22 June 2017
EMA/452304/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Harvoni

International non-proprietary name: ledipasvir / sofosbuvir

Procedure No. EMEA/H/C/003850/II/0039

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
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BCRP	breast cancer resistance protein
BLAST	basic local alignment search tool
BLQ	below the limit of quantitation
BMI	body mass index
CatA	cathepsin A
CDC	Centers for Disease Control
CDM	(Gilead) Clinical Data Management
CES1	carboxylesterase 1
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent clearance
CLcr	creatinine clearance
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
DAA	direct-acting antiviral
DMC	data monitoring committee
DSPH	(Gilead) Drug Safety and Public Health
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EU	European Union
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology, and Nutrition
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDC	fixed-dose combination
FU-x	follow-up visit at x weeks after discontinuing treatment

GGT	gamma-glutamyltransferase
GCP	Good Clinical Practice
Gilead	Gilead Sciences, Inc.
GMR	geometric mean ratio
GSI	Gilead Sciences, Inc.
HbA1c	hemoglobin A1c
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV, HIV-1	human immunodeficiency virus, type 1
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IEC	independent ethics committee
IFN	interferon
IL28B	IL28B gene
IND	Investigational New Drug (application)
INR	international normalized ratio
IRB	institutional review board
IWRS	interactive web response system
Ka	absorption rate constant
LC/MS/MS	liquid chromatography tandem mass spectroscopy
LDV	ledipasvir
LDV/SOF	ledipasvir/sofosbuvir (coformulated; Harvoni®)
LLOQ	lower limit of quantitation
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
N or n	number of subjects in a population (N) or subset (n)
NA	not applicable
NASPGHAN	North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition
NI	nucleoside inhibitor
NS	nonstructural protein
PCR	polymerase chain reaction

Peg-IFN	pegylated interferon
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PT	preferred term
Q1, Q3	first quartile, third quartile
RAV	resistance-associated variant
RBC	red blood cell
RBV	ribavirin
RE	relative error
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SOF	sofosbuvir (Solvaldi®)
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virologic response
TND	target not detected
ULN	upper limit of normal
ULOQ	upper limit of quantitation
UK	United Kingdom
WBC	white blood cell
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences International Ltd submitted to the European Medicines Agency on 11 October 2016 an application for a variation.

The following variation was requested:

Variation 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 add treatment of chronic hepatitis C in adolescents aged 12 to < 18 years.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information on posology, warnings, safety, efficacy and pharmacokinetics.
The Package Leaflet and Risk Management Plan (RMP version 2) are updated in accordance.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0174/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0174/2016 was not yet completed as some measures were deferred.

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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	11 October 2016
Start of procedure:	29 October 2016
CHMP Rapporteur Assessment Report	22 December 2016
PRAC Rapporteur Assessment Report	3 January 2017
PRAC members comments	4 January 2017
PRAC Outcome	12 January 2017
CHMP members comments	16 January 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 January 2017
Request for supplementary information (RSI)	26 January 2017
CHMP Rapporteur Assessment Report	24 March 2017
PRAC Rapporteur Assessment Report	24 March 2017
PRAC members comments	29 March 2017
Updated PRAC Rapporteur Assessment Report	30 March 2017
PRAC Outcome	6 April 2017
CHMP members comments	10 April 2017
Updated CHMP Rapporteur Assessment Report	12 April 2017
2nd Request for supplementary information (RSI)	21 April 2017
CHMP Rapporteur Assessment Report	7 June 2017
Opinion	22 June 2017

2. Scientific discussion

2.1. Introduction

Hepatitis C virus infection is a global health challenge; currently, an estimated 170 million individuals worldwide are chronically infected with HCV. 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. Globally, there are estimated to be 6.6 million HCV RNA-positive individuals 15 years of age or younger.

Recently, there has been a transformation in the treatment of HCV infection with the development of direct-acting antivirals (DAAs) targeting viral proteins essential to viral replication. Recently approved DAA-based treatment regimens are generally well tolerated and result in high rates of sustained virologic response (SVR) at 12 weeks following completion of all treatment (SVR12) across most patient populations (> 90%). However, these newly available therapies are currently limited to the treatment of adults with HCV infection.

The combination of LDV (NS5A inhibitor) and SOF (NS5B inhibitor) was first approved for commercial marketing in the United States (US) on 10 October 2014 and in the European Union (EU) on 17 November 2014, for the treatment of genotype 1, 3 (EU), 4, 5, or 6 HCV infection.

This application was submitted in support of an update to the marketing authorisation to expand the indication of LDV/SOF to adolescent patients (12 to < 18 years old) based on new safety, pharmacokinetic (PK) and efficacy data from an ongoing Phase 2 study.

2.2. Non-clinical aspects

This submission supports proposed updates to the approved Harvoni® (HVN; ledipasvir/sofosbuvir [LDV/SOF]) prescribing information based on results from the ongoing Phase 2 clinical study in adolescent subjects (Group 1; 12 to < 18 years old) with chronic hepatitis C virus (HCV) infection (Study GS-US-337-1116). Harvoni was first approved for the treatment of chronic HCV infection in adults 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), 4, 5, or 6 HCV infection [Gilead Sciences Inc 2016], [Gilead Sciences Inc 2015].

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Introduction

A comprehensive nonclinical pharmacology, pharmacokinetic, and toxicology program has been undertaken in support of the registration of LDV/SOF for the treatment of chronic HCV infection in adults. The results of these evaluations were presented in detail in the Nonclinical Overview included in the original LDV/SOF marketing application. Additionally, carcinogenicity data for LDV was subsequently submitted to the LDV/SOF marketing application. No new nonclinical data have been generated or deemed necessary to support approval of LDV/SOF in the adolescent population.

According to the ICH M3 Guideline titled “Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals,” safety data from previous adult human experience represents the most relevant information to support use in paediatric subjects {ICH Harmonised Tripartite Guideline 2009}. Consistent with ICH M3 recommendations, to the well-defined

and favourable safety profile of LDV/SOF in adults were carefully considered prior to the initiation of Study GS-US-337-1116 in adolescent subjects 12 to < 18 years of age. The findings of these nonclinical studies were previously submitted to the LDV/SOF marketing application.

The agreed initial Paediatric Study Plan (iPSP; 13 December 2013) and Paediatric Investigational Plan (PIP; 10 October 2013) were submitted with the respective original marketing applications for LDV/SOF. Additionally, a paediatric Written Request (WR) was issued by FDA for LDV/SOF.

The well-known nonclinical safety profile of LDV/SOF and safety profile observed in paediatric patients in (Study GS-US-337-1116) support a favourable benefit/risk profile for the proposed use of LDV/SOF for the treatment of chronic HCV infection in adolescent patients 12 to < 18 years of age.

The CHMP considered that no additional non-clinical juvenile toxicity study is required to extend the use of LDV/SOF to adolescent patients (12 to <18 years).

2.2.2. Ecotoxicity / environmental risk assessment

The environmental risk assessment (ERA) was previously submitted for Harvoni (Ledipasvir [LDV]/Sofosbuvir [SOF]) as part of the EU initial marketing authorisation application (MAA). This ERA considered all available data relating to LDV and SOF in accordance with the Committee for Medicinal Products for Human Use (CHMP) guideline on the Environmental Risk Assessment of Medicinal Products for Human Use that was adopted by the CHMP on 01 June 2006 (EMEA/CHMP/SWP/4447/00), and 24 June 2010 (Q&A EMA/CHMP/SWP/44609/2010).

The EMA guideline on the ERA states that “the evaluation of the environmental impact should be made if there is an increase in the environmental exposure, e.g. a new indication may result in a significant increase in the extent of the use.” The MAH provided a justification for not providing an updated ERA was within this application. The MAH predicts that the potential use of Harvoni in adolescent patients is not considered to significantly impact the predicted sales volume.

The Phase II calculations used, predicted sales figures that took into consideration the forecasted use of LDV and SOF (as GS-331007) for the treatment of chronic hepatitis C (CHC) across the European (EEA) economic area. As detailed in the ERA submitted as part of the EU initial MAA, Risk Quotient (RQ) for SOF (as GS-331007) and LDV is less than 1 for compartments such as sewage treatment plant, surface water and groundwater, therefore an increase in sales for Harvoni of greater than 14 times would be needed to pose an unacceptable risk. The CHMP considered the existing ERA as applicable to this application.

2.2.3. Discussion on non-clinical aspects

No additional non-clinical juvenile toxicity study is required to extend the use of LDV/SOF to adolescent patients (12 to <18 years).

2.2.4. Conclusion on the non-clinical aspects

There are no objections from a non-clinical point of view in regard to this extension of the indication in adolescents.

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of ledipasvir/sofosbuvir.

Considering the above data, ledipasvir/sofosbuvir is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

Type of Study	Study Number	Study objectives	Design	Study and control drug regimens	Duration of treatment	Number of subjects	Study population / entry criteria
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-337-1116 (Group1)	PK lead-in phase: to evaluate the steady-state PK and confirm the dose of LDV/SOF FDC in chronic HCV infected pediatric subjects Treatment phase: To evaluate the safety and tolerability of LDV/SOF FDC ± RBV for 12 or 24 weeks in chronic HCV infected pediatric subjects	Phase 2, open-label, multi-cohort, 2-part study	**United Kingdom:** Genotype 1, 4, 5 and 6 HCV infection, treatment-naïve with or without cirrhosis or treatment-experienced without cirrhosis: LDV/SOF 90/400 mg (1 x 90/400 mg FDC tablet or 4 x 22.5/100 mg FDC tablets) QD PO for 12 weeks Genotype 1, 4, 5 and 6 HCV infection, treatment experienced with cirrhosis: LDV/SOF 90/400 mg (1 x 90/400 mg FDC tablet or 4 x 22.5/100 mg FDC tablets) QD PO for 24 weeks Genotype 3 HCV infection, treatment-experienced with or without cirrhosis: LDV/SOF 90/400 mg (1 x 90/400 mg FDC tablet or 4 x 22.5/100 mg FDC tablets) QD + RBV (weight-based dose of 15 mg/kg/day, 600 mg/day, 800 mg/day, 1000 mg/day, 1200 mg/day or 1400 mg/day divided BID) PO for 24 weeks **United States, Australia, New Zealand:** Genotype 1 HCV infection, treatment-naive with or without cirrhosis or treatment-experienced without cirrhosis: LDV/SOF 90/400 mg (1 x 90/400 mg FDC tablet or 4 x 22.5/100 mg FDC tablets) QD PO for 12 weeks Genotype 1 HCV infection, treatment-experienced with cirrhosis: LDV/SOF 90/400 mg (1	12 or 24 weeks	Overall: 100 treated 99 completed treatment	Non-cirrhotic and cirrhotic treatment-naive and treatment-experienced subjects 12 to < 18 years of age with chronic genotype 1, 3, 4, 5, or 6 HCV infection

Type of Study	Study Number	Study objectives	Design	Study and control drug regimens	Duration of treatment	Number of subjects	Study population / entry criteria
				x 90/400 mg FDC tablet or 4 x 22.5/100 mg FDC tablets) QD PO for 24 weeks Genotype 4, 5 and 6 HCV infection, treatment-naive or treatment-experienced with or without cirrhosis: LDV/SOF 90/400 mg (1 x 90/400 mg FDC tablet or 4 x 22.5/100 mg FDC tablets) QD PO for 12 weeks			

2.3.2. Pharmacokinetics and PK modelling

Bioanalytical Methods

Validated bioanalytical methods for sofosbuvir, GS-331007 (validation report QPS 60-1323) and ledipasvir (validation report QPS 60-1433) were used.

Absorption, Distribution, Metabolism and Elimination Characteristics

No new information was submitted. The CHMP considered acceptable as no difference in PK characteristics is expected in patients 12-18 years.

Pharmacokinetics in Adolescent Subjects

Pharmacokinetic (PK) data was collected in GS-US-337-1116, an ongoing phase 2 open-label, multicohort, 2-part study designed to examine the PK, efficacy, and safety of LDV/SOF 90/400 mg FDC tablet (given once daily) +/- RBV (given as a divided dose twice daily) for a treatment duration of 12 or 24 weeks in paediatric subjects aged 3 to < 18 years with chronic genotype 1, 3, 4, 5, or 6 HCV infection. The study consists of a PK lead-in and a treatment phase for each cohort. The pharmacokinetic analysis for adolescent patients was based on data collected from cohort 1 (12 to < 18 years).

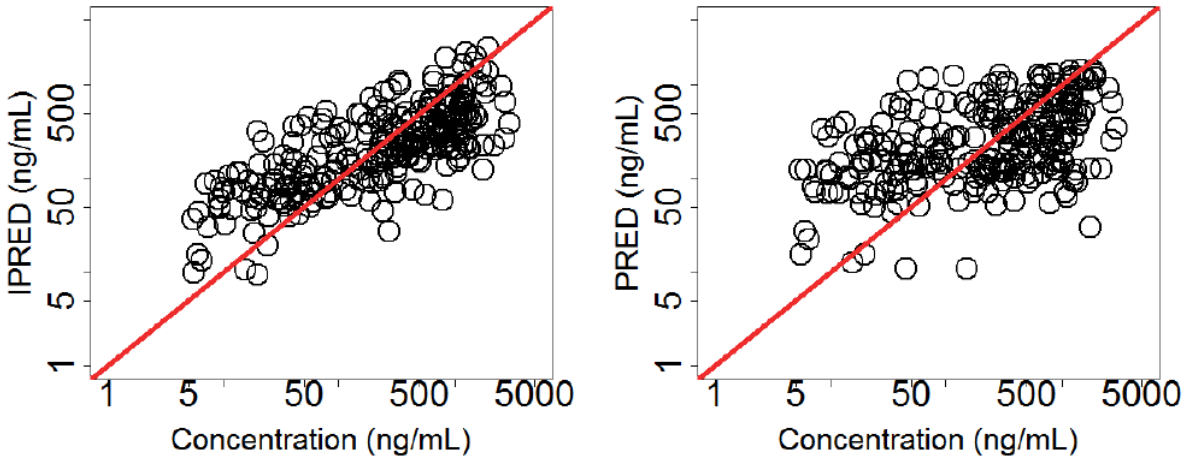
Plasma concentration data from all PK samples (intensive and sparse) were combined and used to generate PK parameters for all subjects in the study population utilizing a population PK model. Previous population PK models have been developed for SOF, GS-331007, and LDV after administration of LDV/SOF in adults. A population PK model is not currently available for GS-566500; as such, PK parameters for this analyte were not determined. Population PK models were developed to characterize the exposures of SOF, GS-331007 and LDV in adolescent HCV-infected subjects administered LDV/SOF 90/400 mg FDC. These models considered models previously developed to describe PK in the adult population however; model development was performed using only data collected from the adolescent population.

Sofosbuvir

The SOF dataset included 570 plasma samples from 100 subjects. A portion of the samples (301 samples) were below-LLOQ, thus were excluded from the analysis along with 17 measureable concentrations beyond 12 hours post dose. The remaining dataset included 252 measureable SOF concentrations from 70 subjects.

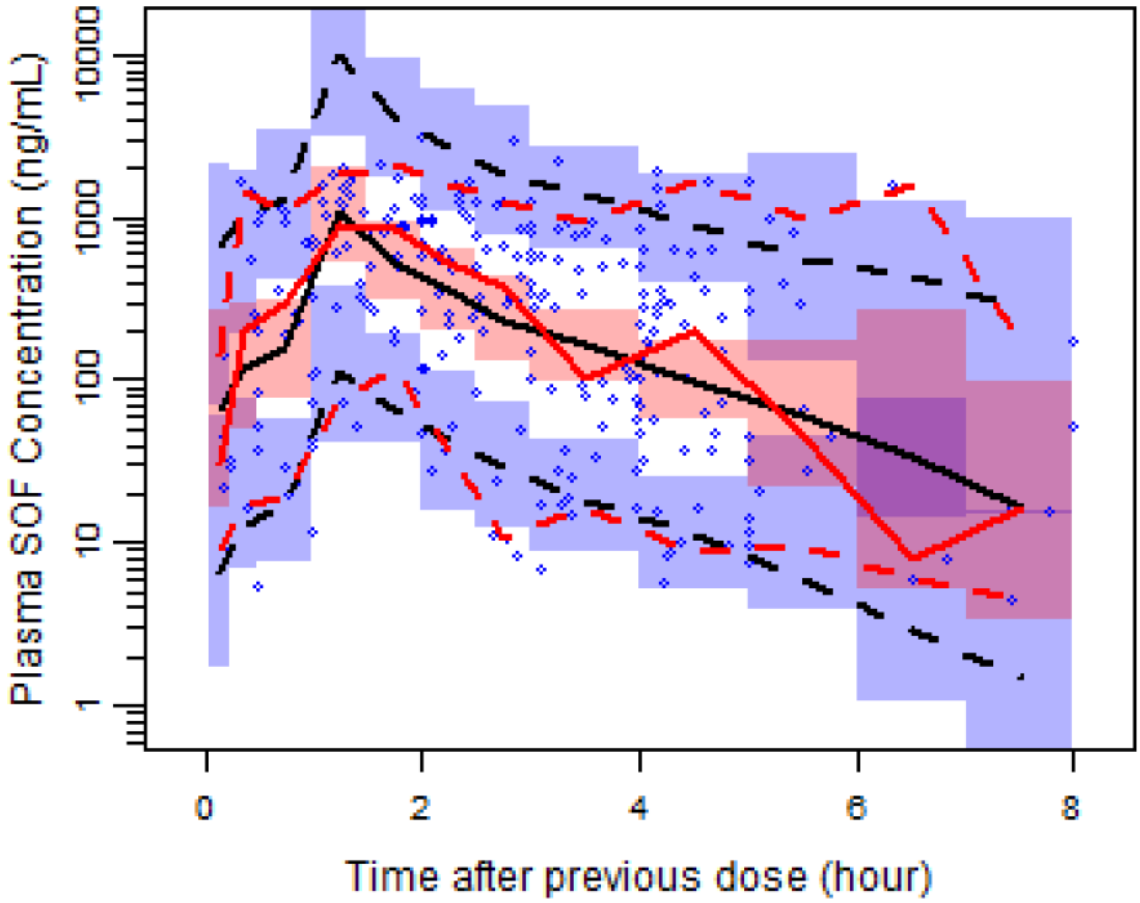
The final SOF model used for the adolescent population was a 1-compartment model with a sequential first/zero order absorption model and linear elimination. No covariate effects were detected. Goodness-of-fit plots and prediction corrected visual predictive checks (pcVPC) are displayed in Figure 1 and Figure 2, respectively. Moderate shrinkage was estimated for inter-individual variability on Vc/F (32.4%), and low shrinkage was estimated for the residual error (6.30%).

Figure 1. Predicted versus observed concentration diagnostics for the final PopPK model for adolescents



Individual predicted (IPRED) plasma SOF concentrations versus observed SOF concentrations (left) and population predicted (PRED) plasma SOF concentrations versus observed plasma SOF concentrations (right) for the final PopPK model on a logarithmic scale. Points are individual data and red lines represent the unit diagonal.

Figure 2. pcVPC of SOF plasma concentration-time profiles

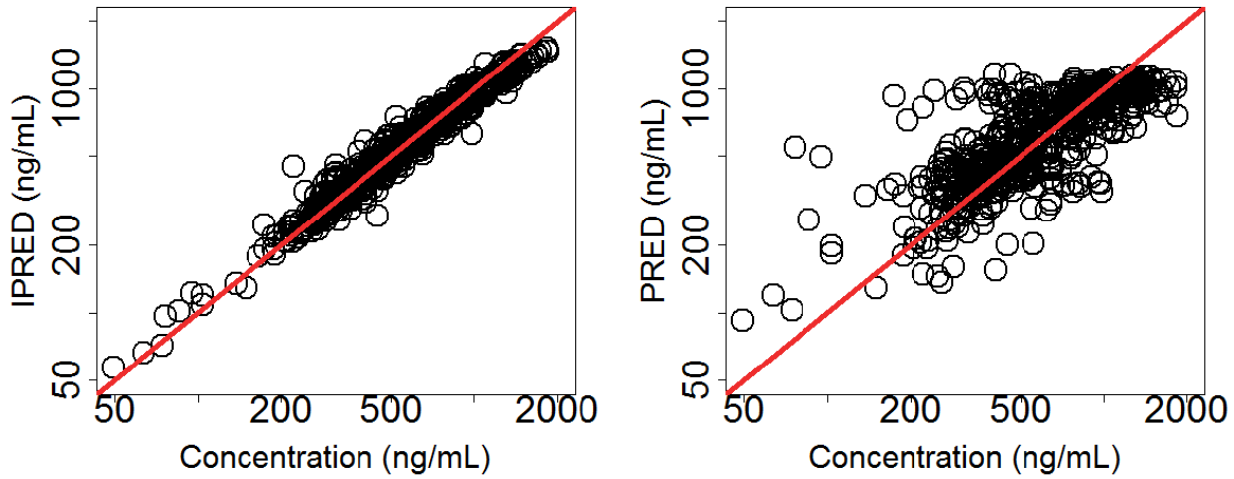


pcVPC plots show the observed concentrations (points), median (solid red lines) and spread (5th to 95th percentile, dashed red line) of the observed concentrations, and median (solid black lines) and spread (5th to 95th percentile, dashed black lines) of the simulated concentrations in all subjects. 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.

GS-331007

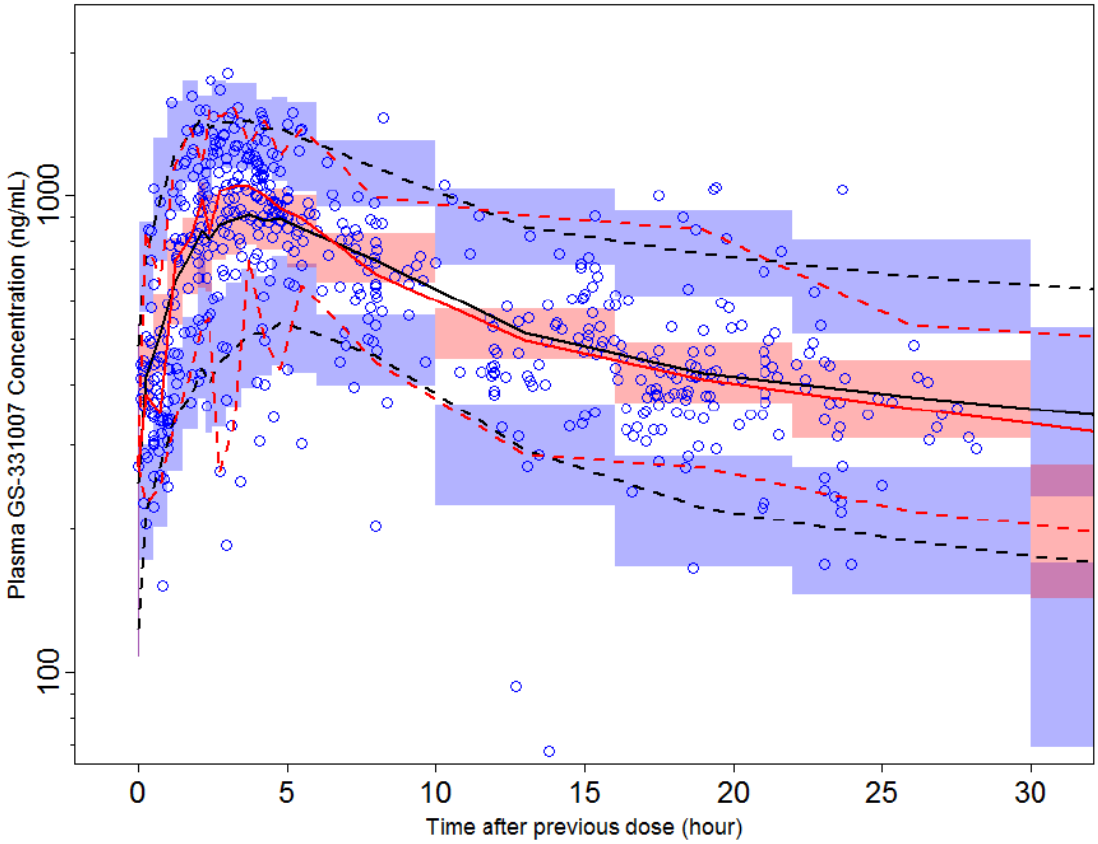
The final GS-331007 PopPK model developed in adolescents, after administration of LDV/SOF 90/400 mg FDC, was best described by a 2-compartment model with zero-order input and first order absorption, linear elimination, inter-individual variability terms on CL/F, Q/F and D1 (duration of zero order input), IOV on Vc/F, Ka/F and D1 and an exponential error model. The covariates included in the final model were ethnicity and creatinine clearance on CL/F. Goodness-of-fit plots and pcVPC are displayed in Figure 3 and Figure 4, respectively. Low shrinkage was estimated for IIV on CL/F (11.2%), and high shrinkage was estimated for IIV on Q/F (53.1%), D1 (58.1%) and residual error (33.0%).

Figure 3. Predicted versus observed concentration diagnostics for the final PopPK model



Individual predicted (IPRED) plasma GS-331007 concentrations versus observed GS-331007 concentrations (left) and population predicted (PRED) plasma GS-331007 concentrations versus observed plasma GS-331007 concentrations (right) for the final PopPK model on a logarithmic scale. Points are individual data, red lines represent loess smooth lines, and the black lines are the unit diagonal.

Figure 4. pcVPC of GS-331007 plasma concentration-time profiles

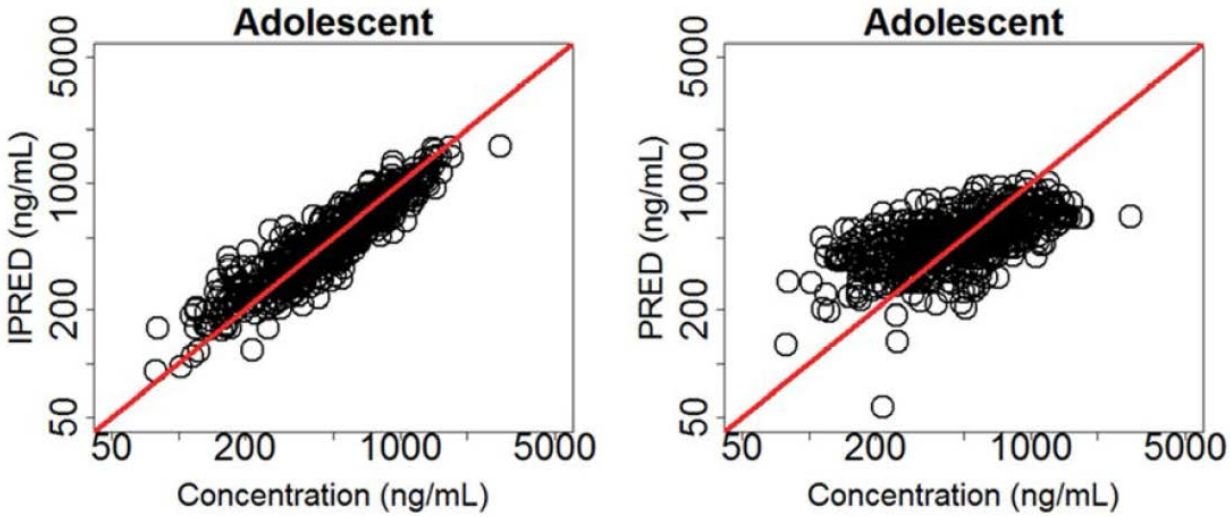


pcVPC plots show the observed concentrations (points), median (solid red lines) and spread (5th to 95th percentile, dashed red line) of the observed concentrations, and median (solid black lines) and spread (5th to 95th percentile, dashed black lines) of the simulated concentrations in all subjects. 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.

Ledipasvir

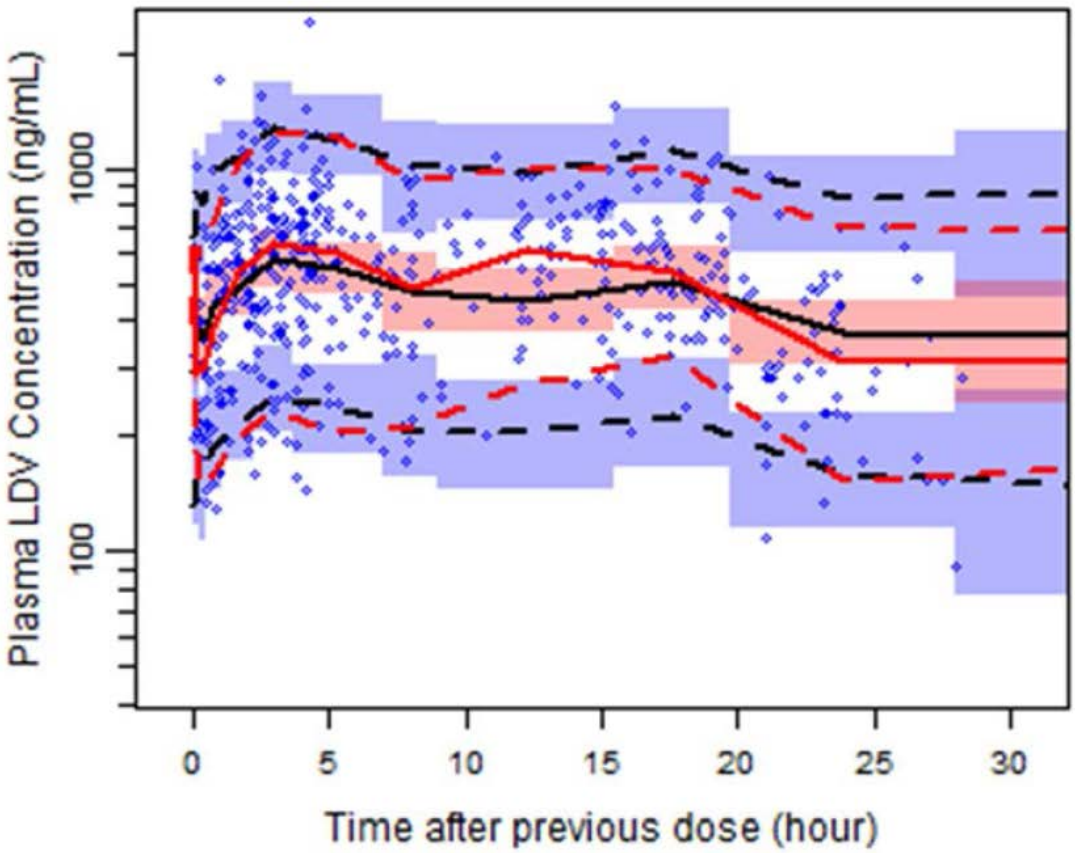
The LDV dataset included 569 plasma samples from 100 subjects. No samples were below-LLOQ and all samples were used in the analysis for LDV. Based on the PopPK model developed in adults, a 2-compartment model with first order absorption, first order elimination from the central compartment and an absorption lag time was considered as the initial base model. A zero order input (depot compartment) followed by first order absorption provided improved characterization of LDV absorption profile. The covariate analysis detected sex and weight (linear relationship) on CL/F, and weight (linear relationship) on Vc/F. A summary of the final parameter estimates is found in Table 3, and goodness-of-fit plots and pcVPC are displayed in Figure 5 and 6, respectively. Low shrinkage was estimated for IIV on CL/F (6%) and residual error (13%), and moderate shrinkage was estimated for IIV on Vc/F.

Figure 5. Predicted versus observed concentration diagnostics for the final PopPK model



Individual predicted (IPRED) plasma LDV concentrations versus observed LDV concentrations (left) and population predicted (PRED) plasma LDV concentrations versus observed plasma LDV concentrations (right) for the final PopPK model on a logarithmic scale. Points are individual data and black lines represent the unit diagonal. The red lines are smooth curves (lowess) showing the relationship between two variables.

Figure 6. pcVPC of LDV plasma concentration-time profiles



pcVPC plots show the observed concentrations (points), median (solid red lines) and spread (5th to 95th percentile, dashed red line) of the observed concentrations, and median (solid black lines) and spread (5th to 95th percentile, dashed black lines) of the simulated 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.

Model Predicted Steady-State Exposure Parameters

Bayesian post-hoc model parameters estimated from the SOF, GS-331007, and LDV models were used to calculate steady-state plasma PK parameters (AUCtau, Cmax, and Ctau as applicable) for SOF, GS-331007 and LDV following administration of LDV/SOF 90/400 mg FDC for each adolescent subject in study GS-US-337-1116. A summary of the plasma exposures are provided in Table 4 in comparison to exposures observed in HCV-infected adults from the adult Harvoni Phase 2/3 Population. The revised models result in modest difference in overall exposure estimates in the adolescent population. Further, comparison of observed and model-generated exposures as presented in the pcVPC plots are similar, with SOF Cmax over predicted by 17% and SOF AUC under predicted by 8%, for GS-331007 and LDV, Cmax and AUCtau were predicted within less than 4%.

Table 1. Summary of steady-state PK exposure for SOF, GS-331007, and LDV in adolescent subjects compared to adults

Analytes	PK Parameter	Adolescents	Adults
SOF		N=71	N=1542
	AUC_{tau} (hr*ng/mL)	1740 (10.0)	1380 (34.0)
	C_{max} (ng/mL)	924 (26.3)	659 (34.0)
GS-331007		N=100	N=2113
	AUC_{tau} (hr*ng/mL)	13,900 (23.8)	12,500 (29.2)
	C_{max} (ng/mL)	974 (15.7)	736 (28.2)
LDV		N=100	N=2113
	AUC_{tau} (hr*ng/mL)	12,500 (45.4)	8530 (60.8)
	C_{max} (ng/mL)	594 (47.6)	364 (51.4)
	C_{tau} (ng/mL)	440 (45.2)	247 (59.2)

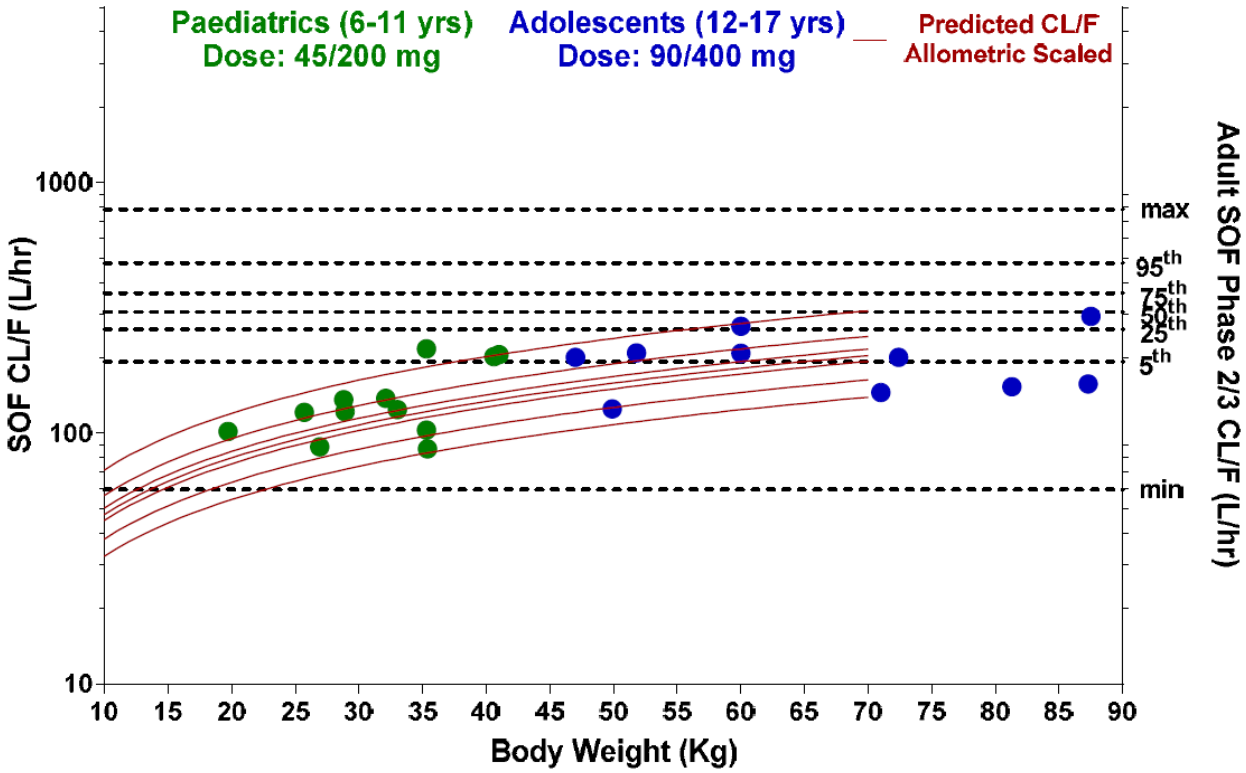
Note: Exposures were calculated for the dose regimen of LDV/SOF 90/400 mg once daily. Values are presented as mean (CV%) to three significant digits. Subjects with all SOF PK samples below LLOQ were not included in the summary of SOF PK parameters.

Evaluation of body size dependence

Sofosbuvir

The model derived individual SOF CL/F estimates (min, 5th, 25th, 50th, 75th, 95th and max) were adjusted for body weight (based on allometric scaling - CL*[BW/70]0.75) and used to generate associated prediction bands across 10 to 70kg body weight. Allometric scaling was used since body weight was not a significant covariate on CL/F in the final SOF model. Observed (intensive sampling; N=12) data from PK Lead-in portion of Study GS-US-337-1116 was used to calculate SOF CL/F values for both adolescent (12-17 yrs) and paediatric (6-11 yrs) subjects. A large overlap between model predicted and observed CL/F values (including low body weight individuals) is observed (Figure 7).

Figure 7. Comparison of Model Predicted versus Observed SOF PK Across Body Weights



Individual estimates for CL/F values were estimated by adding a variability term (ηCL) to the current model. Solid red lines: Prediction bands across body weight range estimated based on weight adjusted CL/F values from adolescent subjects.

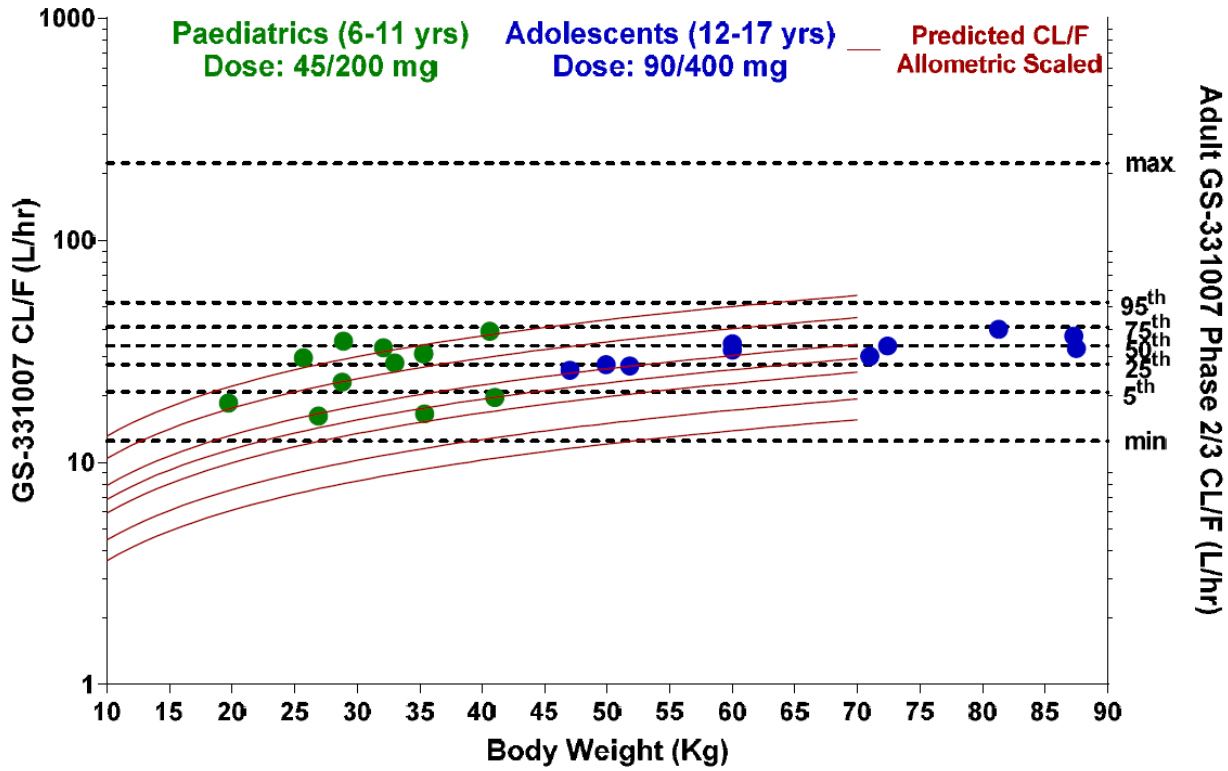
Dashed black lines: Prediction bands based CL/F values estimated based on adult population in Phase 2/3 studies.

Solid Dots: CL/F values estimated from observed data from PK Lead-in portion of Study GS-US-337-1116; blue dots: adolescents, green dots – 6-11 year old subjects.

GS-331007

The model derived individual GS-331007 CL/F estimates (min, 5th, 25th, 50th, 75th, 95th and max) were adjusted for body weight (based on allometric scaling - CL*[BW/70]0.75) and used to generate associated prediction bands across 10 to 70kg body weight. Allometric scaling was used since body weight was not a significant covariate on CL/F in the final GS-331007 model. Observed (intensive sampling; N=11) data from PK Lead-in portion was used to calculate CL/F values (including low body weight individuals) for both adolescent (12-17 yrs) and paediatric (6-11 yrs) subjects. A large overlap between model predicted and observed CL/F values (including low body weight individuals) is observed (Figure 8).

Figure 8. Comparison of Model Predicted versus Observed GS-331007 PK Across Body Weights



Solid red lines: Prediction bands across body weight range estimated based on weight adjusted CL/F values from adolescent subjects.

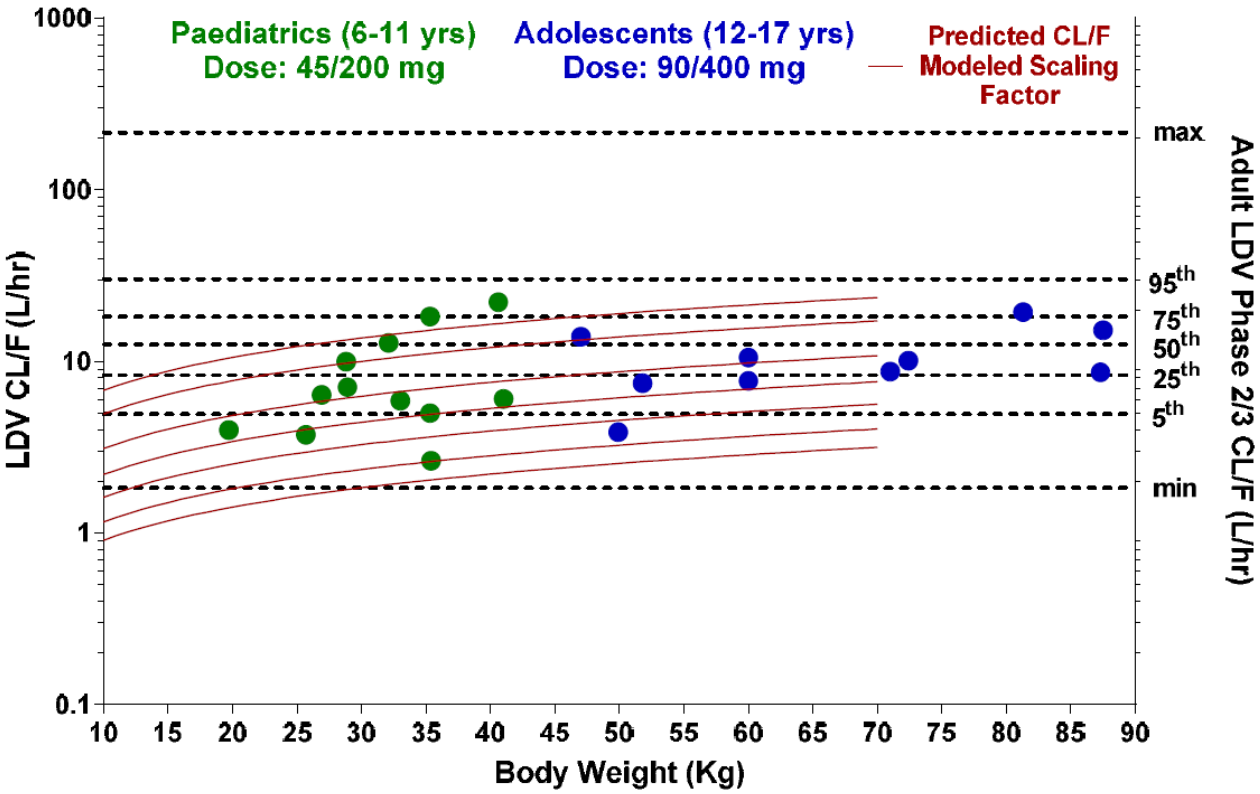
Dashed black lines: Prediction bands based CL/F values estimated based on adult population in Phase 2/3 studies.

Solid Dots: CL/F values estimated from observed data from PK Lead-in portion of Study GS-US-337-1116; blue dots: adolescents, green dots – 6-11 year old subjects.

Ledipasvir

The model derived individual LDV CL/F estimates (min, 5th, 25th, 50th, 75th, 95th and max) were adjusted for body weight (based on model estimated scaling function - CL*[BW/58]0.64) and used to generate associated prediction bands across 10 to 70kg body weight. Observed (intensive sampling; N=12) data from PK Lead-in portion was used to calculate CL/F values for both adolescent (12-17 yrs) and paediatric (6-11 yrs) subjects. A large overlap between model predicted and observed CL/F values (including low body weight individuals) is observed (Figure 9).

Figure 9. Comparison of Model Predicted versus Observed LDV PK AcrossBody Weights



Solid red lines: Prediction bands across body weight range estimated based on weight adjusted CL/F values from adolescent subjects.
Dashed black lines: Prediction bands based CL/F values estimated based on adult population in Phase 2/3 studies.
Solid Dots: CL/F values estimated from observed data from PK Lead-in portion of Study GS-US-337-1116; blue dots: adolescents, green dots – 6-11 year old subjects.

2.3.3. Pharmacodynamics

Mechanism of action

The pharmacodynamics of SOF is well established. This agent (a nucleotide HCV-polymerase inhibitor) has potent activity against all HCV-genotypes. Only one mutation of relevance for SOF resistance (S282T) has been found during in vitro studies. This mutation has been detected at a very low frequency in patients who failed a SOF-containing regimen through relapse, and in these cases the virus reverted back to wild type virus within short (i.e. viral fitness much hampered by this substitution). S282T has not been seen as a naturally occurring polymorphism. There is no cross resistance between NS5A inhibitors and SOF. SOF has been shown to retain its efficacy on retreatment.

While enzymatic assays are not available as NS5A lack a known enzymatic function, LDV has been shown to select for mutations within the NS5A gene in the replicon system conferring a reduction in viral susceptibility. Furthermore, replicons with resistance mutations associated with other NS5A inhibitors are cross resistant to LDV.

It was shown that LDV lacks activity against NS3/4A protease, NS3 helicase, NS5B polymerase, the HCV internal ribosome entry site (IRES), and a broad panel of kinases.

The mean EC50 values for genotype 1a and 1b was 0.03 and 0.004, respectively. Since LDV is highly protein bound, EC50-values were around 10 times higher when adding 40% human serum to cell based assays. The in vitro activity to non-1 subtypes is lower and variable (see Table 5).

Table 2. Ledipasvir in vitro susceptibility

Genotype	HCV Isolate	EC50 nM
1a		0.031
1b		0.004
2a	JFH-1 (L31 in NS5A)	21
2a	J6 (M31 in NS5A)	249
2b	MD2b8-2 (L31 in NS5A)	16
2b	MD2b-1 (M31 in NS5A)	530
3a	S52	168
4a	ED43	0.39
5a	SA13	0.15
6a	Consensus	1.1
6e	D88	264

2.3.4. Discussion on clinical pharmacology

The final models for prediction of SOF, GS-331007, and LDV PK parameters were the same structural and covariate model as identified in adults with comparable model parameter estimates. SOF, GS-331007 and LDV AUC_{tau} and C_{max} in adolescents were within the predefined PK equivalence boundaries of 50% to 200% when compared with adults from Phase 2/3 studies. The upper bound of the 90% CI for LDV C_{tau} was modestly higher than 200% in adolescents (GMR [90% CI]: 184.4 [167.6, 202.8]); this difference was not considered clinically relevant based on established exposure-safety analysis for LDV. It is acknowledged that very little to no difference in drug exposure is expected in a paediatric patient population of ≥45 kg body weight) compared to the adult patient population.

The use of previously developed population PK models for adult SOF, GS-331007, and LDV data, seems appropriate since the expectation is that the pharmacokinetics in adolescents, 12 to 18 years and with ≥45 kg body weight, is similar to adults. In the current analysis no new covariates were found to describe the adolescent PK data. However, the submitted population PK report lack essential information such as parameter uncertainty values, shrinkage values for random effects parameters, and output files; hence a full assessment of the population PK analysis is not possible and the conclusion regarding similarity between adolescent and adult drug exposure is pending an updated report.)

In response to the first request for supplementary information, the Applicant provided a new population PK analysis where adult and adolescent data has been pooled. The population PK report was considerably more detailed than the reports provided at the time of the application submission. The CHMP guideline on reporting population PK reports has been taken into account, which was appreciated. The applicant has partially addressed the concerns raised and the new analysis provided did not solve the concerns. As a consequence the CHMP requested additional information.

In response to the second request for supplementary information, the Applicant provided a new population PK analysis based on the adolescent data. The previously developed adult models were used as a starting point but subsequently revised to fit the adolescent data. The models were revised in terms

of absorption models and covariate relationships, and various random effects (inter-individual variability and inter-occasion variability) were tested but not found significant. Overall, the models fit the data slightly better with acceptable performance for individual predictions. Hence the models are descriptive of the present adolescent data, but not predictive for smaller patients. Models for SOF and GS-33007 do not contain any relationship to body size, which is seems adequate for the adolescents (12-17 years), although clearly show that a body size relationship is necessary to predict data from younger age groups. The MAH committed to provide refined models, including for example body size dependence to support dose selection in smaller children as a post-authorisation measure.

2.3.5. Conclusions on clinical pharmacology

Overall, the models fit the data with acceptable performance for individual predictions. The models for SOF and GS-33007 do not contain any relationship to body size, which is seems adequate for the adolescents (12-17 years) population, however body size relationship is necessary for data prediction in younger age groups. Refined models to support dose selection in smaller children are required to support dose selection in smaller children.

2.4. Clinical efficacy

2.4.1. Main study

Title of Study: *A Phase 2, Open-Label, Multi-centre, Multi-cohort Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination +/- Ribavirin in Adolescents and Children with Chronic HCV-Infection*

Methods

This ongoing Phase 2, open-label, multi-cohort, 2-part study is evaluating the PK, safety, and antiviral activity of LDV/SOF±RBV in paediatric subjects aged 3 to < 18 years with chronic genotype 1, 3, 4, 5, or 6 HCV infection. The study consists of a PK lead-in phase and a treatment phase.

This interim clinical study report (CSR) provides the data for adolescent subjects aged 12 to< 18 years (Group 1). The study design, statistical analyses, and results for subjects aged 3 to < 12 years (Group 2) are not included in this interim CSR but will be included in a separate report. The interim analysis was conducted after all subjects in Group 1 had completed the post-treatment Week 12 visit or had prematurely discontinued from the study. All data collected by the data finalization date (28 April 2016) were included in this interim analysis. Results from the final analysis of Group 1, to be conducted when all subjects have completed the post-treatment Week 24 visit or have prematurely discontinued from the study, will be included in a separate report.

Study participants

Inclusion Criteria

Subjects who met all of the following criteria were eligible for participation in Cohort 1 of the PK lead-in phase and Group 1 of the treatment phase of the study:

1. Parent or legal guardian able to provide written informed consent prior to any screening evaluations and willing to comply with study requirements. Subjects provided assent if possible.

2. Aged 12 years to < 18 years as determined at Day 1 (consent of parent or legal guardian required)
3. PK lead-in only: subjects in Cohort 1 (12 to < 18 years of age) must have weighed ≥ 45 kg
4. PK lead-in only: all subjects must have been treatment naive: no prior exposure to any IFN, RBV, or other approved or experimental HCV-specific DAA agent
5. Treatment-experienced subjects: prior treatment failure on a regimen including IFN either with or without RBV that was completed at least 8 weeks prior to Day 1

a) IFN intolerant: Subject who discontinued therapy (≤ 12 weeks total) due to ≥ 1 AE

b) IFN non-responder: Subject who did not achieve undetectable HCV RNA levels while on treatment

c) Relapse/breakthrough: Subject who achieved undetectable HCV RNA during treatment or within 4 weeks of the end of treatment but did not achieve SVR

6. Chronic HCV infection documented by either:

a) A positive anti-HCV antibody test or positive HCV RNA or positive HCV genotyping test at least 6 months prior to the Day 1 visit, or

b) A liver biopsy performed prior to the Day 1 visit with evidence of chronic HCV infection

7. Infection with HCV as determined at screening:

a) UK only: As of protocol amendment 4.0, the study is enrolling pediatric subjects with genotypes 1, 3, 4, 5, and 6 HCV infection and will subsequently enroll subjects with genotype 2 HCV infection once adult data are available, if appropriate.

b) US/Australia/New Zealand only: As of protocol amendment 4.0, the study is enrolling pediatric subjects with genotype 1, 4, 5, and 6 HCV infection and will subsequently enroll subjects with genotype 2 HCV infection once adult data are available, if appropriate.

8. HCV RNA ≥ 1000 IU/mL at screening
9. Adequate hematologic function (absolute neutrophil count ≥ 1500/mm3; hemoglobin ≥ 11 g/dL or ≥ 12 g/dL for male subjects with genotype 3 infection only)
10. Negative serum β-HCG pregnancy test (for females of childbearing potential only (as defined in clinical trial protocol
11. Subject must have been able to provide written assent, if they had the ability to read and write, as determined by IRB/IEC/local requirements and the investigator's discretion

Exclusion Criteria

Subjects with any of the following were not eligible for participation in the study:

1. Pregnant or lactating subjects
2. Sexually active males or females of childbearing potential who were not willing to use an effective method of contraception during the study (defined in the clinical trial protocol)
3. Treatment-naive subjects with genotype 3 HCV infection as determined at screening. Treatment naive was defined as no prior exposure to any IFN, RBV, or other approved or experimental HCV-specific DAA agent

4. Decompensated liver disease defined as international normalized ratio (INR) > 1.2 x the upper limit of normal (ULN), platelets < 50,000/mm3, serum albumin < 3.5 g/dL, or prior history of clinical hepatic decompensation (eg, ascites, jaundice, encephalopathy, variceal haemorrhage)
5. Chronic liver disease of a non-HCV aetiology (eg, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency)
6. α-fetoprotein > 50 ng/mL

Treatments

Table 3. Treatment Regimens Based on Country of Enrolment, Genotype, Treatment Experience, and Cirrhosis Status

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

a During the enrolment period for Group 1, screening included genotypes 1, 3, and 4 according to the original protocol and amendments 1 to 3.

The adult clinical dose of LDV/SOF 90/400 mg was chosen for evaluation in adolescent subjects (12 to < 18 years old). The appropriateness of the adult dose for this age range was supported by the subsequent data from Cohort 1 of the PK lead-in phase of this study, which demonstrated that LDV, SOF, and GS-331007 exposures were comparable between adolescent subjects in this study and adult subjects included in the Phase 2/3 population PK analyses.

Subjects who participated in Cohort 1 of the PK lead-in phase continued in Group 1 (12 to < 18 years old) of the treatment phase with no interruption of study drug administration. Additional subjects were enrolled in the treatment phase after the appropriateness of the dose was confirmed.

Subjects received the first dose of study drug at the study site at baseline/Day 1. At that time, subjects were provided with study drug for subsequent self-administration. The LDV/SOF tablet was administered once daily with or without food. Each subject was given instructions to maintain approximately the same daily dosing interval between study drug doses.

Subjects were instructed that if vomiting occurred within 5 hours of dosing, an additional tablet should be taken. If vomiting occurred more than 5 hours after dosing, no further dose was needed.

If a dose was missed and it was within 18 hours of the normal time of administration, subjects were instructed to take the tablet as soon as possible and to take the next dose at the usual time. If it was after 18 hours then subjects were instructed to wait and take the next dose at the usual time. Subjects were instructed not to take a double dose. No subject in Group 1 (12 to < 18 years old) received RBV as part of their treatment regimen.

Objectives

Primary objectives

Pharmacokinetic (PK) lead-in phase:

- To evaluate the steady-state PK and confirm the dose of ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) in chronic hepatitis C virus (HCV)-infected paediatric subjects

Treatment phase:

- To evaluate the safety and tolerability of LDV/SOF FDC ± ribavirin (RBV) for 12 or 24 weeks in chronic HCV-infected paediatric subjects

Secondary objectives

PK lead-in phase:

- To evaluate the safety, tolerability, and antiviral activity of 10 days of dosing of LDV/SOF FDC in chronic HCV-infected paediatric subjects

Treatment phase:

- To determine the antiviral efficacy of 12 or 24 weeks of LDV/SOF FDC ± RBV treatment in chronic HCV-infected subjects (including the impact of HCV genotype, IL28B genotype, and prior treatment experience), as assessed by the proportion of subjects with sustained viral response (SVR) 12 weeks after completion of treatment (SVR12)
- To determine the antiviral efficacy of 12 or 24 weeks of LDV/SOF FDC ± RBV treatment in chronic HCV-infected subjects, as assessed by the proportion of subjects with SVR 4 and 24 weeks after completion of treatment (SVR4 and SVR24)
- To evaluate the kinetics of circulating HCV RNA during treatment and after completion of treatment
- To evaluate the emergence of viral resistance to LDV and SOF during treatment and after completion of treatment
- To evaluate the effect on growth and development of paediatric subjects during and after treatment

Exploratory objective

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

Outcomes/endpoints

Efficacy

The key efficacy endpoint was SVR12, defined as HCV RNA < LLOQ 12 weeks after discontinuation of the study drug, in the FAS. The key efficacy endpoint analysis (for SVR12) in this interim CSR was conducted after all subjects in Group 1 (12 to < 18 years old) completed the posttreatment Week 12 visit or prematurely discontinued from the study. The point estimate of the SVR12 rate and 2-sided 95% exact CI based on the Clopper-Pearson method were provided by treatment experience (treatment naive with or without cirrhosis, treatment experienced without cirrhosis) and overall.

Secondary efficacy endpoints included SVR4, SVR24, proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through end of treatment, and proportion of subjects with virologic failure.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, and maximum) by treatment experience (treatment naive with or without cirrhosis, treatment experienced without cirrhosis) and overall (as appropriate). All categorical endpoints were summarized by number and percentage of subjects who met the endpoint definition.

Pharmacokinetics

The previously established population PK model based on adult data was applied to the combined data from both intensive PK samples collected from subjects in Cohort 1 in the PK lead-in phase and sparse PK samples collected from all subjects in Group 1 in the treatment phase to characterize the PK of SOF, GS-331007, and LDV.

PK parameters (AUC_{tau}, C_{max}, and C_{tau}) were estimated from the SOF, GS-331007, and LDV concentration data using the population PK models. The population PK model-derived PK parameters for SOF, GS-331007, and LDV were summarized and listed.

The population PK model-derived PK parameters for SOF, GS-331007, and LDV were compared between the adolescent population from this study and the LDV/SOF FDC adult patient population (which includes population PK-derived PK exposure data from Phase 2 and 3 studies) following administration of LDV/SOF FDC. The geometric mean ratio (GMR) and its 90% CI were provided. I addition, PK parameters were summarized by statistically significant intrinsic covariates identified in the population PK models: SOF and GS-331007 PK parameters were summarized by quartiles of estimated glomerular filtration rate (eGFR using the Schwartz formula), and LDV PK parameters were summarized by sex and quartiles of body mass index (BMI).

Safety

All enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, Tanner pubertal stage assessments, height and weight measurements, vital signs measurements, and symptom-directed physical examinations. Safety data included all data collected on or after the first dose of any study drug up to the date of the last dose of study drug plus 30 days. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1.

Sample size

Planned: Approximately 100 subjects in Group 1 (12 to < 18 years old)

Analyzed:

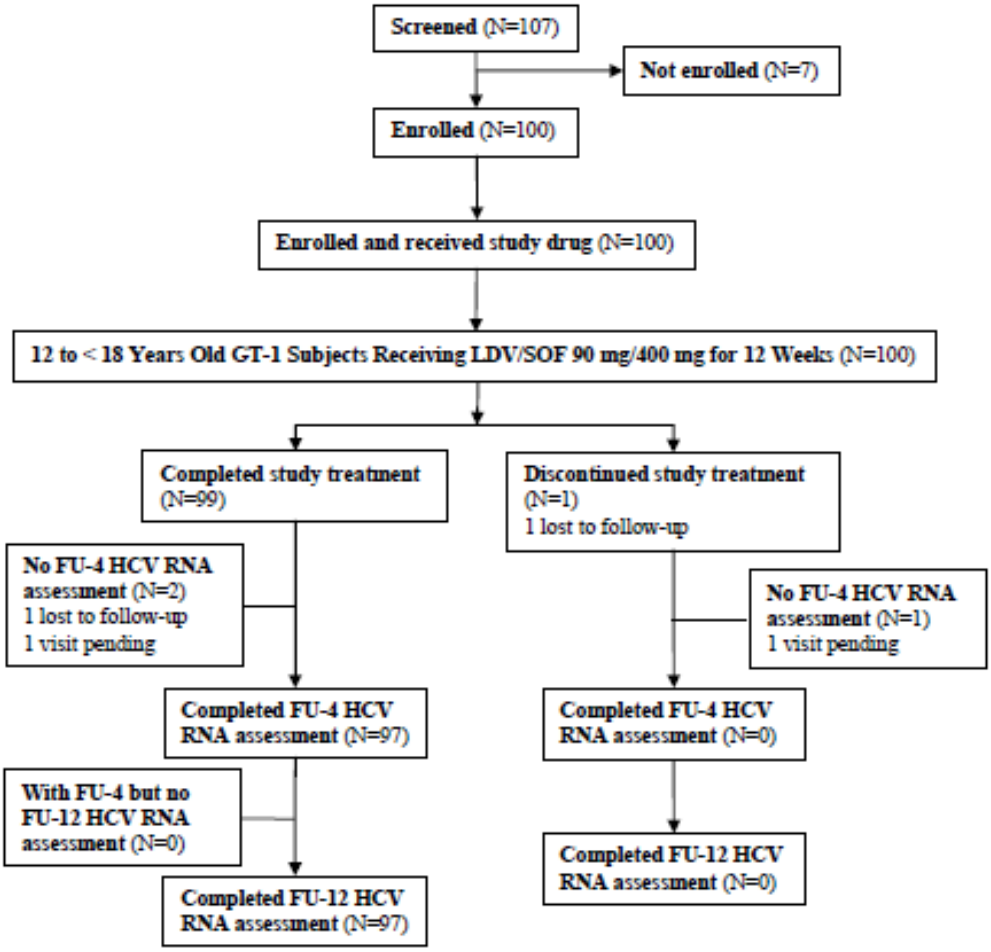
- Full Analysis Set (FAS): 100 subjects
- Safety Analysis Set: 100 subjects

- PK Analysis Set: 100 subjects

Results

Participant flow

Figure 10. GS-US-337-1116: Disposition of Subjects for Group 1 (12 to < 18 Years Old) (Screened Subjects)



FU-x = follow-up visit at x weeks after discontinuing treatment

Table 4. GS-US-337-1116: Key Dates for Group 1 (12 to < 18 Years Old)

Event	Date
First Subject Screened	05 November 2014
First Subject Enrolled	24 November 2014
Last Subject Enrolled	29 October 2015
Last Subject Observation for this Report	28 April 2016
Last Subject Observation for the Primary Endpoint	28 April 2016
Database Finalization	28 April 2016

A total of 107 subjects were screened for Group 1, and 7 subjects (6.5%) failed screening. For the 4 screen failure subjects who did not meet eligibility criteria, the 2 reasons for screen failure were α-fetoprotein not within the acceptable range (75.0%, 3 subjects) and did not meet the inclusion criterion of weight of at least 45 kg for the PK lead-in phase (25.0%, 1 subject). Of the 3 screen failure subjects who did meet eligibility criteria, the reasons for not enrolling were outside of visit window (66.7%, 2 subjects), and withdrawal of consent by subject or parent/guardian (33.3%, 1 subject).

Of the 100 enrolled subjects, all 100 received at least 1 dose of study drug and were included in the Safety Analysis Set and FAS (80 treatment-naive with or without cirrhosis and 20 treatment-experienced without cirrhosis).

The majority of subjects (99.0%) completed study treatment. Of the 100 enrolled and treated subjects, 1 subject (1.0%) prematurely discontinued study treatment due to lost to follow-up.

Conduct of the study

Study GS-US-337-1116 was conducted under a US Investigational New Drug (IND) application and in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the European Community Directive 2001/20/EC, as well as other local legislation.

Changes in the Conduct of the Study or Planned Analyses

The original protocol (10 July 2014) was amended 4 times.

Amendment 1

The protocol was first amended on 07 October 2014 to reflect the following key changes that affected subjects in Group 1:

- Removed Russia from the list of study site countries participating in the trial
- Updated the futility rule to suspend enrolment if 3 or more of the first 10 subjects enrolled have viral breakthrough or are non-responders at or prior to Week 8
- Included genotype 3 HCV infection as an exclusion criterion
- Updated the formulation, packaging and labelling, and storage and handling information to include information on the lower dose strength tablet (LDV/SOF 22.5/100 mg and placebo-to-match).
- Clarified that subjects who do not attain SVR24 will also be enrolled in the separate registry study (GS-US-334-1113).
- Changed the growth and development measurements from a PK lead-in secondary endpoint to a treatment phase secondary endpoint.
- Added clarification on pregnancy notification timelines for partners of male subjects participating in the trial.
- Additional administrative updates were made.

Amendment 2

The protocol was next amended on 08 December 2014 to reflect the following key changes that affected subjects in Group 1:

- The study design was updated to include a treatment period of 24 weeks with LDV/SOF for treatment-experienced subjects with cirrhosis, to comply with the approved US prescribing information.
- Added clarification on the exclusion criteria (with a history of cirrhosis) for the PK lead-in phase
- Additional statistical analysis was added to include analysis of the LDV/SOF 24-week treatment group (treatment-experienced subjects with cirrhosis)
- Added language in the introduction to reflect the approval of LDV/SOF in the US and EU
- Language added to clarify the re-consent requirement for subjects who become adults while on the study
- Revised statistical endpoints to be consistent with the protocol objectives
- Additional administrative, formatting, section number, and minor grammatical corrections and updates were made throughout the document.

Amendment 3

The protocol was next amended on 28 May 2015 to reflect the following key changes that affected subjects in Group 1:

- The study design was updated to add treatment with LDV/SOF+RBV for 24 weeks for subjects with genotype 3 HCV infection, to comply with the approved UK prescribing information.
- The study design was updated to reflect that subjects with genotypes 3 or 4 HCV infection would only be enrolled in the UK, to comply with the approved UK prescribing information.
- The study design for the long-term follow-up study (GS-US-334-1113) was updated to reduce the number of visits, fulfilling the regulatory requirement minimum.
- The statistical methods were updated to align with the updated treatment regimens.
- New clinical data available for subjects with genotype 3 and 4 HCV infection were added to the introduction to reflect the approved UK prescribing information.
- Added information on RBV to the introduction, investigational medicinal products section, and to the inclusion criteria
- The exclusion criteria contraception language within the synopsis was updated to clarify the contraception requirements.
- Amiodarone was been added to the disallowed agents list in the prior and concomitant medications section
- Pregnancy tests and prevention requirements and RBV toxicity management were added for the subjects receiving RBV.
- References for new clinical data and Tanner Stage Scale were added.

Amendment 4

The protocol was next amended on 15 March 2016 to reflect the following key changes:

- The study design was updated to include additional genotypes (genotypes 5 and 6) following the availability of supporting data within the adult population. Updates were also made to the background consistent with these changes.

- The study procedures and statistical methods sections were updated to remove the collection and analysis of age of first menses.
- Clarifications were made to the estimated glomerular filtration rate (eGFR) calculation.
- Additional minor updates were made throughout the document.

Protocol Deviations

A total of 7 important protocol deviations occurred in 6 subjects during the study. Of the 6 subjects, 5 subjects had a single important deviation and 1 subject had 2 important deviations. The majority of important protocol deviations (4 of 7) were for deviations of eligibility criteria. Relevant protocol deviations were proportionally distributed between treatment groups and study sites.

Table 5. GS-US-337-1116: Important Protocol Deviations for Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

	Genotype 1 LDV/SOF 12 Weeks		
Protocol Deviation[a], n (%)	**Treatment Naive, With or Without Cirrhosis (N = 80)**	**Treatment Experienced, Without Cirrhosis (N = 20)**	**Total (N = 100)**
Number of Subjects with at Least 1 Important Protocol Deviation	5 (6.3)	1 (5.0)	6 (6.0)
Deviation of Inclusion/Exclusion Criteria	3 (3.8)	1 (5.0)	4 (4.0)
Informed Consent Not Obtained Properly	1 (1.3)	0	1 (1.0)
Subject not Managed According to Protocol	1 (1.3)	0	1 (1.0)
Study Medication	1 (1.3)	0	1 (1.0)

Baseline data

Table 6. GS-US-337-1116: Demographic and Baseline Characteristics for Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

Characteristic	Genotype 1 LDV/SOF 12 Weeks		
	Treatment Naive, With or Without Cirrhosis (N = 80)	Treatment Experienced, Without Cirrhosis (N = 20)	Total (N = 100)
Age at Baseline (Years)			
Mean (SD)	15 (1.7)	15 (1.7)	15 (1.7)
Median	15	15	15
Q1, Q3	13, 16	13, 16	13, 16
Min, Max	12, 17	12, 17	12, 17
Baseline Age Category			
≤ 15 years old	52 (65.0%)	11 (55.0%)	63 (63.0%)
> 15 years old	28 (35.0%)	9 (45.0%)	37 (37.0%)
Sex			
Male	30 (37.5%)	7 (35.0%)	37 (37.0%)
Female	50 (62.5%)	13 (65.0%)	63 (63.0%)
Race			
Black or African American	7 (8.8%)	0	7 (7.0%)
White	71 (88.8%)	19 (95.0%)	90 (90.0%)
Asian	2 (2.5%)	0	2 (2.0%)
Not Disclosed	0	1 (5.0%)	1 (1.0%)
Ethnicity			
Hispanic or Latino	10 (12.5%)	3 (15.0%)	13 (13.0%)
Not Hispanic or Latino	68 (85.0%)	17 (85.0%)	85 (85.0%)
Not Disclosed	2 (2.5%)	0	2 (2.0%)
Baseline Body Mass Index (kg/m^2)			
Mean (SD)	22.9 (5.55)	23.2 (4.37)	23.0 (5.32)
Median	20.9	22.2	21.0
Q1, Q3	18.6, 26.0	19.9, 24.7	19.0, 25.9
Min, Max	13.1, 36.6	17.6, 31.7	13.1, 36.6

Table 7. GS-US-337-1116: Baseline Disease Characteristics for Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

Disease Characteristic	Genotype 1 LDV/SOF 12 Weeks		
	Treatment Naive, With or Without Cirrhosis (N = 80)	Treatment Experienced, Without Cirrhosis (N = 20)	Total (N = 100)
HCV Genotype			
1a	66 (82.5%)	15 (75.0%)	81 (81.0%)
1b	14 (17.5%)	5 (25.0%)	19 (19.0%)
Cirrhosis			
No	31 (38.8%)	11 (55.0%)	42 (42.0%)
Yes	1 (1.3%)	0	1 (1.0%)
Unknown	48 (60.0%)	9 (45.0%)	57 (57.0%)
IL28B			
CC	20 (25.0%)	4 (20.0%)	24 (24.0%)
CT	42 (52.5%)	11 (55.0%)	53 (53.0%)
TT	18 (22.5%)	5 (25.0%)	23 (23.0%)
Baseline HCV RNA (IU/mL)			
Mean (SD)	1851748 (2207321)	2292700 (2195097)	1939938 (2200943)
Median	957500	1925000	984500
Q1, Q3	378000, 2405000	434500, 3840000	379500, 2550000
Min, Max	47400, 9900000	109000, 6470000	47400, 9900000

Disease Characteristic	Genotype 1 LDV/SOF 12 Weeks		
	Treatment Naive, With or Without Cirrhosis (N = 80)	Treatment Experienced, Without Cirrhosis (N = 20)	Total (N = 100)
Baseline HCV RNA Category			
< 800,000 IU/mL	36 (45.0%)	9 (45.0%)	45 (45.0%)
≥ 800,000 IU/mL	44 (55.0%)	11 (55.0%)	55 (55.0%)
Baseline HCV RNA (log_{10} IU/mL)			
Mean (SD)	6.0 (0.55)	6.1 (0.56)	6.0 (0.55)
Median	6.0	6.3	6.0
Q1, Q3	5.6, 6.4	5.6, 6.6	5.6, 6.4
Min, Max	4.7, 7.0	5.0, 6.8	4.7, 7.0
Baseline HCV RNA Category			
< 6 log_{10} IU/mL	42 (52.5%)	9 (45.0%)	51 (51.0%)
≥ 6 log_{10} IU/mL	38 (47.5%)	11 (55.0%)	49 (49.0%)
Baseline ALT (U/L)			
Mean (SD)	54 (56.2)	50 (36.2)	53 (52.7)
Median	36	38	36
Q1, Q3	28, 53	25, 60	28, 53
Min, Max	9, 349	13, 139	9, 349
Baseline ALT Category			
≤ 1.5 × ULN	61 (76.3%)	13 (65.0%)	74 (74.0%)
> 1.5 × ULN	19 (23.8%)	7 (35.0%)	26 (26.0%)
Interferon Eligibility			
IFN Eligible	79 (98.8%)	0	79 (79.0%)
IFN Ineligible	1 (1.3%)	0	1 (1.0%)
Response to Prior HCV Treatment			
Nonresponder	0	13 (65.0%)	13 (13.0%)
Relapse/Breakthrough	0	6 (30.0%)	6 (6.0%)
IFN Intolerant	0	1 (5.0%)	1 (1.0%)
Estimated Glomerular Filtration Rate Using Schwartz Formula (mL/min/1.73 m^2)			
Mean (SD)	153.6 (36.86)	144.9 (32.99)	151.9 (36.13)
Median	145.3	142.8	145.3
Q1, Q3	128.8, 171.4	124.1, 158.7	127.5, 167.1
Min, Max	93.1, 287.3	93.2, 233.8	93.1, 287.3

Disease Characteristic	Genotype 1 LDV/SOF 12 Weeks		
	Treatment Naive, With or Without Cirrhosis (N = 80)	Treatment Experienced, Without Cirrhosis (N = 20)	Total (N = 100)
Mode of HCV Infection			
Contaminated Needle or IV Drug Use (Current/Past)	5 (6.3%)	0	5 (5.0%)
Blood Product Transfusion	1 (1.3%)	1 (5.0%)	2 (2.0%)
Contact With Infected Individual (Other Than Vertical Transmission)	2 (2.5%)	0	2 (2.0%)
Vertical Transmission (Infected Mother)	65 (81.3%)	19 (95.0%)	84 (84.0%)
Unknown	7 (8.8%)	0	7 (7.0%)

Outcomes and estimation

The key efficacy endpoint was SVR12, defined as HCV RNA < LLOQ 12 weeks after discontinuation of the study drug, in the FAS. The key efficacy endpoint analysis (for SVR12) in this interim CSR was conducted after all subjects in Group 1 (12 to < 18 years old) completed the posttreatment Week 12 visit or prematurely discontinued from the study.

Table 8. GS-US-337-1116: SVR by Visit During Posttreatment Follow-Up for Group 1 (12 to < 18 Years Old) (Full Analysis Set)

	Genotype 1 LDV/SOF 12 Weeks		
	Treatment Naive, With or Without Cirrhosis (N = 80)	Treatment Experienced, Without Cirrhosis (N = 20)	Total (N = 100)
SVR4	77/80 (96.3%)	20/20 (100.0%)	97/100 (97.0%)
95% CI	89.4% to 99.2%	83.2% to 100.0%	91.5% to 99.4%
SVR12	77/80 (96.3%)	20/20 (100.0%)	97/100 (97.0%)
95% CI	89.4% to 99.2%	83.2% to 100.0%	91.5% to 99.4%

HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation of 15 IU/mL.

SVRx was sustained virologic response (HCV RNA < LLOQ) x weeks after stopping study treatment.

A missing SVR value was imputed as a success if it was bracketed by values that were termed successes (ie, "< LLOQ TND" or "< LLOQ detected"); otherwise, the missing SVR value was imputed as a failure. TND = target not detected.

The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.

No subject had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse). A total of 3 of 100 subjects (3.0%), all treatment naive, did not achieve SVR12:

One subject completed the Week 4 visit (31 days of treatment), but has not returned for any subsequent study visits. The subject had HCV RNA < LLOQ at the Week 2 and Week 4 visits.

One subject completed study treatment and the Week 12 visit, but did not return for any subsequent study visits and was lost to follow-up. The subject had HCV RNA < LLOQ at the Week 8 and Week 12 visits.

One subject completed study treatment and the Week 12 visit, but has not returned for any subsequent study visits. The subject had HCV RNA < LLOQ at the Week 8 and Week 12 visits.

One subject who achieved SVR and did not have HCV RNA measurements at the posttreatment Week 12 visit was imputed to achieve SV12 based on bracketed success (achieving SVR4 and having observed HCV RNA values < LLOQ at the posttreatment Week 24 visit).

Virology outcomes

Resistance to NS5A inhibitors in genotype 1 HCV infection has been associated with amino acid variants at positions 24, 26, 28, 30, 31, 32, 38, 58, 92, and 93 in the NS5A protein. For the purposes of this report, NS5A LDV resistance-associated variants (RAVs) were defined as specific amino acid changes in genotype 1a or 1b that conferred > 2.5-fold reduced susceptibility to LDV.

NS5B nucleoside inhibitor (NI) RAVs were defined as follows: S96T, N142T, L159F, E237G, S282any, M289L/I, L320F/I/V, and V321A/I.

Baseline RAV analyses were performed at a 1% and a 15% threshold. Overall, for the 1% cut-off, LDV RAVs were detected in 8 of 97 subjects (8.2%). For the 15% cut-off, LDV RAVs were detected in 5 of 97 subjects (5.2%).

Table 9. GS-US-337-1116: Subjects with Baseline LDV RAVs and Treatment Outcome

HCV Subtype	Treatment	Cirrhotic (Y/N)	TN/TE	Baseline LDV RAVs	Treatment Outcome
1a	LDV/SOF 12 Weeks	N	TN	Y93C (48.5%)	SVR12
1a	LDV/SOF 12 Weeks	N	TN	K24G (>99%)	SVR12
1b	LDV/SOF 12 Weeks	N	TN	Y93H (28.1%)	SVR12
1a	LDV/SOF 12 Weeks	N	TN	Q30H (60.5%)	SVR12
1a	LDV/SOF 12 Weeks	N	TN	K24R (3.1%)	SVR12
1b	LDV/SOF 12 Weeks	N	TN	L31M (1.5%)	SVR12
1b	LDV/SOF 12 Weeks	N	TN	L31I (3.5%) L31M (96.1%)	SVR12
1a	LDV/SOF 12 Weeks	N	TN	K24R (2.9%)	SVR12

LDV = ledipasvir; RAV = resistance-associated variants; TE = treatment experienced; TN = treatment naive

At both the 1% and 15% cutoff, NS5B NI RAVs were detected in 5 of 97 subjects (5.2%).

Table 10. GS-US-337-1116: Subjects with Baseline NS5B NI RAVs and Treatment Outcome

HCV Subtype	Treatment	Cirrhotic (Y/N)	TN/TE	Baseline NS5B NI RAVs	Treatment Outcome
1a	LDV/SOF 12 Weeks	N	TN	L159F (98.5%)	SVR12
1a	LDV/SOF 12 Weeks	N	TN	E237G (>99%)	SVR12
1a	LDV/SOF 12 Weeks	N	TN	N142T (90.6%)	SVR12
1b	LDV/SOF 12 Weeks	N	TN	L159F (>99%)	SVR12
1b	LDV/SOF 12 Weeks	N	TN	L159F (>99%)	SVR12

LDV = ledipasvir; RAV = resistance-associated variants; TE = treatment experienced; TN = treatment naive

2.4.2. Discussion on clinical efficacy

Although the study is open-labelled and uncontrolled, it provides a good estimate of efficacy as very few patients are expected to spontaneously resolve their chronic HCV infection during a comparable time interval. Screening failures and protocol violations were few, indicating that the study data is reliable and applicable to real-world settings.

Only GT1 patients were de facto included, and all but one subject were non-cirrhotic. However, the liver is enzymatically mature far earlier than the age of 12 and the baseline factors such as viral load and fibrosis grade are generally more favourable in the paediatric population. Also, efficacy studies with interferon and ribavirin in the paediatric population indicates that cure rates were similar between adults and adolescents across genotypes (Wirth et al, Journal of Hepatology 2010).

Therefore, it should be possible to extrapolate efficacy in children aged 12 to <18 years who are infected with other HCV genotypes, as well as cirrhotic patients, from adult efficacy data as long as the drug exposure is similar.

2.4.3. Conclusions on the clinical efficacy

The combination of sofosbuvir and ledipasvir is efficacious in the treatment of paediatric patients aged 12 to <18 with chronic HCV at levels comparable to what is seen in adults, and should provide a valuable contribution to the pharmacological armamentarium for HCV infected adolescents.

2.5. Clinical safety

Introduction

In adults, the safety profile of the sofosbuvir/ledipasvir combination is considered favourable and well-characterized in subjects with compensated liver disease and GFR > 60 ml/min.

Patient exposure

In adults, the estimate of patient exposure since first marketing to the latest PSUSA Data Lock Point (09 April 2016) is 105,243 patient-years. As of 09 April 2016, approximately 5,447 subjects have been exposed to SOF/LDV in clinical trials.

In this study, the mean (SD) duration of exposure to the study regimen was 12.1 (0.81) weeks overall, 12.0 (0.89) weeks for treatment naïve subjects, and 12.2 (0.32) weeks for treatment-experienced subjects. The majority of all subjects (89.0%) received study drug for 12 weeks.

Adverse events

The majority of subjects (71.0%) experienced at least 1 AE and all AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. No subjects experienced Grade 3 or 4 AEs or SAEs, and no deaths were reported. No subject prematurely discontinued study drug due to an AE.

Table 11. GS-US-337-1116: Overall Summary of Adverse Events for Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

Number (%) of Subjects Experiencing Any	Genotype 1 LDV/SOF 12 Weeks (N = 100)
Adverse Event	71 (71.0%)
Grade 3 or Above Adverse Event	0
Treatment-Related Adverse Event	25 (25.0%)
Grade 3 or Above Treatment-Related Adverse Event	0
Serious Adverse Event	0
Treatment-Related Serious Adverse Event	0
Adverse Event Leading to Premature Discontinuation of LDV/SOF	0
Adverse Event Leading to Interruption of LDV/SOF	0
All Deaths	0

Table 12. GS-US-337-1116: Adverse Events Reported for at Least 5% of Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

	Genotype 1 LDV/SOF 12 Weeks (N = 100)
Number (%) of Subjects Experiencing Any Adverse Event	71 (71.0%)
Headache	27 (27.0%)
Diarrhoea	14 (14.0%)
Fatigue	13 (13.0%)
Nausea	11 (11.0%)
Vomiting	11 (11.0%)
Cough	10 (10.0%)
Oropharyngeal pain	10 (10.0%)
Abdominal pain	7 (7.0%)
Abdominal pain upper	7 (7.0%)
Nasopharyngitis	7 (7.0%)
Nasal congestion	6 (6.0%)
Upper respiratory tract infection	6 (6.0%)
Dysmenorrhoea	5 (5.0%)

Table 13. GS-US-337-1116: Treatment-Related Adverse Events Reported for > 1 Subject in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

	Genotype 1 LDV/SOF 12 Weeks (N = 100)
Number (%) of Subjects Experiencing Any Treatment-Related Adverse Event	25 (25.0%)
Headache	13 (13.0%)
Fatigue	11 (11.0%)
Diarrhoea	3 (3.0%)
Abdominal pain	2 (2.0%)
Abdominal pain upper	2 (2.0%)

Serious adverse event/deaths/other significant events

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

No deaths were reported during the study for subjects enrolled in Group 1 (12 to < 18 years old)

No treatment-emergent SAEs were reported during the study. Non-treatment emergent SAEs were reported for 3 subjects: pain, substance-induced psychotic disorder, and appendicitis, respectively.

Laboratory findings

Haematology

Grade 3 haematology laboratory abnormalities were reported for decreased haemoglobin and decreased lymphocytes. No subjects had a Grade 4 haematology abnormality.

A Grade 3 decrease in haemoglobin (9.4 g/dL) was reported for 1 subject at Week 8 (Grade 2 at Week 12); an AE of iron deficiency was reported at Week 12.

A Grade 3 decrease in lymphocytes was reported for 1 subject at the Week 8 visit, which was transient; the subject had an AE of viral pharyngitis at the Week 8 visit.

Table 14. GS-US-337-1116: Grade 3 Haematology Laboratory Abnormalities for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

	Genotype 1 LDV/SOF 12 Weeks (N = 100)
Hematology	
Hemoglobin	100
Grade 3	1 (1.0%)
Lymphocytes	100
Grade 3	1 (1.0%)

Figure 11. GS-US-337-1116: Median (Q1, Q3) Neutrophils (x 10^3/µL) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

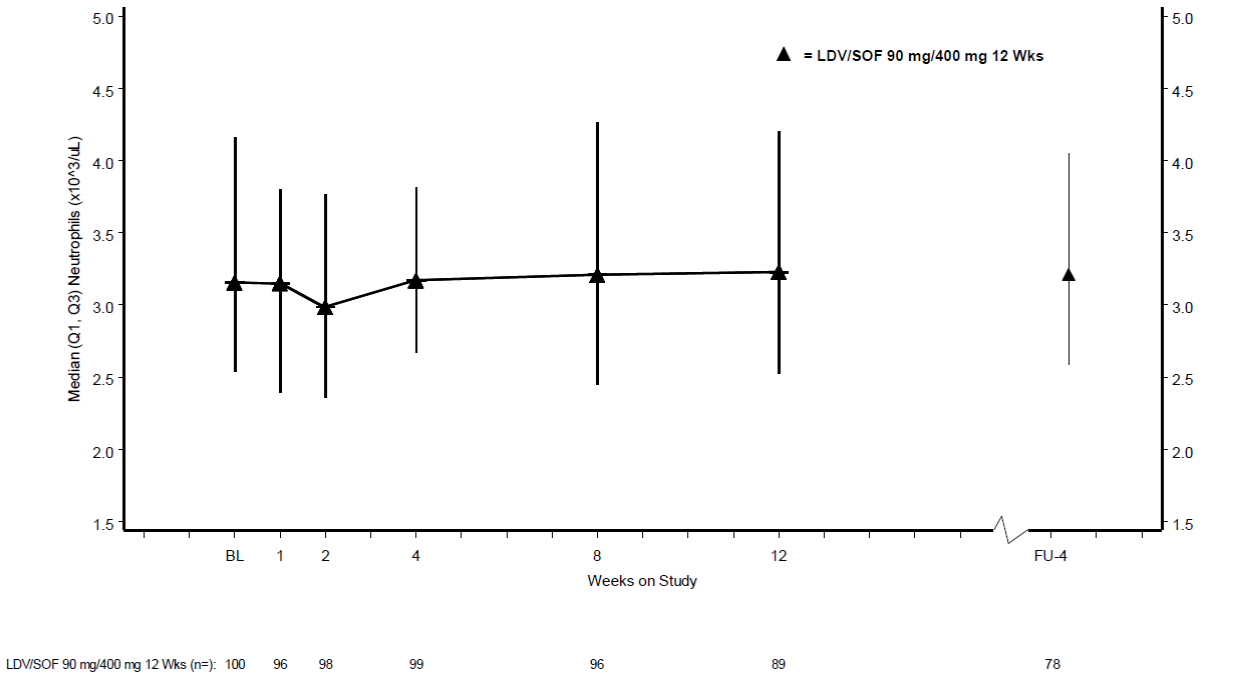


Figure 12. GS-US-337-1116: Median (Q1, Q3) Lymphocyte (x 10^3/µL) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

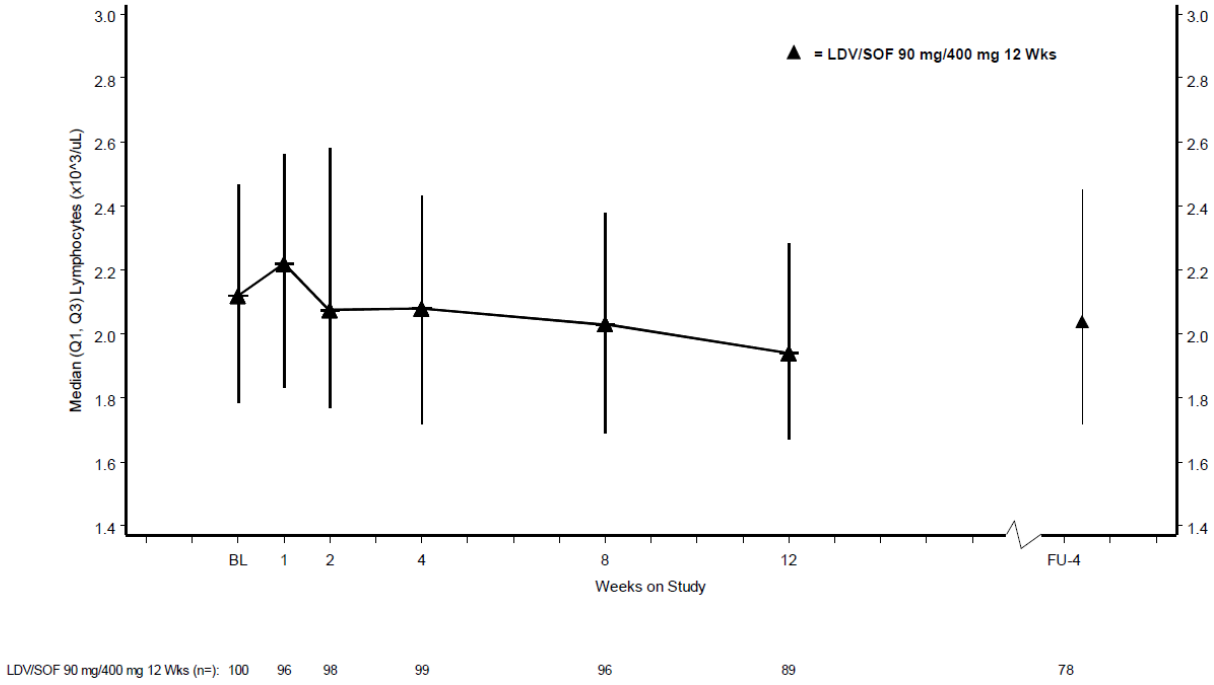


Figure 13. GS-US-337-1116: Median (Q1, Q3) Haemoglobin (g/dL) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

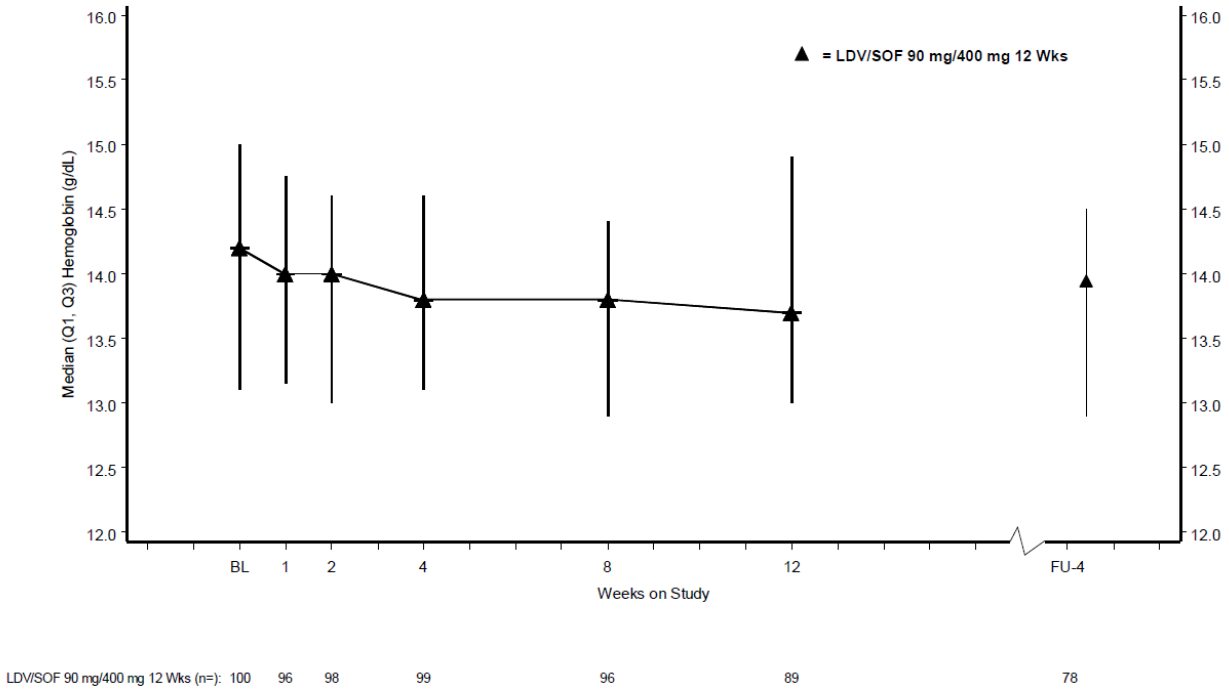


Figure 14. GS-US-337-1116: Median (Q1, Q3) Reticulocytes (x 10^3/µL) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

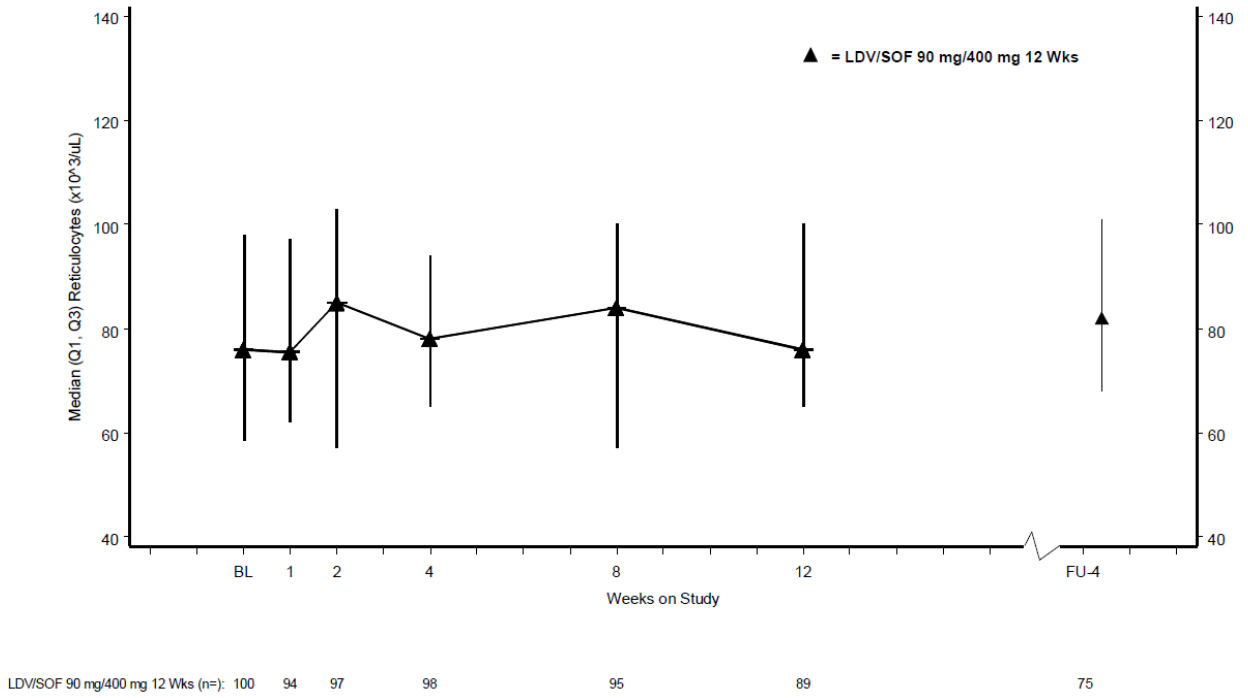
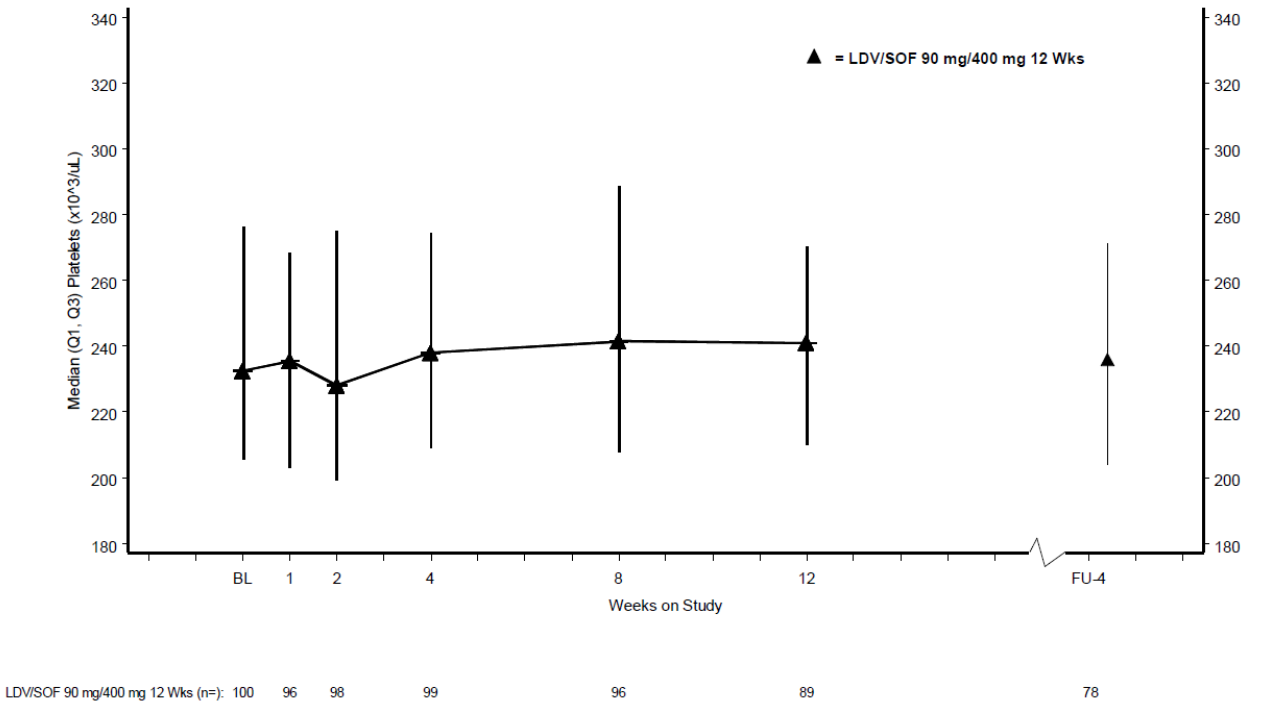


Figure 15. GS-US-337-1116: Median (Q1, Q3) Platelets (x 10^3/µL) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)



Chemistry

Grade 3 chemistry laboratory abnormalities were reported for INR, creatine kinase, potassium, serum amylase, and total bilirubin, and 1 Grade 4 laboratory abnormality of increased AST was reported.

A transient Grade 3 increase in INR was reported for 1 subject at Week 1, who had Grade 1 INR at baseline.

A Grade 3 increase in creatine kinase was reported for 1 subject at Week 12, which was transient, asymptomatic, and reported by the investigator to be associated with intense exercise. This subject also had asymptomatic Grade 3 increased serum amylase at Weeks 2 and 4 (Grade 2 at baseline and all other visits). Lipase levels remained largely unchanged and were within normal limits.

Two additional subjects experienced Grade 3 increases in serum amylase. One subject had an asymptomatic Grade 3 increase in amylase at Week 8, concurrent with Grade 2 increased lipase. This subject had Grade 1 or 2 increased amylase at baseline and all other visits prior to and after the Week 8 visit. Lipase levels had returned to normal by posttreatment Day 82, and the abnormalities were not associated with any AEs.

One subject had an asymptomatic Grade 3 increase in amylase at Week 8, with Grade 1 or 2 increased amylase at baseline and all other visits prior to and after the Week 8 visit. Lipase levels remained largely unchanged and were within normal limits.

A Grade 3 increase in potassium was reported for 1 subject at Week 1, which was transient and isolated.

A Grade 3 increase in total bilirubin was reported for 1 subject at Week 1. This subject had Grade 2 increased total bilirubin at baseline and all other visits except for Week 8 (Grade 1). Direct bilirubin levels were within the normal range at all study visits.

A Grade 4 increase in AST was reported for 1 subject. This subject experienced the Grade 4 elevated AST at the posttreatment Week 4 visit (posttreatment Day 28), which was also reported as a Grade 2 AE. The Grade 4 elevation was isolated, transient, and associated with the start of treatment with isotretinoin for acne on posttreatment Day 25. Concurrently, the subject had a Grade 2 elevation in ALT but no changes in bilirubin. The subject's AST levels subsequently normalized with continued isotretinoin administration.

Table 15. GS-US-337-1116: Grade 3 or 4 Coagulation or Chemistry Laboratory Abnormalities for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

	Genotype 1 LDV/SOF 12 Weeks (N = 100)
Coagulation	
INR	100
Grade 3	1 (1.0%)
Chemistry	
AST	100
Grade 4	1 (1.0%)
Creatine Kinase	100
Grade 3	1 (1.0%)
Potassium (Hyperkalemia)	100
Grade 3	1 (1.0%)
Serum Amylase	100
Grade 3	3 (3.0%)
Total Bilirubin (Hyperbilirubinemia)	100
Grade 3	1 (1.0%)

Figure 16. GS-US-337-1116: Median (Q1, Q3) ALT (U/L) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

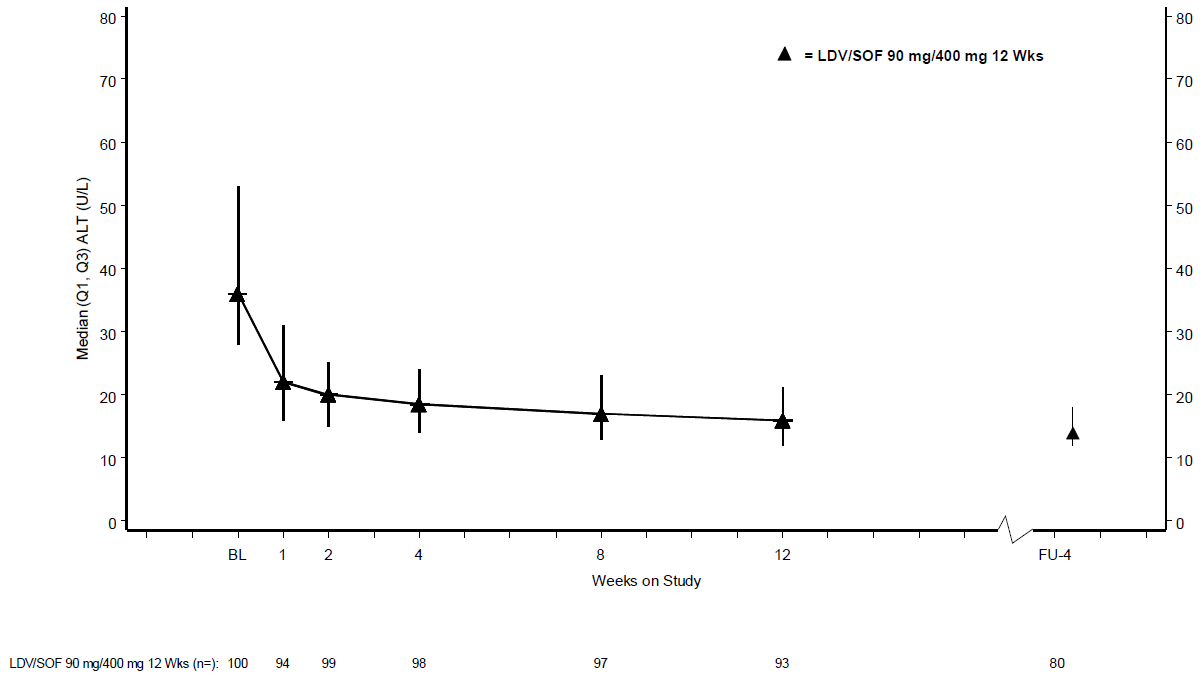


Figure 17. GS-US-337-1116: Median (Q1, Q3) Total Bilirubin (mg/dL) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

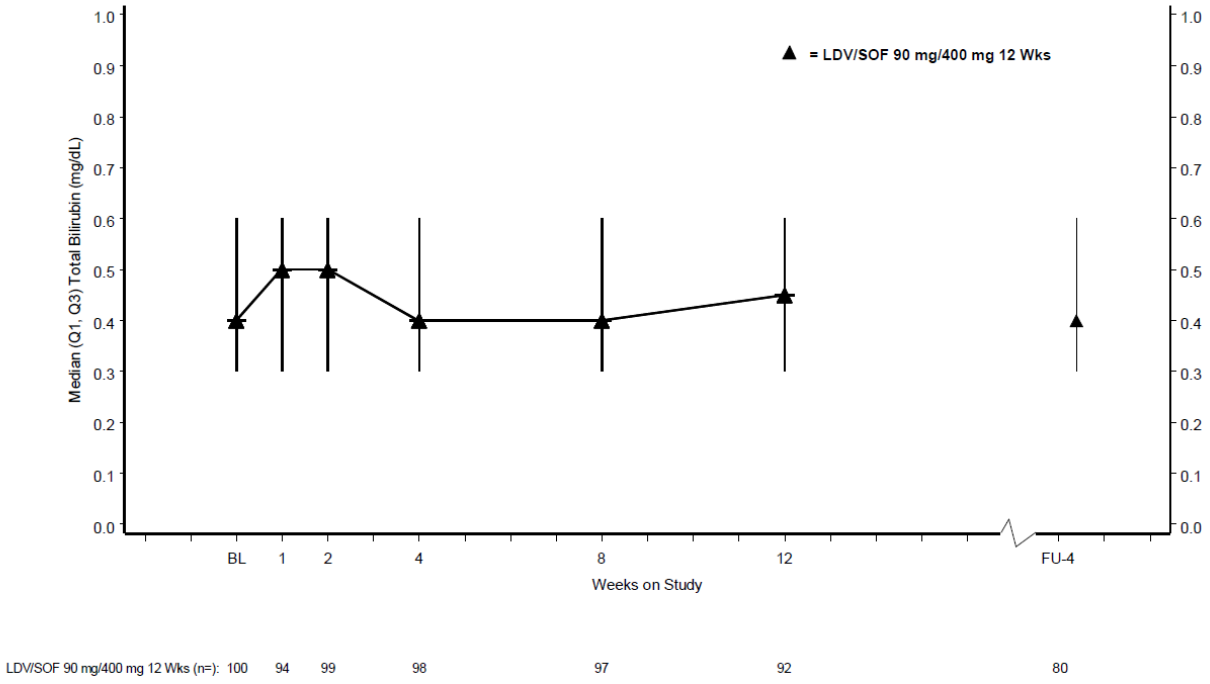


Figure 18. GS-US-337-1116: Median (Q1, Q3) Serum Creatinine (mg/dL) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

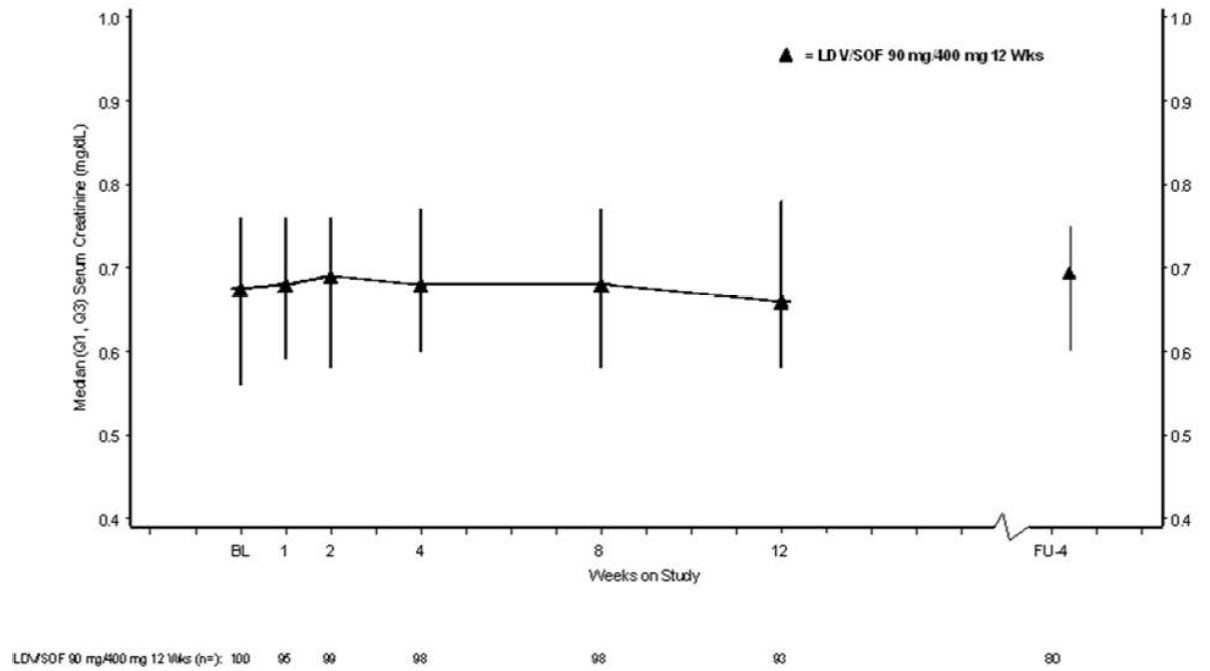
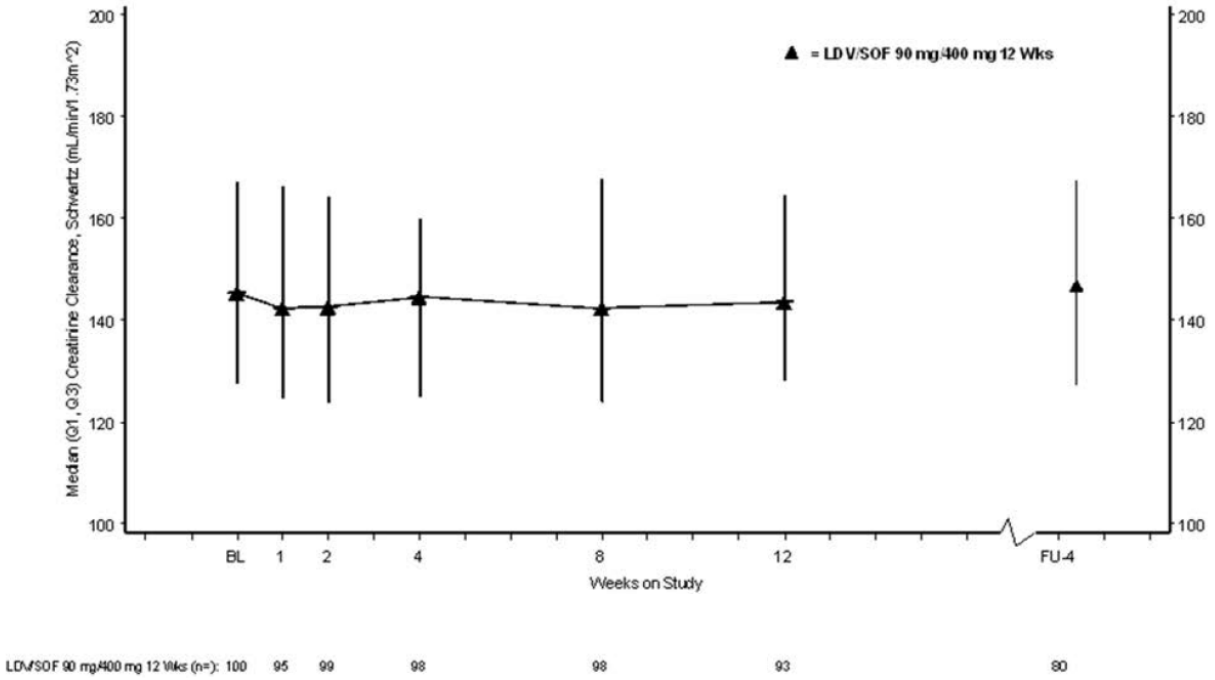


Figure 19. GS-US-337-1116: Median (Q1, Q3) eGFR (mL/min/1.73 m^2) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)



Additional clinical data

No notable effects of study treatment on development or growth as assessed by changes from baseline through posttreatment Week 12 in Tanner pubertal stages, and by changes from baseline to posttreatment Week 4 in height, weight, and BMI were observed.

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

No pregnancies were reported during the study for subjects enrolled in Group 1.

2.5.1. Discussion on clinical safety

Assessment of paediatric data on clinical safety

In this limited paediatric dataset, there are no signs that the safety profile differs from what is previously known from studies of adult subjects and the post-marketing experience in adult patients. SOF/LDV was generally well-tolerated and very few severe or serious adverse events were observed.

2.5.2. Conclusions on clinical safety

The safety profile sofosbuvir/ledipasvir is favourable in paediatric patients aged 12-18 years.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 is acceptable. The PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

Safety concerns

Only Missing information section was changed as follows;

Missing Information	Safety in children **< 12 years of age**
	Safety in pregnant or breastfeeding women
	~~Safety in patients with HCV/HIV coinfection~~
	Safety in patients with HCV/HBV coinfection
	Safety in patients with severe renal impairment or end-stage renal disease
	Development of resistance

Pharmacovigilance plan

Modifications of the PV plan are highlighted in bold

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Category 3 (Interventional studies)				
GS-US-337-1116 (formerly GS-US-337-0104) A 2-part, open-label, single-arm study to investigate pharmacokinetics, biodistribution, efficacy and safety of LDV/SOF for 12 weeks in adolescents and children with GT-1-6 chronic HCV infection	To evaluate the PK, efficacy, and safety of LDV/SOF for 12 weeks in adolescents and children	Safety in children	**Started**	Final study report June 2019

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
GS-US-334-0154 A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir+RBV for 24 Weeks in Genotype 1 or 3 HCV-Infected Subjects with Renal Insufficiency	To evaluate the safety, efficacy and pharmacokinetics of treatment with SOF+RBV for 24 weeks in subjects with chronic genotype 1 or 3 HCV infection and severe renal impairment	Safety in patients with severe renal impairment or end-stage renal disease	Started	Final study report
GS-US-344-1887 A clinical study to assess the effect of LDV on CYP3A probe midazolam	To assess the effect of LDV on a CYP3A probe drug	Drug interaction	**Started**	**April 2016**

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Category 3 (Non-interventional studies)				
BP-US-337-1117 A 5-year follow-up study of pediatric patients from study GS-US-337-1116 (formerly BP-US-337-0104)	To evaluate growth, development, and viral relapse in adolescents and children who received LDV/SOF in study GS-US-337-1116	Growth Long-term safety	Planned	
GS-US-248-0123 A Long Term Follow-up Registry Study of Subjects Who Did Not Achieve Sustained Virologic Response in Gilead-Sponsored Trials in Subjects with Chronic Hepatitis C Infection	To evaluate HCV viral sequences and the persistence or evolution of treatment-emergent viral mutations in subjects who fail to achieve an SVR after treatment with a Gilead oral antiviral containing regimen in a previous Gilead-sponsored hepatitis C study	Development of resistance	Started	
GS- EU-337-1820 A prospective observational drug utilization study of LDV/SOF in adults with HCV/HIV coinfection is planned	To characterize the frequency of postmarketing co-use of LDV/SOF+TDF+PK enhancer in adult HCV/HIV coinfected patients and the rates of renal ADRs	HCV/HIV coinfection	**Started**	To be determined

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
-GS-EU-337-2030 A survey is planned to measure the effectiveness of the DHCP communication for the important risk of clinically significant arrhythmias when Harvoni is used with concomitant amiodarone	**To investigate health care provider awareness of the risk of clinically significant arrhythmias when SOF or LDV / SOF is prescribed concurrently with amiodarone, and determines perceptions of co-medication frequency, reported changes in prescribing behaviour, and reported approaches to patient monitoring following dissemination of a direct healthcare professional communication.**	Safety in patients using concomitant amiodarone	Planned	To be determined

Risk minimisation measures

Modifications of the RMMS are highlighted in bold

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important identified risk(s)		
Severe bradycardia and heart block when used with concomitant amiodarone (LDV, SOF)	The SmPC (Sections 4.4, 4.5, and 4.8) includes information that cases of severe bradycardia and heart block have been observed when Harvoni is used in combination with amiodarone, that amiodarone should only be used in patients on Harvoni when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated, and that patients who must take amiodarone with Harvoni should be closely monitored.	Direct Healthcare Professional Communication
Important potential risk(s)		
Drug-drug interaction with potent Pgp inducers (LDV, SOF)	**The SmPC (Section 4.3) includes information that use of LDV / SOF with potent Pgp inducers (eg, rifampicin, rifabutin, St. John's wort [Hypericum perforatum], carbamazepine, phenobarbital and phenytoin) is contraindicated.**	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Administration of proton pump inhibitors (LDV)	The SmPC (Section 4.5) includes information about the maximum allowed dose and simultaneous coadministration of LDV/SOF and proton pump inhibitors, as staggered dosing has the potential for decreases in LDV plasma concentrations, which may lead to reduced therapeutic effect of LDV/SOF.	None
Drug-drug interaction with TDF + PK enhancer (LDV)	The SmPC (Sections 4.4 and 4.5) includes information of how administration of LDV/SOF with TDF+PK enhancer increases tenofovir concentrations, safety is not established, consider risks and benefits particularly in patients at increased risk for renal dysfunction, monitor for tenofovir-associated ADRs, and refer to SmPCs for Viread, Truvada, or Stribild for renal monitoring recommendations.	None
Drug-drug interaction with rosuvastatin (LDV)	The SmPC (Section 4.3, 4.5) includes information that use of rosuvastatin with LDV/SOF is contraindicated due to the potential for significant increases in rosuvastatin.	None
Drug-drug interaction with digoxin (LDV)	The SmPC (Section 4.5) includes information that coadministration of LDV/SOF and digoxin should be used with caution due to the potential for an increase in digoxin concentration and that therapeutic concentration monitoring of digoxin is recommended.	None
Missing information		
Safety in children **< 12 years of age**	The SmPC states that the safety and efficacy of LDV/SOF in pediatric subjects have not been established and that LDV/SOF is not recommended for use in children and adolescents < 12 years of age (Sections 4.2, 4.4, 4.8) and that the PK of LDV/SOF and GS-331007 have not been established in children (Section 5.2).	None
Safety in pregnant or breastfeeding women	The SmPC (Sections 4.4 and 4.6) states that there are no or limited amount of data (less than 300 pregnancy outcomes) from the use of LDV/SOF in pregnant women, that animal studies do not indicate direct or indirect harmful effects for reproductive toxicity or fetal development, and that, as a preventive measure, use of LDV/SOF should be avoided during pregnancy.	None
Safety in patients with HCV/HBV coinfection	The SmPC (Section 4.4) states that there are no data in this population. No additional risk minimization measures are considered necessary for this population.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Safety in patients with severe renal impairment or end-stage renal disease	The SmPC (Sections 4.2, 4.4, and 5.2) states that no dose adjustment of LDV/SOF is required for patients with mild or moderate renal impairment and that the safety of LDV/SOF has not been assessed in patients with severe renal impairment eGFR < 30 mL/min/1.73m^2) or ESRD requiring hemodialysis.	None
Development of resistance	The SmPC (Section 4.4) states that in patients who fail treatment with LDV/SOF, selection of NS5A resistance mutations that substantially reduce the susceptibility to LDV is seen in the majority of cases. Limited data indicate that such NS5A mutations do not revert on long term follow up. The efficacy of ledipasvir as part of a retreatment regimen in patients with prior exposure and selection of resistance to a NS5A inhibitor has not been established. The need for risk minimization measures will be reassessed following the availability of the results from studies or from routine pharmacovigilance.	None

2.7. Update of the Product information

As a consequence of an extension of indication to add treatment of chronic hepatitis C in adolescents aged 12 to < 18 years, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information on posology, warnings, safety, efficacy and pharmacokinetics.

2.7.1. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Harvoni (sofosbuvir/ledipasvir) is included in the additional monitoring list from the time of marketing 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

Hepatitis C virus infection is a global health challenge; currently, an estimated 170 million individuals worldwide are chronically infected with HCV (WHO 2014).

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 et al 2013). Globally, there are estimated to be 6.6 million HCV RNA-positive individuals 15 years of age or younger (El-Sayed et al 2015).

3.1.1. Disease or condition

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. In Europe, an approximately 86,000 deaths occur each year due to HCV infection (WHO 2011, Muhlberger et al 2009).

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. The primary mechanism of HCV infection in children is vertical transmission, with parenteral transmission secondary (Wirth et al 2011).

Most children chronically infected with HCV are asymptomatic or have mild, nonspecific symptoms. Despite the overall more favourable prognosis compared to 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 for end-stage liver disease as a consequence of HCV infection (Hu et al 2010).

3.1.2. Available therapies and unmet medical need

Paediatric treatment is controversial as the current treatment options are limited and severe side effects and tolerability can limit or preclude their use. Despite well-established guidelines for the treatment of HCV in adults, there is no universal consensus on when or if to treat chronic HCV infection in children.

Currently approved treatments for HCV infection in adolescent patients (12 to < 18 years old) include regimens with IFN or Peg-IFN and weight-based RBV. Recommendations are that patients with genotype 2 or 3 HCV infection be treated with Peg-IFN+RBV for 24 weeks and those with genotype 1 or 4 infection should receive Peg-IFN+RBV for 48 weeks (Wirth 2012). The concern for growth and development in this age group and the role that both Peg-IFN and RBV potentially play in reducing growth rates has initiated significant debate among paediatricians as to whether these treatments should even be considered in the paediatric population.

3.1.3. Main clinical studies

Study GS-US-337-1116 was designed is to demonstrate the safety and tolerability of LDV/SOF±RBV in children and adolescents (3 to < 18 years old), and to assess the efficacy of LDV/SOF±RBV in this population. The open-labelled and uncontrolled design provided a good estimate of efficacy as very few patients are expected to spontaneously resolve chronic HCV infection.

Efficacy studies with interferon and ribavirin in the paediatric population indicates that cure rates were similar between adults and adolescents across genotypes (Wirth et al, Journal of Hepatology 2010). As a consequence it is possible to extrapolate efficacy in children aged 12 to <18 years who are infected with other HCV genotypes, as well as cirrhotic patients, from adult efficacy data as long as the drug exposure is similar.

3.2. Favourable effects

The combination of sofosbuvir and ledipasvir is previously known to be efficacious in the treatment of adults chronically infected with HCV, and the data from this study gives a comparable estimate of efficacy also in children aged 12 to <18 years. Although only GT 1 non-cirrhotic patients were included in the study, it should be possible to extrapolate efficacy in paediatric patients infected with other HCV genotypes, as well as cirrhotic patients, from adult efficacy data as long as the drug exposure is similar.

3.3. Uncertainties and limitations about favourable effects

No uncertainties of regulatory relevance have been identified.

3.4. Unfavourable effects

The safety profile and tolerability of sofosbuvir/ledipasvir is favourable in adults, and there are no indications in this limited safety dataset that the safety profile is any different in children aged 12 to <18 years.

3.5. Uncertainties and limitations about unfavourable effects

The extrapolation from adults to adolescents is based on an acceptable PK bridge. The submitted popPK models display some deficiencies on a population level, however the prediction of individual exposures seems reasonable and the extrapolation from adults to adolescents is hence accepted.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The combination of sofosbuvir and ledipasvir is expected to provide an important addition to the pharmacological armamentarium as the currently approved treatment options (pegylated interferon in combination with ribavirin) has a less favourable safety profile and lower efficacy.

Unfavorable effects are generally few and in line with the safety profile in adults. No new safety signal has been identified.

3.6.2. Balance of benefits and risks

The GS-US-337-1116 study shows that the combination of sofosbuvir and ledipasvir is effective in HCV GT 1 infected paediatric patients aged 12 to <18 years. The popPK model used to demonstrate that the dose is adequate also for the smaller and younger individuals is not currently acceptable. It is recognised that the pivotal study for this application did not show any emergent safety issues.

The response to the major objection raised on the popPK in the second request of supplementary is satisfactory for the sought indication. As a consequence, efficacy and safety supported by adult data from clinical pivotal studies, can be extrapolated to provide a posology for paediatric patients aged 12 and above in all genotypes and clinical scenarios where Harvoni is currently recommended for use in adult patients. The use of Harvoni for 24 weeks is not anticipated to alter the safety profile, while the safety profile of ribavirin in children, as well as the safety of Harvoni in combination with ribavirin in adults, is well established.

The CHMP recommends the MAH to provide refined pharmacokinetic models to support dose selection in smaller children as a post-authorisation measure.

3.7. Conclusions

The overall B/R of Harvoni is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**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 add treatment of chronic hepatitis C in adolescents aged 12 to < 18 years.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information on posology, warnings, safety, efficacy and pharmacokinetics.
The Package Leaflet and Risk Management Plan (RMP version 2.1) are updated in accordance.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0174/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to add treatment of chronic hepatitis C in adolescents aged 12 to < 18 years.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information on posology, warnings, safety, efficacy and pharmacokinetics.
The Package Leaflet and Risk Management Plan (RMP version 2.1) are updated in accordance.

Summary

Please refer to the Scientific Discussion Harvoni EMEA/H/C/003850/II/0039.