 Weeks
	GT1 or GT4 TN With or Without Cirrhosis (N = 34)
SVR12	33/34 (97.1%)
Overall Virologic Failure	0/34
Other	1/34 (2.9%)

GT = genotype; TN = treatment-naive
HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation of 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: GS-US-337-1116 Final, Table 15.9.2.1

It is clear that LDV/SOF is highly effective in the patient population studied. Due to the close to 100% SVR12 rate (98.9 and 97.1%, 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

Pre-treatment NS5A and NS5B NI resistance-associated variants (RAVs) were observed in 14.1% (13 of 92) and 3.2% (3 of 92) of subjects 6 to < 12 years old, respectively. The presence of pre-treatment NS5A and/or NS5B RAVs did not impact treatment outcome, as all subjects with pre-treatment RAVs achieved SVR12 and SVR24. One subject infected with genotype 1a HCV failed to achieve SVR12 and SVR24. This subject had no pre-treatment NS5A or NS5B NI RAVs at baseline and had emergent NS5A RAV Y93H at relapse.

Subjects 3 to < 6 Years Old

Pre-treatment NS5A and NS5B NI RAVs were observed in 12.1% (4 of 33) and 6.1% (2 of 33) of subjects 3 to < 6 years old with virologic outcome, respectively. The presence of pre-treatment NS5A and/or NS5B RAVs did not impact treatment outcome as all subjects with pre-treatment RAVs achieved SVR12 and SVR24.

2.4.6. Discussion on clinical efficacy

The GS-US-337-1116 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 were limited mainly to non-cirrhotic GT1 patients treated for 12 weeks with LDV/SOF without ribavirin. Given that exposure is comparable, efficacy across genotypes and into the subset of cirrhotic patients can be extrapolated from the adult phase 3 programme.

2.4.7. Conclusions on clinical efficacy

The CHMP concluded that LDV/SOF 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, 92 subjects 6 to < 12 years old were enrolled and received at least 1 dose of study drug. The mean (standard deviation [SD]) duration of exposure to study drug for subjects 6 to < 12 years old was 12.1 (0.25) weeks for the 89 subjects in the LDV/SOF 12 Week group, 24.0 weeks for the single subject in the LDV/SOF 24 Week group, and 24.2 (0.10) weeks for the 2 subjects in the LDV/SOF+RBV 24 Week group. All but 1 subject (LDV/SOF 12 Week group) completed their assigned treatment duration. One subject in the LDV/SOF 12-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 Day 79 when the last on-treatment study visit was performed, rather than continuing until Day 84.

Subjects 3 to < 6 years old

Overall, 34 subjects 3 to < 6 years old were enrolled and received at least 1 dose of study drug. The mean (SD) duration of exposure to study drug for subjects 3 to < 6 years old was 11.7 (1.96) weeks. The majority of subjects (94.1%, 32 of 34 subjects) completed their assigned treatment duration. Two subjects were counted as not having completed the assigned treatment duration; however, study drug accountability data indicate that one of these subjects did actually complete all 84 days of treatment (GS-US-337-1116 Final, Listing 16.2.5.2). The remaining subject prematurely discontinued study drug on Day 5 due to an AE of product taste abnormal.

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 LDF/SOF in adults.

2.4.8.2. Adverse events

Subjects 6 to < 12 years old

The majority of subjects (70.7%, 65 of 92 subjects) experienced at least 1 AE (69.7% [62 of 89] of subjects in the LDV/SOF 12 week group; all 3 subjects in the LDV/SOF±RBV 24 week groups experienced at least 1 AE).

All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. One subject in the LDV/SOF 12 week group experienced SAEs that were assessed by the investigator as not related to study drug (tooth abscess, abdominal pain, and gastroenteritis). No deaths were reported. No subjects prematurely discontinued LDV/SOF or RBV due to an AE, and no subjects had AEs that led to interruption of LDV/SOF dosing or modification or interruption of RBV dosing. 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 11 GS-US-337-1116: Overall Summary of Adverse Events (6 to < 12 Years Old) (Safety Analysis Set)

	6 to < 12 Years old			
	Total (N = 92)	**LDV/SOF FDC (45/200 mg) 12 Weeks (N = 89)**	**LDV/SOF FDC (45/200 mg) 24 Weeks (N = 1)**	**LDV/SOF FDC (45/200 mg) + RBV 24 Weeks (N = 2)**
Number (%) of Subjects Experiencing Any				
Treatment-Emergent Adverse Event	65 (70.7%)	62 (69.7%)	1 (100.0%)	2 (100.0%)
Grade 3 or Above Treatment-Emergent Adverse Event	0	0	0	0
Grade 2 or Above Treatment-Emergent Adverse Event	14 (15.2%)	14 (15.7%)	0	0
Treatment-Emergent Treatment-Related Adverse Event	25 (27.2%)	23 (25.8%)	0	2 (100.0%)
Grade 3 or Above Treatment-Emergent Treatment-Related Adverse Event	0	0	0	0
Grade 2 or Above Treatment-Emergent Treatment-Related Adverse Event	1 (1.1%)	1 (1.1%)	0	0
Treatment-Emergent Serious Adverse Event	1 (1.1%)	1 (1.1%)	0	0
Treatment-Emergent Treatment-Related Serious Adverse Event	0	0	0	0
Adverse Event Leading to Premature Discontinuation of Any Study Drug	0	0	0	0
Adverse Event Leading to Premature Discontinuation of LDV/SOF	0	0	0	0
Adverse Event Leading to Premature Discontinuation of RBV	0	N/A	N/A	0
Adverse Event Leading to Premature Discontinuation of All Study Drugs	0	N/A	N/A	0
Adverse Event Leading to Modification or Interruption of Any Study Drug	0	0	0	0
Adverse Event Leading to Interruption of LDV/SOF	0	0	0	0
Adverse Event Leading to Modification or Interruption of RBV	0	N/A	N/A	0
All Deaths	0	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 12 presents a summary of AEs reported for at least 10% of subjects 6 to < 12 years old in any treatment group by PT. Among subjects in the LDV/SOF 12 week group, the most 3 commonly reported AEs were headache (18.0%), pyrexia (16.9%), and abdominal pain (15.7%). For the 3 subjects in the LDV/SOF±RBV 24 week groups, the only AE reported in > 1 subject was cough.

Table 12 GS-US-337-1116: Adverse Events Reported for at Least 10% of Subjects in Any Treatment Group (6 to <12 years Old) (Safety Analysis Set)

	6 to < 12 Years old			
	Total (N = 92)	LDV/SOF FDC (45/200 mg) 12 Weeks (N = 89)	LDV/SOF FDC (45/200 mg) 24 Weeks (N = 1)	LDV/SOF FDC (45/200 mg) + RBV 24 Weeks (N = 2)
Number (%) of Subjects Experiencing Any Treatment-Emergent Adverse Event	65 (70.7%)	62 (69.7%)	1 (100.0%)	2 (100.0%)
Headache	17 (18.5%)	16 (18.0%)	0	1 (50.0%)
Pyrexia	16 (17.4%)	15 (16.9%)	0	1 (50.0%)
Fatigue	14 (15.2%)	13 (14.6%)	0	1 (50.0%)
Abdominal pain	14 (15.2%)	14 (15.7%)	0	0
Vomiting	13 (14.1%)	12 (13.5%)	0	1 (50.0%)
Cough	13 (14.1%)	11 (12.4%)	1 (100.0%)	1 (50.0%)
Diarrhoea	11 (12.0%)	11 (12.4%)	0	0
Nausea	10 (10.9%)	9 (10.1%)	0	1 (50.0%)
Oropharyngeal pain	10 (10.9%)	10 (11.2%)	0	0
Nasal congestion	6 (6.5%)	5 (5.6%)	1 (100.0%)	0
Rhinorrhoea	4 (4.3%)	3 (3.4%)	1 (100.0%)	0
Nasopharyngitis	3 (3.3%)	2 (2.2%)	0	1 (50.0%)
Epistaxis	3 (3.3%)	2 (2.2%)	1 (100.0%)	0

Adverse events were mapped according to MedDRA Version 20.1.
Subjects were 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 13 presents an overall summary of AEs for subjects 3 to < 6 years old. The majority of subjects (73.5%, 25 of 34) experienced at least 1 AE. All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. No subjects experienced SAEs. No deaths were reported. One subject prematurely discontinued LDV/SOF due to an AE (Section 11.3.5). No subjects had AEs that led to interruption of LDV/SOF dosing. 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 13 GS-US-337-1116: Overall Summary of Adverse Events (3 to <6 years Old) (Safety Analysis Set)

	3 to < 6 Years Old LDV/SOF FDC (45/200 mg or 33.75/150 mg) 12 Weeks (N = 34)
Number (%) of Subjects Experiencing Any	
Treatment-Emergent Adverse Event	25 (73.5%)
Grade 3 or Above Treatment-Emergent Adverse Event	0
Grade 2 or Above Treatment-Emergent Adverse Event	4 (11.8%)
Treatment-Emergent Treatment-Related Adverse Event	10 (29.4%)
Grade 3 or Above Treatment-Emergent Treatment-Related Adverse Event	0
Grade 2 or Above Treatment-Emergent Treatment-Related Adverse Event	0
Treatment-Emergent Serious Adverse Event	0
Treatment-Emergent Treatment-Related Serious Adverse Event	0
Adverse Event Leading to Premature Discontinuation of LDV/SOF	1 (2.9%)
Adverse Event Leading to Interruption of LDV/SOF	0
All Deaths	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 14 presents a summary of AEs reported for at least 10% of subjects 3 to < 6 years old by PT. The most 3 commonly reported AEs were vomiting (23.5%), and pyrexia and cough (each 20.6%).

Table 14 GS-US-337-1116: Adverse Events Reported for at Least 10% of Subjects in Any Treatment Group (3 to < 6 years Old) (Safety Analysis Set)

	3 to < 6 Years Old LDV/SOF FDC (45/200 mg or 33.75/150 mg) 12 Weeks (N = 34)
Number (%) of Subjects Experiencing Any Treatment-Emergent Adverse Event	25 (73.5%)
Vomiting	8 (23.5%)
Pyrexia	7 (20.6%)
Cough	7 (20.6%)
Rhinorrhoea	6 (17.6%)
Pharyngitis streptococcal	4 (11.8%)

Adverse events were mapped according to MedDRA Version 20.1.
Subjects were 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

The adverse events presented are in line with the currently established favourable safety profile of LDV/SOF. In comparison to the terms listed in SmPC section 4.8, it is clear that gastrointestinal AEs such as nausea, vomiting and diarrhoea are quite common. The lack of a control arm makes assessment of causality difficult and the data should be seen in the context that GI symptoms are overall relatively common in children.

2.4.8.3. Serious adverse events and deaths

In the group of subjects 6 to < 12 years old, three treatment-emergent SAEs and 1 nontreatment-emergent SAE were reported in 1 subject in the LDV/SOF 12 week group. The subject experienced treatment-emergent SAEs of Grade 2 tooth abscess on Day 13, Grade 2 abdominal pain on Day 25, and Grade 2 gastroenteritis on Day 89, and a nontreatment-emergent SAE of allergic oedema 167 days after the end of treatment. None of the events were assessed by the investigator as related to study drug or led to dose modification. All events resolved.

No treatment-emergent SAEs were reported during the study for subjects 3 to < 6 years old and

There were no deaths in the study.

The low level of treatment-emergent SAEs (1/126 study subjects aged 3-12 years), absence of deaths and overall high adherence to treatment is in line with the established favourable safety profile of LDV/SOF.

2.4.8.4. Laboratory findings

Subjects 6 to < 12 years old

The majority of subjects 6 to < 12 years old (57.6%, 53 of 92) had at least 1 laboratory abnormality reported (57.3% [51 of 89] of subjects in the LDV/SOF 12 week group, 100.0% [1 of 1] of subjects in the LDV/SOF 24 week group, and 50.0% [1 of 2] of subjects in the LDV/SOF+RBV 24 week group). For all but 4 subjects, the maximum laboratory abnormality grade was Grade 1 (43.5% [40 of 92 subjects]) or Grade 2 (9.8% [9 of 92 subjects]). Grade 3 and 4 laboratory abnormalities were reported for 4.3% (4 of 92) of subjects, all of whom were in the LDV/SOF 12 week group.

Haematology

Table 15 presents a summary of subjects 6 to < 12 years old with Grade 3 or 4 Haematology laboratory abnormalities by treatment group. Among subjects in the LDV/SOF 12 week group, Grade 3 and 4 Haematology laboratory abnormalities were reported for decreased haemoglobin and decreased neutrophils. No Grade 3 or 4 Haematology laboratory abnormalities were reported for the 3 subjects in the LDV/SOF±RBV 24 week groups.

A Grade 3 decrease in haemoglobin (defined as a > 4.5-g/dL decrease from baseline) was reported for 1 subject (LDV/SOF 12 week group) at Weeks 1, 8, and the posttreatment visits. The subject's haemoglobin value at baseline was 18.3 g/dL, and was within normal range at all postbaseline time points (range: 13.0 to 14.4 g/dL).

A Grade 4 decrease in neutrophils was reported for 1 subject (LDV/SOF 12 week group) at Week 1. At all other visits, the subject had normal values for neutrophils, except for Grade 1 decreased neutrophils on posttreatment Day 85.

Overall, 1 subject experienced postbaseline haemoglobin < 10 g/dL, and no subject had postbaseline haemoglobin values < 8.5 g/dL. One subject (LDV/SOF 12 week group) with a history of celiac disease had a Grade 2 decrease in haemoglobin to 9.3 g/dL at Week 2 followed by return to normal haemoglobin level at Week 4 and for the remainder of the study.

Table 15 GS-US-337-1116: Grade 3 Hematology Laboratory Abnormalities (6 to <12 years old) (Safety Analysis Set)

	6 to < 12 Years old			
	Total (N = 92)	LDV/SOF FDC (45/200 mg) 12 Weeks (N = 89)	LDV/SOF FDC (45/200 mg) 24 Weeks (N = 1)	LDV/SOF FDC (45/200 mg) + RBV 24 Weeks (N = 2)
Hematology				
Hemoglobin				
Grade 3	1 (1.1%)	1 (1.1%)	0	0
Neutrophils				
Grade 4	1 (1.1%)	1 (1.1%)	0	0

Laboratory abnormalities were graded using GSI Grading Scale, 1 April 2015 version.
Toxicity grade must have increased at least 1 toxicity grade from baseline value (missing was considered grade 0) to be included.
Subjects counted once at maximum toxicity grade (hyper [+] and hypo [-] when applicable) for each laboratory test.
Data included up to the last dose date of any study drug + 30 days.
Source: Table 15.11.6.3.1

Chemistry

Table 16 presents a summary of subjects 6 to < 12 years old with Grade 3 or 4 coagulation or chemistry laboratory abnormalities by treatment group.

Grade 3 chemistry laboratory abnormalities were reported for amylase (2.2%, 2 of 92 subjects). No Grade 4 chemistry laboratory abnormalities or Grade 3 or 4 coagulation laboratory abnormalities were reported.

One subject (LDV/SOF 12 week group) had a transient and asymptomatic Grade 3 increase in serum amylase at Week 1. The subject's serum amylase values were Grade 2 at all other time points, including screening and baseline. Another subject (LDV/SOF 12 week group) had asymptomatic Grade 3 increases in serum amylase at Weeks 1, 2, 8, 12, and posttreatment visits. The subject had Grade 3 increased amylase at screening and Grade 2 increased amylase at baseline. No AEs of clinical pancreatitis were reported for either subject.

Table 16 GS-US-337-1116: Grade 3 or 4 Coagulation or Chemistry Laboratory Abnormalities (6 to < 12 Years Old) (Safety Analysis Set)

	6 to < 12 Years old			
	Total (N = 92)	LDV/SOF FDC (45/200 mg) 12 Weeks (N = 89)	LDV/SOF FDC (45/200 mg) 24 Weeks (N = 1)	LDV/SOF FDC (45/200 mg) + RBV 24 Weeks (N = 2)
Chemistry				
Amylase				
Grade 3	2 (2.2%)	2 (2.2%)	0	0

Laboratory abnormalities were graded using GSI Grading Scale, 01 April 2015 version.
Toxicity grade must have increased at least 1 toxicity grade from baseline value (missing was considered grade 0) to be included.
Subjects counted once at maximum toxicity grade (hyper [+] and hypo [-] when applicable) for each laboratory test.
Data included up to the last dose date of any study drug + 30 days.
Toxicity grading of INR based on upper limit of normal = 1.2.
Source: Table 15.11.6.3.1

Subjects 3 to < 6 years old

The majority of subjects 3 to < 6 years old had at least 1 laboratory abnormality reported (70.6%, 24 of 34). The maximum laboratory abnormality grades for all subjects were Grade 1 or Grade 2.

Haematology

No Grade 3 or 4 Haematology laboratory abnormalities were reported in subjects 3 to < 6 years old. There were no subjects with postbaseline haemoglobin < 10 g/dL.

Chemistry

No Grade 3 or 4 coagulation or chemistry laboratory abnormalities were reported in subjects 3 to < 6 years old.

Overall, the haematology and chemistry data appear to be in line with the currently established safety profile of LDV/SOF. However, when viewing the chemistry data in detail it seems that amylase abnormalities of grade 1-2 are relatively common which suggests that the grade 3 abnormality described is not a random finding (see Table 17 below).

Table 17 Treatment-emergent graded laboratory abnormalities

Table 15.11.6.2.1: Treatment-Emergent Graded Laboratory Abnormalities
Safety Analysis Set

	12 to < 18 Years Old	3 to < 12 Years Old			
	LDV/SOF (90/400 mg) 12 Weeks (N=100)	Total (N=126)	LDV/SOF (45/200 mg or 33.75/150 mg) 12 Weeks (N=123)	LDV/SOF (45/200 mg) 24 Weeks (N=1)	LDV/SOF + RBV (45/200 mg) 24 Weeks (N=2)
Chemistry (cont)					
Alkaline Phosphatase	100	126	123	1	2
Grade 1	1 (1.0%)	3 (2.4%)	2 (1.6%)	1 (100.0%)	0
Grade 2	0	0	0	0	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Amylase	100	126	123	1	2
Grade 1	15 (15.0%)	17 (13.5%)	17 (13.8%)	0	0
Grade 2	6 (6.0%)	7 (5.6%)	7 (5.7%)	0	0
Grade 3	3 (3.0%)	2 (1.6%)	2 (1.6%)	0	0
Grade 4	0	0	0	0	0
Creatine Kinase	100	126	123	1	2
Grade 1	3 (3.0%)	1 (0.8%)	1 (0.8%)	0	0
Grade 2	1 (1.0%)	0	0	0	0
Grade 3	1 (1.0%)	0	0	0	0
Grade 4	0	0	0	0	0

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: Listing 16.2.8.1.5.1, 16.2.8.1.5.2, 16.2.8.1.5.3, 16.2.8.1.6, 16.2.8.1.7.1, and 16.2.8.1.7.2.

Amylase abnormalities did not appear to be related to GI symptoms, indicating that pancreatitis and no such AEs were reported in the paediatric study. Given that comparable 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.

2.4.9. Discussion on clinical safety

Overall, the LDV/SOF safety data set in patients aged 3-<6 and 6-<12 years is in line with the established favourable safety profile in adults. Gastrointestinal AEs such as nausea, vomiting and diarrhoea were observed quite commonly. However, considering that gastrointestinal symptoms are relatively common in children regardless of treatment as well as given the lack of a control causal relationship has not been established. Therefore, the CHMP did not request their addition to the Product Information.

The low level of treatment-emergent SAEs (1/126 study subjects aged 3-<12 years), no deaths and overall high adherence to treatment was also in line with the established favourable safety profile of LDV/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 LDV/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	Severe bradycardia and heart block when used with concomitant amiodarone
	HBV reactivation in HBV/HCV coinfected patients
Important Potential Risks	Recurrence of HCC
	Emergence of HCC
Missing Information	~~Safety in patients with severe renal impairment or ESRD~~
	Development of resistance
	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 7 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), 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-337-1116 was a Phase 2 study evaluating the PK, safety, and antiviral activity of LDV/SOF±RBV in paediatric subjects aged 3 to < 18 years old. 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. A separate population PK analysis for ledipasvir provided an adequate description of ledipasvir data. The population PK predicted exposures metrics (AUCtau, Cmax, and Cav[LDV]) 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-337-1116 study, SVR12 was achieved in 33/34 (97.1%) patients in the group 3 to <6 years old and 91/92 (98.9%) 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 GS-US-337-1116 study has been performed mainly in non-cirrhotic patients with HCV GT1 and hence paediatric efficacy data in other genotypes and clinical subgroups were missing. However, given that exposure of LDV/SOF is comparable, efficacy across genotypes and into the subgroup of cirrhotic patients can be extrapolated from adult efficacy data.

3.4. Unfavourable effects

Overall, the LDV/SOF safety data set in patients aged 3-<6 and 6-<12 years is in line with the established favourable safety profile in adults. Gastrointestinal AEs such as nausea, vomiting and diarrhoea were observed quite commonly. However, considering that gastrointestinal symptoms are relatively common in children regardless of treatment as well as given the lack of a control causal relationship has not been established.

The low level of treatment-emergent SAEs (1/126 study subjects aged 3-<12 years), no deaths and overall high adherence to treatment was also in line with the established favourable safety profile of LDV/SOF.

Overall, 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 dataset is of limited size, particularly in patients aged 3 to <6 years (34 subjects). However, given the established safety profile of LDV/SOF and that the exposure is comparable, this remaining uncertainty is acceptable.

3.6. Effects Table

Table 18. *Favourable Effects (exposure) for Harvoni 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] (90% CI)	173.80 (159.98, 188.82)	101.41 (95.28, 107.94)	Model predicted	***Table 4***
Cmax (ng/mL)	Maximum steady-state concentration	Geometric mean ratio[1] (90% CI)	168.24 (150.36, 188.25)	103.53 (95.28, 112.50)	Model predicted	***Table 4***
GS-331007						
AUC,ss (day·µg/mL)	Steady-state daily exposure	Geometric mean ratio[1] (90% CI)	93.69 (86.28, 101.73)	77.03 (73.23, 81.03)	Model predicted	***Table 4***
Cmax (ng/mL)	Maximum steady-state concentration	Geometric mean ratio[1] (90% CI)	147.96 (136.41, 160.50)	120.38 (114.54, 126.52)	Model predicted	***Table 4***
Ledipasvir						
AUC,ss (day·µg/mL)	Steady-state daily exposure	Geometric mean ratio[1] (90% CI)	140.76 (122.31, 161.99)	121.50 (111.50, 132.39)	Model predicted	***Table 4***
Cmax (ng/mL)	Maximum steady-state concentration	Geometric mean ratio[1] (90% CI)	117.97 (100.18, 138.92)	120.37 (108.96, 132.97)	Model predicted	***Table 4***

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

Adequate population PK analyses of sofosbuvir and selected metabolites, and ledipasvir, respectively, has been performed and the models were considered adequate to provide predicted exposure metrics in the paediatric population. The model predicted sofosbuvir, GS-331007, and ledipasvir 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, GS-331007, and ledipasvir PK in adults and children is considered sufficient to support the efficacy and safety results 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 benefit-risk balance of Harvoni 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 Harvoni 45 mg / 200 mg film-coated tablets, 45 mg / 200 mg coated granules and 33.75 mg / 150 mg coated granules is favourable in the following indication:

- Harvoni is indicated 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 using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol. The final study report shall be submitted by:	**Q2 2023**

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0063/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

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

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

Extension of indication to include paediatric use in patients aged 3 to < 12 years to the existing presentations

of 90/400 mg film-coated tablets. Sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated to support the extended indication. Furthermore, sections 5.3 and 6.6 of the SmPC are updated to include new information with regards to the environmental risk assessment of ledipasvir. The RMP (version 7.0) is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial updates and linguistic corrections throughout the Product Information.