20 July 2017
EMA/508676/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sovaldi

International non-proprietary name: sofosbuvir

Procedure No. EMEA/H/C/002798/II/0036

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
BID	twice daily
BMI	body mass index
BQL	below quantification limit
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CSR	clinical study report
DAA	direct-acting antiviral
DSPH	(Gilead) Drug Safety and Public Health
EMEA	European Medicines Evaluation Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gilead	Gilead Sciences
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus type 1
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IFN	interferon
IL28B	IL28B gene
IND	investigational new drug (application)
INR	international normalized ratio
LLOQ	lower limit of quantitation
N or n	number of subjects in a population (N) or subset (n)
NDA	new drug application
NI	nucleoside inhibitor
NS	non-structural protein
PBRER	Periodic Benefit-Risk Evaluation Report
PDCO	Pediatric Development Committee
Peg-IFN	pegylated interferon

PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PO	orally
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update Report
QD	once daily
RAV	resistance-associated variant
RBV	ribavirin
RNA	ribonucleic acid
SD	standard deviation
SOF	sofosbuvir (Sovaldi®)
SVR, SVRxx	sustained virologic response, sustained virologic response at “xx” weeks following completion of all treatment
TND	target not detected
US, USA	United States, United States of America
WHO	World Health Organization
WR	Written Request

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 10 November 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, II, IIIA 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 5.0) are updated in accordance.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.
Furthermore, the Product Information is brought in line with the latest QRD template version 10.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0178/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0178/2014 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 applicant 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: Alar Irs

Timetable	Actual dates
Start of procedure:	26 November 2016
CHMP Co-Rapporteur Assessment Report	23 January 2017
CHMP Rapporteur Assessment Report	20 January 2017
PRAC Rapporteur Assessment Report	26 January 2017
PRAC members comments	1 February 2017
Updated PRAC Rapporteur Assessment Report	NA
PRAC Outcome	9 February 2017
CHMP members comments	13 February 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 February 2017
Request for Supplementary Information	23 February 2017
Submission of Responses	17 March 2017
Restart	20 March 2017
CHMP Rapporteur Assessment Report	19 April 2017
PRAC Rapporteur Assessment Report	21 April 2017
PRAC members comments	26 April 2017
Updated PRAC Rapporteur Assessment Report	NA
PRAC Outcome	5 May 2017
CHMP members comments	8 May 2017
Updated CHMP Rapporteur Assessment Report	11 May 2017
2nd Request for Supplementary Information	18 May 2017
Submission	20 June 2017
Start	21 June 2017
CHMP Rapporteur Assessment Report	3 July 2017
CHMP members comments	10 July 2017
Opinion	20 July 2017

2. Scientific discussion

2.1. Introduction

Sofosbuvir (SOF) is a hepatitis C virus (HCV) non-structural protein (NS) 5B polymerase inhibitor. It was first approved for commercial marketing in the United States (US) on 06 December 2013 and in the European Union (EU) on 17 January 2014. Sofosbuvir is indicated for the treatment of genotypes 1 to 4 (US), and genotypes 1 to 6 (EU) HCV infection.

The current indication for SOF excludes patients younger than 18 years of age. The natural history of chronic HCV infection in children is generally similar to that in adults although HCV infection in children is relatively mild. However, despite the overall more favourable prognosis in children 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). Currently approved regimens are complicated by the associated tolerability issues and limited efficacy, as well as safety concerns for growth and development in this age group (Wirth 2012).

Gilead Sciences is submitting this dossier in support of an update to the marketing application to expand the potential benefit of SOF to the adolescent population (12 to < 18 years old) based on new safety and efficacy data from an ongoing Phase 2 study.

2.2. Non-clinical aspects

A comprehensive nonclinical pharmacology, pharmacokinetic, and toxicology program has been undertaken in support of the registration of SOF for the treatment of chronic HCV infection in adults.

No new nonclinical data have been generated to support approval of 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, the well-defined and favourable safety profile of SOF in adults was carefully considered prior to the initiation of Study GS-US-334-1112 in adolescent subjects 12 to < 18 years of age.

Taken together the known nonclinical safety profile for SOF with the clinical data from Study GS-US-334-1112 and the established safety profile in paediatric patients, support a favourable benefit/risk profile for the proposed use of SOF for the treatment of genotype 2 or 3 chronic HCV infection in adolescent patients 12 to < 18 years of age.

2.2.1. Ecotoxicity / environmental risk assessment

The environmental risk assessment (ERA) was previously submitted for Sovaldi (Sofosbuvir [SOF]) as part of the EU initial marketing authorisation application (MAA). This ERA considered all available data relating to 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.

The MAH provided a justification for not providing an updated ERA within this application. The MAH predicts that the potential use of Sovaldi in adolescent patients is not considered to significantly impact the predicted sales volume. The Phase II calculations presented in this ERA used predicted sales

figures that took into consideration the forecasted use of SOF (as GS-331007) for the treatment of chronic hepatitis C (CHC) across the European Economic Area (EEA). As detailed in the ERA submitted as part of the EU initial MAA Day 120 response to questions in October 2013, Risk Quotient (RQ) for SOF (as GS-331007) is less than 1 for compartments such as sewage treatment plant, surface water and groundwater, therefore an increase in sales for Sovaldi of greater than 3906 times would be needed to pose an unacceptable risk. The existing ERA is therefore considered applicable to the current Type II variation application.

2.2.2. 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).

2.2.3. 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.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The applicant 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.

Table 1. Clinical Study Included in the SOF Update to the Marketing Application for Adolescents

Study	Study Design	Treatment Regimen	N	Subject Population
GS-US-334-1112 (Group 1)	Phase 2, open-label, multicohort, 2-part study	**Genotype 2 HCV infection:** SOF 400 mg QD + RBV BID PO for 12 weeks **Genotype 3 HCV infection:** SOF 400 mg QD + RBV BID PO for 24 weeks	**Genotype 2 HCV infection:** 13 **Genotype 3 HCV infection:** 37	Treatment-naive and treatment-experienced subjects 12 to < 18 years of age with chronic genotype 2 or 3 HCV infection

BID = twice daily; CSR = clinical study report; PO = orally; QD = once daily; RBV = ribavirin; SOF = sofosbuvir

2.3.2. Pharmacokinetics

Bioanalytical Methods

Validated bioanalytical methods for SOF and GS-331007 (validation report QPS 60-1323) were used.

Absorption, Distribution, Metabolism and Elimination Characteristics

No new information was submitted.

Pharmacokinetics in Adolescent Subjects

The PK of SOF and SOF's major circulating metabolite GS-331007 were evaluated in adolescent subjects in Study GS-US-334-1112 (Group 1) enrolled as of 07 October 2015, who received the adult dose of SOF 400 mg, using all available intensive and sparse plasma concentration data (N = 50).

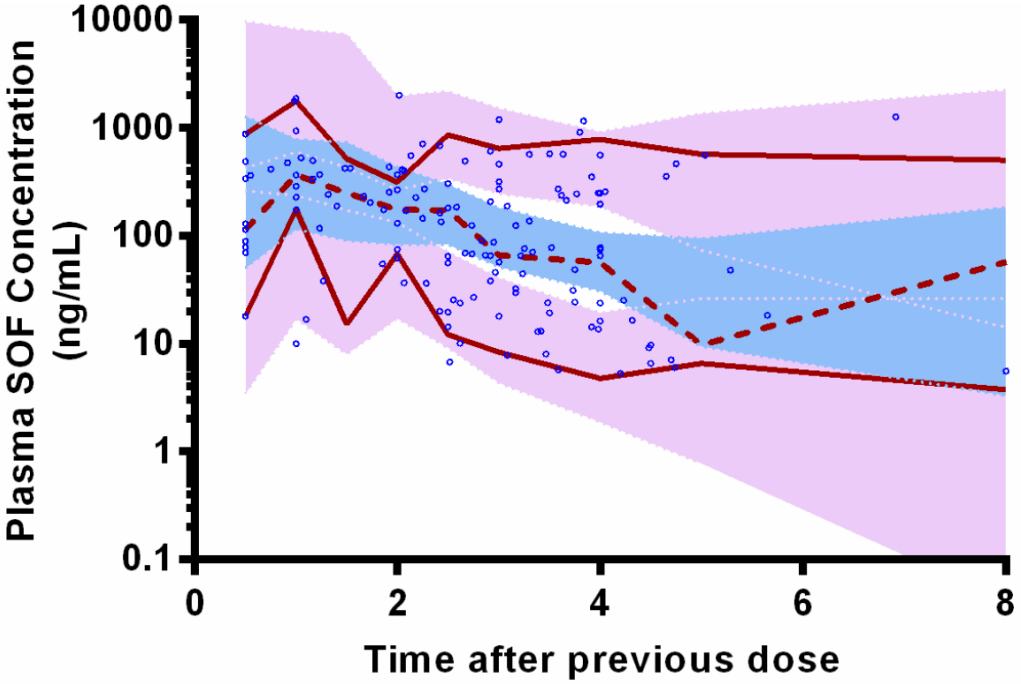
The PK lead-in phase evaluated the intensive PK of SOF and GS-331007 after 7days of SOF + RBV dosing in 10 subjects. Plasma samples were collected up to 12 hours post-dose and PK data were used to confirm the SOF dose. Once confirmed, the treatment phase was opened up to enrol an additional 40 subjects. A single PK sample was collected at all visits while on-treatment. The plasma concentrations of SOF and GS-331007 were assessed.

Sofosbuvir

The SOF dataset included 50 subjects with 428 plasma samples of which 151 were above the limit of quantitation. Data exploration identified 6 measurable PK samples as outliers and thus was excluded from the analysis. The remaining dataset included 145 measureable SOF concentrations from 28 subjects.

In the original PopPK model, the plasma PK of SOF after administration of SOF 400 mg was best described with a 1-compartment model with first order absorption, first order elimination from the central compartment, and an absorption lag time. The PK model was parameterized in terms of apparent oral clearance (CL/F), apparent central volume (Vc/F), absorption rate constant (Ka), and lag time (Tlag) with interindividual variability terms on CL/F, Vc/F, and Ka parameters. The relevant covariates in the model are patient status (HCV infected vs. healthy) on CL/F and Ka. The full covariate model was utilized for characterizing the disposition of SOF in this population. The prediction corrected visual predicted check of SOF plasma concentrations from adolescent patients is presented in Figure 1.

Figure 1. Prediction corrected VPC of SOF Plasma Concentrations



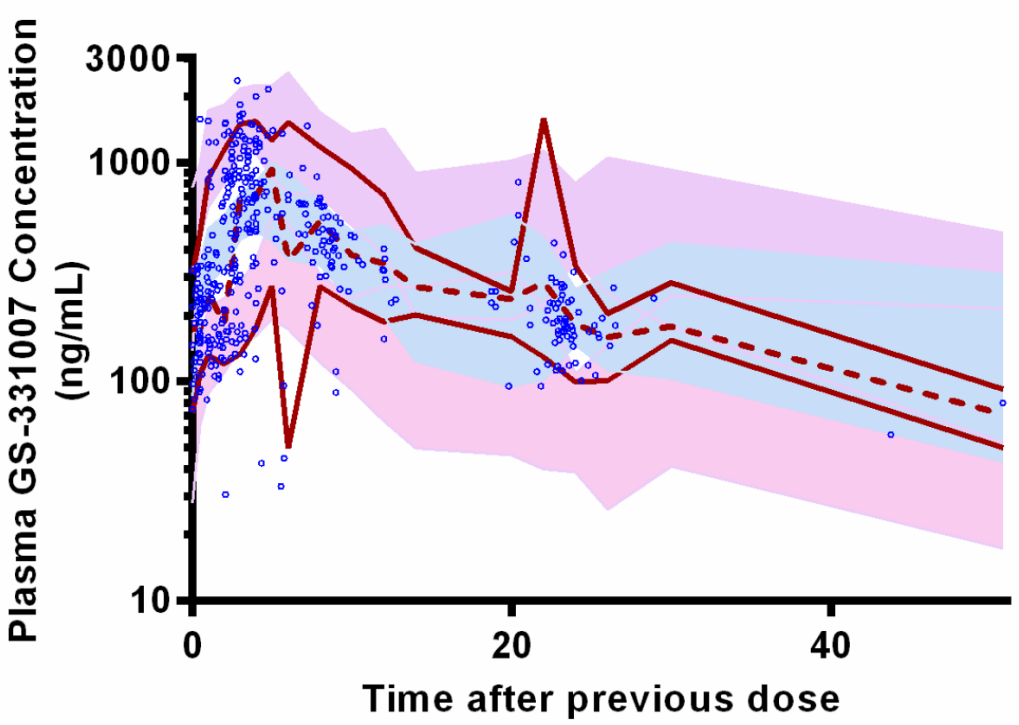
Points are the observed plasma SOF concentrations, solid red lines represent the median observed value, and dashed lines represent 5th percentile and 95th percentiles of the observed values. Blue shaded areas represent the spread of the median predicted values (5th to 95th percentile), and red shaded areas represent the spread (5th percentile and 95th percentile) of the 5th and 95th predicted percentile concentrations.

GS-331007

The GS-331007 dataset included 428 plasma samples from 50 subjects. Seven samples were below-LLOQ and data exploration identified 6 PK samples as outliers excluded from the analysis. The remaining dataset included 415 measureable GS-331007 concentrations from 50 subjects.

In the original PopPK model, the plasma PK of GS-331007 after administration of SOF 400 mg was best described by a 2-compartment model with zero and first order absorption, first order elimination from the central compartment, and an absorption lag time. The PK model was parameterized in apparent oral clearance (CL/F), apparent central volume (Vc/F), apparent inter-compartmental clearance (Q/F), apparent peripheral volume (Vp/F), a zero order (D2) and first-order absorption rate constant (Ka), and an absorption lag time (Tlag) with interindividual variability terms on CL/F, Vc/F, and Ka parameters. Creatinine clearance (CLCR) and patient status (HCV infected vs. healthy) on CL/F were the only significant covariates in the model. The full covariate model was utilized for characterizing the disposition of GS-331007 in this study. The prediction corrected visual predicted check of GS-331007 plasma concentrations from adolescent patients is presented in Figure 2.

Figure 2. Prediction-corrected VPC of GS-331007 Plasma Concentrations



Points are the observed GS-331007 plasma concentrations, solid red lines represent the median observed value, and dashed lines represent 5th percentile and 95th percentiles of the observed values. Blue shaded areas represent the spread of the median predicted values (5th to 95th percentile), and red shaded areas represent the spread (5th percentile and 95th percentile) of the 5th and 95th predicted percentile concentrations.

Model Predicted Steady-State Exposure Parameters

To evaluate the exposures of SOF and GS-331007 achieved in paediatric subjects of this study are similar to the exposures observed in adult patients, SOF and GS-331007 exposure data from this study will be compared to the integrated adult data by carrying out an analysis of variance for log-transformed AUC_{tau} and C_{max}. The 90% confidence intervals will be constructed for the ratio of geometric means of each PK parameters. The equivalence boundary is set as 50% to 200%.

Sofosbuvir and GS-331007 population PK-based exposure parameters are presented in Table 2 for adolescent subjects with at least 1 measurable plasma concentration for SOF or GS-331007. The SOF and GS-331007 exposures in adolescents were compared with exposures in adults with HCV infection from the SOF Phase 2/3 population. Additionally, SOF and GS-331007 exposures in adolescents were evaluated across quartiles of CLcr (evaluated by quartiles of eGFR using the Schwartz formula) as it was the only statistically significant intrinsic covariate of GS-331007 identified in the population PK model.

Table 2. Comparison of Mean (%CV) SOF and GS-331007 Exposures Between Adolescents in Group 1 (12 to <18 Years Old) and Adults from the SOF Phase 2/3 Population (PK Analysis Set)

PK Parameter Mean (%CV)	Adolescents Group 1 (12 to < 18 Years Old) (N = 50)	Adults SOF Phase 2/3 Population (N = 1695)	Adolescents vs Adults % GMR (90% CI)
SOF[a]			
AUC_{tau} (h•ng/mL)	1157 (50.6)	1027 (36.5)	109.7 (98.4, 122.3)
C_{max} (ng/mL)	546 (53.0)	511 (32.5)	98.5 (86.7, 111.9)
GS-331007			
AUC_{tau} (h•ng/mL)	7969 (32.8)	7123 (30.7)	111.5 (103.5, 120.1)
C_{max} (ng/mL)	621 (40.7)	582 (36.3)	105.5 (96.2, 115.6)

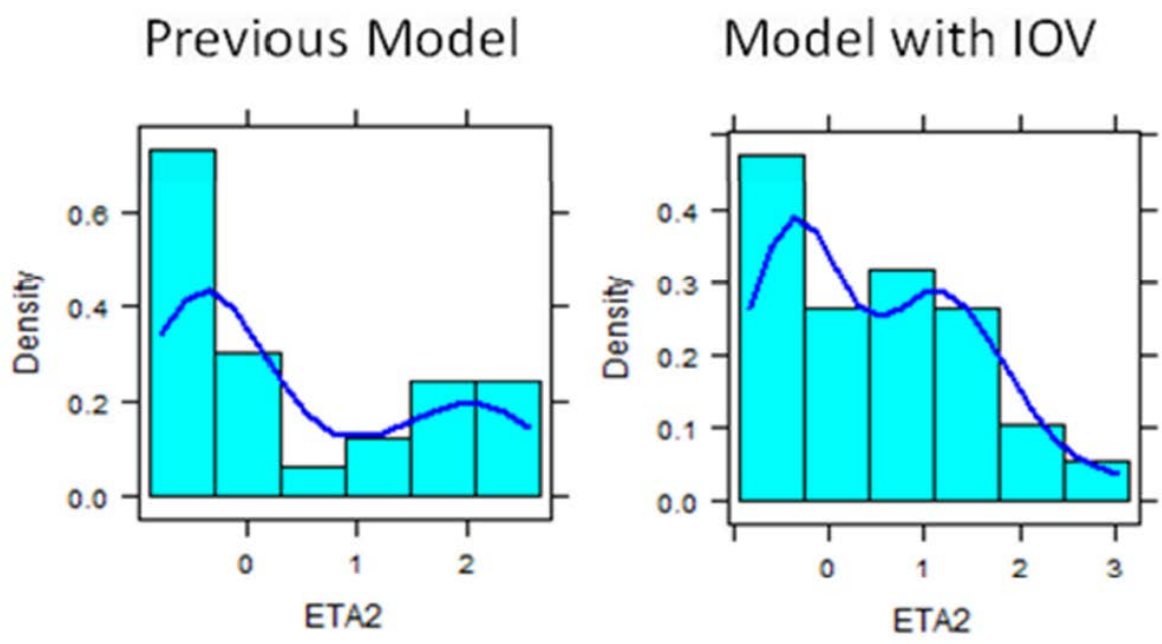
GMR = geometric mean ratio

a N = 28 (Adolescents) or 838 (Adult SOF Phase 2/3 Population)

Final Population PK model

Population pharmacokinetic (PopPK) models have been developed for SOF and its metabolite GS-331007, based on data from 14 clinical trials including adult HCV-infected subjects and healthy volunteers. The understanding of the disposition of sofosbuvir (SOF) and GS-331007, in conjunction with intensive pharmacokinetic (PK)-lead-in data in adolescent subjects, informed that exposures of SOF and GS-331007 in the broader adolescent population would be comparable to the adult population. The initial population PK analyses for adolescents aged 12-<18 years was a fit for purpose approach to adequately describe the observed plasma concentration data with the intent of generating exposure estimates for comparison to that observed in the adult population administered SOF 400 mg + RBV. An external model validation type approach was implemented using the final model developed in the adult population. The goodness-of-fit plots indicated that the model adequately described the observed data and allowed for estimation of exposures to support the comparison to the adult population. To confirm the initial understanding of SOF and GS-331007 exposures in adolescent subjects, population PK models for SOF and GS-331007 were reassessed utilizing a combination of adult and adolescent data to enhance identifiability and stability of the models. was amended to evaluate inter-occasion variability on SOF Ka and Vc/F for its influence on the distribution of ETA2 (inter-individual variability on Vc/F). The addition of inter-occasion variability on Vc corrected the bimodality of ETA2 is shown in Figure 3.

Figure 3. Comparison of SOF ETA2 distribution from original and amended report QP-2017-1002



2.3.3. Pharmacodynamics

Mechanism of action

The pharmacodynamics of SOF is well established. This agent (a nucleotide NS5B 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.

2.3.4. Discussion on clinical pharmacology

It is acknowledged that no substantial difference in drug exposure is expected in an adolescent patient population (12-18 years) compared to the adult patient population. Adult and adolescent SOF and GS-331007 data, respectively, has been pooled in the model development. Individual model predictions have been obtained for both sofosbuvir and GS-331007.

Initially, in the population PK analyses, all samples below LLOQ were discarded from the analysis which can be accepted if the fraction of excluded samples is relatively low. It is acknowledged that the MAH is planning to improve the rate of samples below limit of quantification, and that the BQL samples have been taken into account in the updated modelling approach.

The MAH is also strongly advised to develop a more sensitive bioanalytical method for sofosbuvir for coming paediatric cohorts. If more patients are excluded from the analysis, the comparison of predicted exposures between adult and paediatric patients will become inconclusive due to data loss.

For upcoming population PK analyses, in younger patients and patients with lower body weight, it will become essential to assess a dependence on body weight in the PK models. In future applications of population PK analyses of sofosbuvir and GS-331007 in paediatric populations, it is important that the model parameters are estimated on the paediatric data and that relevant covariate relations are investigated in the model(s).

2.3.5. Conclusions on clinical pharmacology

Roughly similar exposure in adolescents and adults has been shown without any apparent body weight dependent exposures.

2.4. Clinical efficacy

2.4.1. Main study

GS-US-334-1112 - Study Title: A Phase 2, Open-Label, Multicenter, Multi-cohort, Single-Arm Study to Investigate the Safety and Efficacy of Sofosbuvir + Ribavirin in Adolescents and Children with Genotype 2 or 3 Chronic HCV Infection

Methods

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

Study participants

This interim clinical study report (CSR) provides the data for adolescent subjects aged 12 to < 18 years (Group 1). The interim analysis was conducted after subjects in Group 1, enrolled as of 07 October 2015, had completed the posttreatment Week 12 visit or had prematurely discontinued from the study.

Number of participants

Approximately 50 subjects were planned for inclusion in Group 1 (12 to < 18 years old)

Analysed:

- Full Analysis Set: 50
- Safety Analysis Set: 50
- PK Analysis Set: 50

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
5. Treatment experienced subjects: must have had prior treatment failure to a regimen including IFN either with or without RBV that was completed at least 8 weeks prior to Day 1.
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 genotype 2 or genotype 3 HCV as determined at screening
8. HCV RNA ≥ 1000 IU/mL at screening
9. Adequate hematologic function (absolute neutrophil count ≥ 1500/mm3; haemoglobin ≥ 12 g/dL for males and ≥ 11g/dL for females.)
10. Negative serum beta-human chorionic gonadotropin pregnancy test (for females of childbearing potential only
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

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
3. 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)
4. Chronic liver disease of a non-HCV aetiology (eg, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency)
5. α-fetoprotein > 50 ng/mL
6. Serum creatinine > 1.5 mg/dL
7. Estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73m2, as calculated by the Schwartz Formula
8. Evidence of hepatocellular carcinoma or other malignancy (with the exception of certain resolved skin cancers)
9. Coinfection with HIV, acute hepatitis A virus (HAV), or hepatitis B virus (HBV)

10. Significant cardiovascular, pulmonary or neurological disease
11. Evidence of a gastrointestinal malabsorption syndrome that may have interfered with absorption of orally administered medications
12. History of solid organ or bone marrow transplantation
13. Chronic daily nonsteroidal anti-inflammatory drug therapy
14. Systemic corticosteroid use for ≥ 5 days (pulmonary/nasal administration was permitted)
15. Investigational agents taken within the past 28 days (except with the expressed approval of the sponsor)
16. Clinically-relevant alcohol or drug abuse within 12 months of screening. A positive drug screen excluded subjects unless it could be explained by a prescribed medication; the diagnosis and prescription must have been approved by the investigator.
17. Known hypersensitivity to the study drugs, the metabolites or formulation excipients
18. Any other condition (including alcohol or substance abuse) or prior therapy that, in the opinion of the investigator, would have made the subject unsuitable for the study or unable to comply with dosing requirements
19. Use of any prohibited concomitant medications as described in Section 7.4.7 within 28 days of the Day 1 visit
20. Psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 5 years. Subjects with psychiatric illness (without the prior mentioned conditions) that was well controlled on a stable treatment regimen for at least 12 months prior to enrolment or had not required medication in the last 12 months may have been included.

Treatments

In the treatment phase, subjects received the following treatments:

- Subjects with genotype 2 HCV infection: SOF 400 mg + RBV for 12 weeks

- Subjects with genotype 3 HCV infection: SOF 400 mg + RBV for 24 weeks

Objectives

The primary objectives of this study were as follows:

- Pharmacokinetic (PK) lead-in phase: To evaluate the steady state PK and confirm the dose of SOF in HCV-infected paediatric subjects
- Treatment phase: To evaluate the safety and tolerability of SOF+RBV for 12 or 24 weeks in HCV-infected paediatric subjects with genotype 2 or genotype 3 HCV infection, respectively

The secondary objectives of this study were as follows:

PK lead-in phase:

- To evaluate the safety and tolerability of 7 days of dosing of SOF+RBV in HCV-infected paediatric subjects

Treatment phase:

- To determine the antiviral efficacy of SOF+RBV treatment in subjects with genotype 2 or genotype 3 HCV infection separately, as assessed by the proportion of subjects with SVR12
- To determine the antiviral efficacy of SOF+RBV treatment in subjects with genotype 2 or genotype 3 HCV infection separately, 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 SOF during treatment and after completion of treatment
- To evaluate the palatability of SOF oral granules at Day 1, as applicable.
- To evaluate the effect of growth and development on pediatric subjects during and after treatment

The exploratory objective of this study was as follows:

- 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

Outcomes/endpoints

Efficacy

The key efficacy endpoint was SVR12, defined as HCV RNA < LLOQ 12 weeks after discontinuation of the study drug, in the Full Analysis Set.

The key efficacy endpoint analysis (for SVR12) in this interim CSR was conducted after all subjects in Group 1 (12 to < 18 years old), enrolled as of 07 October 2015, completed the posttreatment Week 12 visit or prematurely discontinued from the study.

Secondary efficacy endpoints include:

- Proportions of subjects with SVR4 and SVR24
- Proportion of Subjects with HCV RNA < LLOQ by Study Visit
- HCV RNA Absolute Values and Changes from Baseline Through End of Treatment
- Virologic Failure
- Virologic Resistance Analysis

Exploratory efficacy endpoints include:

- ALT Normalization
- Health-Related Quality of Life
- Pharmacogenomics

Subgroup analyses include:

- Age group on date of first dose of study regimen (≤ 15 years, > 15 years)
- Sex at birth (male, female)

- Race (black, non-black)
- Ethnicity (Hispanic or Latino, non-Hispanic or Latino)
- Baseline HCV RNA (< 800,000 IU/mL, ≥ 800,000 IU/mL)
- Baseline weight (≤ median, > median)
- Baseline ALT (≤ 1.5 × ULN, > 1.5 × ULN)
- IL28B genotype (CC, non-CC [further broken down to CT, TT])
- Prior HCV treatment experience (treatment naive, treatment experienced)
- IFN eligibility (IFN eligible, IFN ineligible)
- Response to prior HCV treatment (IFN intolerant, non-responder, relapse/breakthrough)
- Study treatment status (completed study treatment, discontinued study treatment)
- Adherence to study regimen (< 80%, ≥ 80%)

Safety

Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0.

Treatment-emergent AEs were defined as events that met 1 or both of the following criteria:

- Any AEs with onset dates on or after the study drug start date and no later than 30 days after the permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug

If the date of onset was incomplete, then the month and year (or year alone if month was not recorded) of onset were used to determine whether the AE was treatment emergent. All AEs discussed in this CSR were treatment emergent and are referred to as AEs for the purposes of this report.

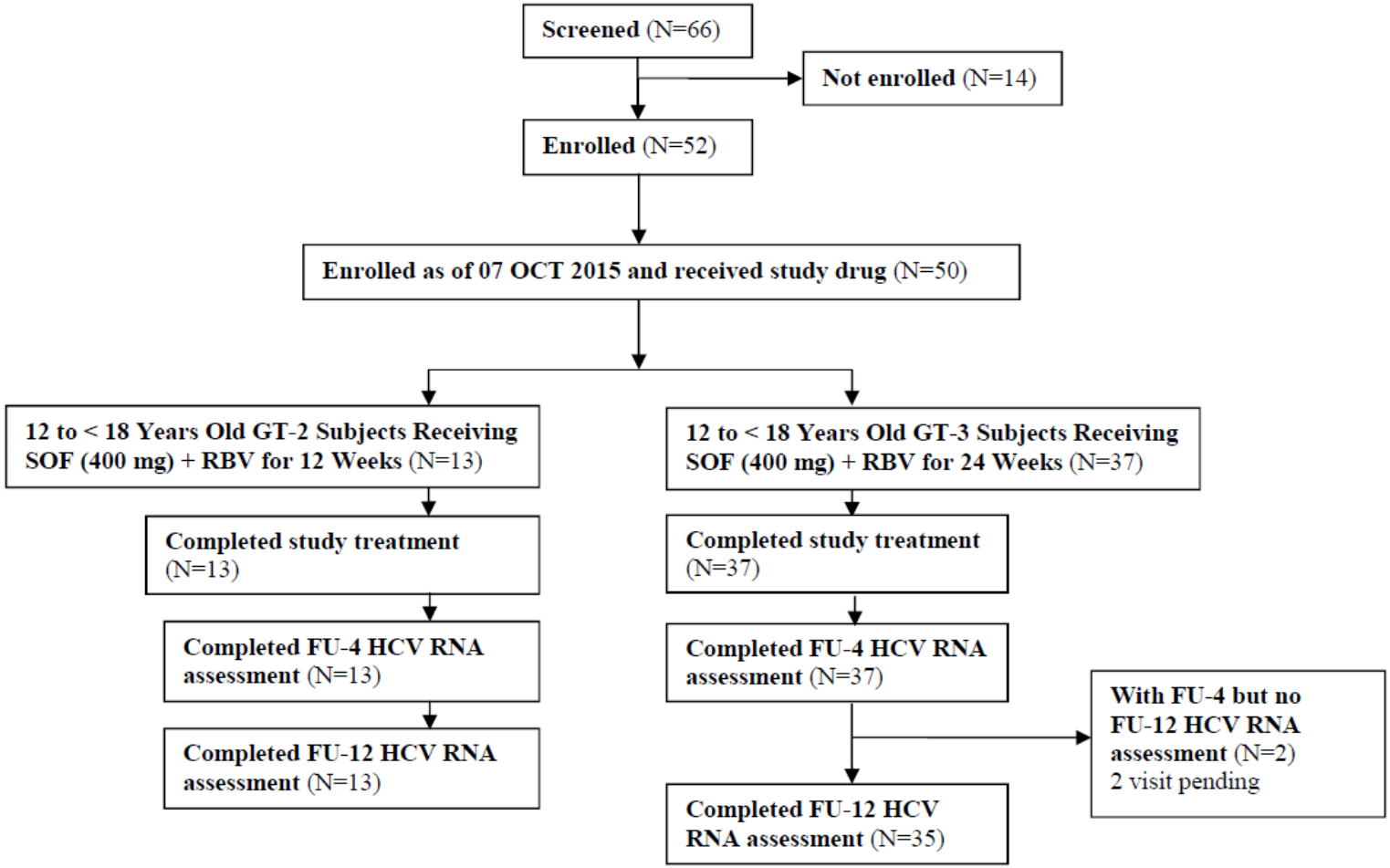
Laboratory data were summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) with corresponding changes from baseline for ALT, AST, total bilirubin, alkaline phosphatase, haemoglobin, reticulocytes, white blood cell (WBC) counts, neutrophils, lymphocytes, platelets, and INR.

Tanner Pubertal Stage, Height/Weight/Body Mass Index, Bone Age Assessments, Vital Signs and Concomitant Medications were also included among safety endpoints.

Results

Participant flow

Figure 4. GS-US-334-1112: Disposition of Subjects for Group 1 (12 to < 18 Years Old) (Screened Subjects)



Recruitment

Table 3. GS-US-334-1112: Key Dates for Group 1 (12 to < 18 Years Old)

Event	Date
First Subject Screened	07 July 2014
First Subject Enrolled	07 October 2014
Last Subject Enrolled	07 October 2015
Last Subject Observation for this Report	15 June 2016
Last Subject Observation for the Primary Endpoint	15 June 2016
Database Finalization	12 July 2016

Subjects were included who were enrolled into the study as of 07 October 2015

Subjects were enrolled across 28 sites in the United States, Germany, United Kingdom, Italy, the Russian Federation, New Zealand, and Australia.

A total of 66 subjects were screened for Group 1, and 14 subjects (21.2%) failed screening. For the 9 screen failure subjects who did not meet eligibility criteria, the 2 primary reasons for screen failure were not meeting the inclusion criterion of infection with genotype 2 or genotype 3 HCV infection as determined at Screening (44.4%; 4 subjects) and having any other condition (including alcohol or substance abuse) or prior therapy which was specified as an exclusion criterion (22.2%; 2 subjects). Of the 5 screen failure subjects who did meet eligibility criteria, the reasons for not enrolling were withdrawal of consent (40.0%, 2 subjects), and adverse event, outside of visit window, and other (20.0%; 1 subject each). Two subjects in Group 1 were enrolled after the 07 October 2015 date and are not included in this interim report.

Of the 50 subjects enrolled in Group 1 as of 07 October 2015, all 50 received at least 1 dose of study drug and were included in the Safety Analysis Set and Full Analysis Set (13 subjects with genotype 2 HCV infection and 37 subjects with genotype 3 HCV infection).

All subjects (100.0%) completed study treatment.

Conduct of the study

Study GS-US-334-1112 was conducted under a US investigational new drug (IND) application and in accordance with the laws and regulations of the country in which the research was conducted, and in accordance with recognized international scientific and ethical standards, including but not limited to the International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21 CFR 312), and the European Community Directive 2001/20/EC, as well as other local legislation.

A total of 6 important protocol deviations occurred in 4 subjects during the study. Of the 4 subjects, 2 subjects had a single important deviation and 2 subjects had 2 important deviations. The majority of important protocol deviations were for deviations of wrong treatment or incorrect dose (3 of 6) and for eligibility criteria (2 of 6). Relevant protocol deviations were proportionally distributed between study sites in subjects treated with SOF+RBV for 24 weeks.

Table 4. GS-US-334-1112: Important Protocol Deviations for Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

Protocol Deviation, n (%)	Genotype 2 SOF+RBV 12 Weeks (N = 13)	Genotype 3 SOF+RBV 24 Weeks (N = 37)	Total (N = 50)
Number of Subjects with at Least 1 Important Protocol Deviation	0	4	4
Deviation of Inclusion/Exclusion Criteria	0	2	2
Informed Consent Not Obtained Properly	0	1	1
Study Medication	0	3	3

Baseline data

Table 5. GS-US-334-1112: Demographic and Baseline Characteristics for Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

Characteristic	Genotype 2 SOF+RBV 12 Weeks (N = 13)	Genotype 3 SOF+RBV 24 Weeks (N = 37)	Total (N = 50)
Age at Baseline (years)			
Mean (SD)	15 (1.9)	15 (1.8)	15 (1.9)
Median	14	16	15
Q1, Q3	13, 16	13, 16	13, 16
Min, Max	12, 17	12, 17	12, 17
Baseline Age Category			
≤ 15 years old	8 (61.5%)	18 (48.6%)	26 (52.0%)
> 15 years old	5 (38.5%)	19 (51.4%)	24 (48.0%)
Sex (n, %)			
Male	8 (61.5%)	21 (56.8%)	29 (58.0%)
Female	5 (38.5%)	16 (43.2%)	21 (42.0%)
Race			
Black or African American	2 (15.4%)	0	2 (4.0%)
White	11 (84.6%)	34 (91.9%)	45 (90.0%)
Asian	0	1 (2.7%)	1 (2.0%)
Hawaiian or Pacific Islander	0	1 (2.7%)	1 (2.0%)
Other	0	1 (2.7%)	1 (2.0%)
Ethnicity			
Hispanic or Latino	0	2 (5.4%)	2 (4.0%)
Not Hispanic or Latino	13 (100.0%)	35 (94.6%)	48 (96.0%)
Baseline Body Mass Index (kg/m^2)			
Mean (SD)	21.1 (3.39)	22.8 (4.27)	22.4 (4.09)
Median	21.2	22.0	21.8
Q1, Q3	19.0, 22.5	19.7, 24.7	19.3, 24.0
Min, Max	16.1, 28.2	16.1, 32.4	16.1, 32.4

Table 6. GS-US_334-1112: Baseline Disease Characteristics for Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

Disease Characteristic	Genotype 2 SOF+RBV 12 Weeks (N = 13)	Genotype 3 SOF+RBV 24 Weeks (N = 37)	Total (N = 50)
HCV Genotype			
2	6 (46.2%)	0	6 (12.0%)
2b	5 (38.5%)	0	5 (10.0%)
2a/2c	2 (15.4%)	0	2 (4.0%)
3	0	1 (2.7%)	1 (2.0%)
3a	0	36 (97.3%)	36 (72.0%)
Cirrhosis			
No	4 (30.8%)	16 (43.2%)	20 (40.0%)
Unknown	9 (69.2%)	21 (56.8%)	30 (60.0%)
IL28B			
CC	3 (23.1%)	16 (43.2%)	19 (38.0%)
CT	9 (69.2%)	19 (51.4%)	28 (56.0%)
TT	1 (7.7%)	2 (5.4%)	3 (6.0%)
Baseline HCV RNA (log10 IU/mL)			
Mean (SD)	5.9 (0.98)	6.2 (0.78)	6.1 (0.83)
Median	6.2	6.2	6.2
Q1, Q3	5.0, 6.6	5.7, 6.9	5.7, 6.8
Min, Max	3.6, 6.9	4.5, 7.3	3.6, 7.3
Baseline HCV RNA Category			
$<$ 800,000 IU/mL	5 (38.5%)	12 (32.4%)	17 (34.0%)
$\geq$ 800,000 IU/mL	8 (61.5%)	25 (67.6%)	33 (66.0%)
Baseline HCV RNA Category			
$<$ 6 $\log_{10}$ IU/mL	5 (38.5%)	16 (43.2%)	21 (42.0%)
$\geq$ 6 $\log_{10}$ IU/mL	8 (61.5%)	21 (56.8%)	29 (58.0%)
Baseline ALT (U/L)			
Mean (SD)	37 (25.1)	61 (58.8)	55 (53.0)
Median	30	37	37
Q1, Q3	24, 46	28, 68	28, 60
Min, Max	10, 108	12, 296	10, 296
Baseline ALT Category			
$\leq$ 1.5 × ULN	12 (92.3%)	25 (67.6%)	37 (74.0%)
$>$ 1.5 × ULN	1 (7.7%)	12 (32.4%)	13 (26.0%)

Disease Characteristic	Genotype 2 SOF+RBV 12 Weeks (N = 13)	Genotype 3 SOF+RBV 24 Weeks (N = 37)	Total (N = 50)
Prior HCV Treatment Experience			
Treatment Naive	13 (100.0%)	28 (75.7%)	41 (82.0%)
Interferon Eligibility			
IFN Eligible	12 (92.3%)	27 (96.4%)	39 (95.1%)
IFN Ineligible	1 (7.7%)	1 (3.6%)	2 (4.9%)
Treatment Experienced	0	9 (24.3%)	9 (18.0%)
Response to Prior HCV Treatment			
Nonresponder	0	6 (66.7%)	6 (66.7%)
Relapse/Breakthrough	0	2 (22.2%)	2 (22.2%)
IFN Intolerant	0	1 (11.1%)	1 (11.1%)
Estimated Glomerular Filtration Rate Using Schwartz Formula (mL/min/1.73 m2)			
Mean (SD)	147.5 (25.22)	150.1 (24.27)	149.4 (24.29)
Median	143.1	149.6	146.6
Q1, Q3	137.6, 157.3	132.2, 164.2	132.9, 164.2
Min, Max	100.0, 202.1	105.6, 195.9	100.0, 202.1
Mode of HCV Infection[a]			
Contaminated Needle or IV Drug Use (Current/Past)	1 (7.1%)	0	1 (1.9%)
Blood Product Transfusion	0	5 (13.2%)	5 (9.6%)
Vertical Transmission (Infected Mother)	8 (57.1%)	28 (73.7%)	36 (69.2%)
Surgery/Operation	0	1 (2.6%)	1 (1.9%)
Unknown	5 (35.7%)	4 (10.5%)	9 (17.3%)

Outcomes and estimation

The key efficacy endpoint was SVR12, defined as HCV RNA < LLOQ 12 weeks after discontinuation of the study drug, in the Full Analysis Set. 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 7. GS-US-334-1112: SVR12 for Group 1 (12 to < 18 Years Old) (Full Analysis Set)

	Genotype 2 SOF+RBV 12 Weeks (N = 13)	Genotype 3 SOF+RBV 24 Weeks (N = 37)	Total (N = 50)
SVR12	13/13 (100.0%)	35/37 (94.6%)	48/50 (96.0%)
95% CI	75.3% to 100.0%	81.8% to 99.3%	86.3% to 99.5%
p-value (Compared to 80%)			0.003

HCV RNA was analyzed using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with an LLOQ of 15 IU/mL.

SVR12 was sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.

A missing SVR12 value was imputed as a success if it was bracketed by values that are termed successes (ie, '< LLOQ TND' or '< LLOQ detected'); otherwise, the missing SVR12 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.

The p-value was obtained from the 2-sided exact 1-sample binomial test for the superiority over the performance goal of 80%.

No subject had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse) or relapsed. All subjects with genotype 2 HCV infection treated with SOF+RBV for 12 weeks achieved SVR12.

Two of 37 subjects with genotype 3 HCV infection (5.4%) treated with SOF+RBV for 24 weeks achieved SVR4, but did not return for their posttreatment Week 12 visit (categorized as "other" in Table 8).

Table 8. GS-US-334-1112: Virologic Outcomes for Group 1 (12 to < 18 Years Old) (Full Analysis Set)

	Genotype 2 SOF+RBV 12 Weeks (N = 13)	Genotype 3 SOF+RBV 24 Weeks (N = 37)
SVR12	13/13 (100.0%)	35/37 (94.6%)
Overall Virologic Failure	0/13	0/37
Relapse	0/13	0/37
Study Drug Completer	0/13	0/37
Study Drug Non-Completer	0/0	0/0
On-Treatment Virologic Failure	0/13	0/37
Other	0/13	2/37 (5.4%)

HCV RNA was analyzed using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with an LLOQ of 15 IU/mL.
Relapse = confirmed HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at the last on-treatment visit.
On-treatment virologic failure = breakthrough (confirmed HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while on treatment), rebound (confirmed >1 log10 IU/mL increase in HCV RNA from nadir while on treatment), or non-response (HCV RNA persistently ≥ LLOQ through 8 weeks of treatment).
Other = subject who did not achieve SVR12 and did not meet virologic failure criteria.

2.4.2. Discussion on clinical efficacy

In this limited dataset, the estimates of clinical efficacy are high and indicate that the combination of SOF+RBV is effective in the treatment of adolescents with GT2 and GT3 HCV infection.

Only GT2 and GT3 patients were included in the study, and there were no patients with verified cirrhosis. It is possible to extrapolate efficacy from adults to adolescents infected with other HCV genotypes as well as cirrhotic patients from adult efficacy data as long as the drug exposure is similar, which is anticipated.

2.4.3. Conclusions on the clinical efficacy

Given that exposure is comparable to that of adult phase 3 studies, it can be concluded that SOF is effective in the treatment of adolescents with HCV infection.

2.5. Clinical safety

Introduction

In adults, the safety profile of the sofosbuvir is considered favourable and well-characterized in subjects with compensated liver disease and GFR > 30 ml/min.

Patient exposure

The mean (SD) duration of exposure to the study regimen was 12.1 (0.16) weeks for subjects treated for 12 weeks, and 24.1 (0.17) weeks for subjects treated for 24 weeks. The majority of subjects in the 12-week treatment regimen (92.3%) received study drug for 12 weeks and the majority of subjects in the 24-week treatment regimen (91.9%) received study drug for 24 weeks.

Table 9. GS-US-334-1112: Duration of Exposure to Study Regimen for Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

	SOF+RBV 12 Weeks (N = 13)	**SOF+RBV 24 Weeks (N = 37)**
Duration of Exposure to Study Regimen (Weeks)		
Mean (SD)	12.1 (0.16)	24.1 (0.17)
Median	12.1	24.1
Q1, Q3	12.0, 12.1	24.0, 24.1
Min, Max	11.9, 12.4	23.9, 24.6
Cumulative N (%) of Subjects Exposed Through		
Baseline (Day 1)	13 (100.0%)	37 (100.0%)
Week 1 (Day 7)	13 (100.0%)	37 (100.0%)
Week 2 (Day 14)	13 (100.0%)	37 (100.0%)
Week 4 (Day 28)	13 (100.0%)	37 (100.0%)
Week 8 (Day 56)	13 (100.0%)	37 (100.0%)
Week 12 (Day 84)	12 (92.3%)	37 (100.0%)
Week 16 (Day 112)	NA	37 (100.0%)
Week 20 (Day 140)	NA	37 (100.0%)
Week 24 (Day 168)	NA	34 (91.9%)

Weeks on Study Drug = (last dose date of individual study drug - first dose date of individual study drug + 1) divided by 7.

Adverse events

The majority of subjects treated with SOF+RBV for 12 or 24 weeks (92.3% and 75.7%, respectively) experienced at least 1 AE. All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity with the exception of 1 subject treated with SOF+RBV for 24 weeks who experienced a Grade 3 AE of shoulder trauma. No subjects experienced SAEs. No deaths were reported. No subject prematurely discontinued SOF due to an AE. One subject had a modification or interruption of RBV dosing.

Table 10. GS-US-334-1112: Overall Summary of Adverse Events for Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

Number (%) of Subjects Experiencing Any	SOF+RBV 12 Weeks (N = 13)	SOF+RBV 24 Weeks (N = 37)
AE	12 (92.3%)	28 (75.7%)
Grade 3 or Above AE	0	1 (2.7%)
Treatment-Related AE	3 (23.1%)	19 (51.4%)
Grade 3 or Above Treatment-Related AE	0	0
SAE	0	0
Treatment-Related Serious AE	0	0
AE Leading to Premature Discontinuation of SOF	0	0
AE Leading to Premature Discontinuation of RBV	0	0
AE Leading to Interruption of SOF	0	0
AE Leading to Modification or Interruption of RBV	0	1 (2.7%)
Deaths	0	0

The denominator for percentages was based on the number of subjects in the safety analysis set.

Table 11. GS-US-334-1112: Treatment-Related Adverse Events Reported for > 1 Subject in Any Treatment Group in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

	SOF+RBV 12 Weeks (N = 13)	SOF+RBV 24 Weeks (N = 37)
Number (%) of Subjects Experiencing Any Treatment-Related AE	3 (23.1%)	19 (51.4%)
Nausea	0	7 (18.9%)
Asthenia	1 (7.7%)	4 (10.8%)
Headache	0	5 (13.5%)
Fatigue	0	3 (8.1%)
Abdominal pain upper	0	2 (5.4%)
Alopecia	0	2 (5.4%)
Decreased appetite	0	2 (5.4%)
Dizziness	0	2 (5.4%)

Adverse events were mapped according to MedDRA Version 19.0.

Subjects were counted once for each AE preferred term.

AEs were related to treatment if related to study treatment = "Related" on the AE CRF.

Data included to last dose date of any study drug + 30 days.

Serious adverse event/deaths/other significant events

All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity with the exception of 1 subject treated with SOF+RBV for 24 weeks who experienced a Grade 3 joint injury (shoulder trauma). This AE was not

considered serious or related to study drug by the investigator. No subject experienced a Grade 4 (life threatening) AE. No deaths were reported during the study for subjects enrolled in Group 1 differs from what is seen in the adult population.

Laboratory findings

Haematology

Grade 3 haematology laboratory abnormalities were reported for decreased haemoglobin in 3 of 37 subjects (8.1%) and decreased white blood cells in 1 of 37 subjects (2.7%) treated with SOF+RBV for 24 weeks. There were no Grade 3 or 4 haematology laboratory abnormalities in subjects treated with SOF+RBV for 12 weeks, and no Grade 4 haematology laboratory abnormalities in subjects treated with SOF+RBV for 24 weeks. All Grade 3 haematology laboratory abnormalities were isolated and transient.

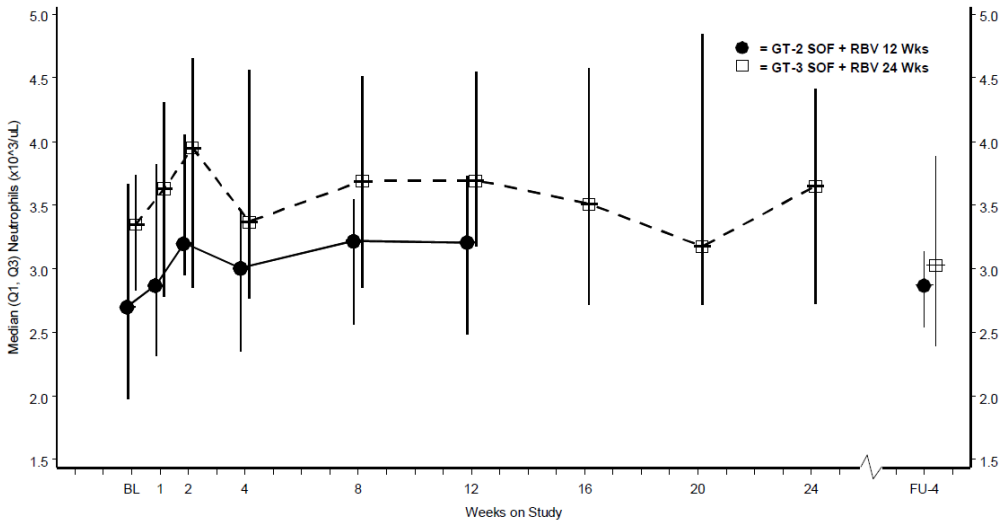
There were no subjects with post-baseline haemoglobin < 10 g/d, the protocol guideline threshold for RBV dose reduction/modification.

Table 12. GS-US-334-1112: Grade 3 Haematology Laboratory Abnormalities for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

	SOF+RBV 12 Weeks (N = 13)	SOF+RBV 24 Weeks (N = 37)
Hematology		
Hemoglobin		
Grade 3	0	3 (8.1%)
WBC		
Grade 3	0	1 (2.7%)

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

Figure 5. GS-US-334-1112: Median (Q1, Q3) Neutrophils (x103/µL) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)



GT-2 SOF + RBV 12 Wks (n=):	13	13	13	12	13	13				12
GT-3 SOF + RBV 24 Wks (n=):	37	37	37	37	36	36	33	34	32	26

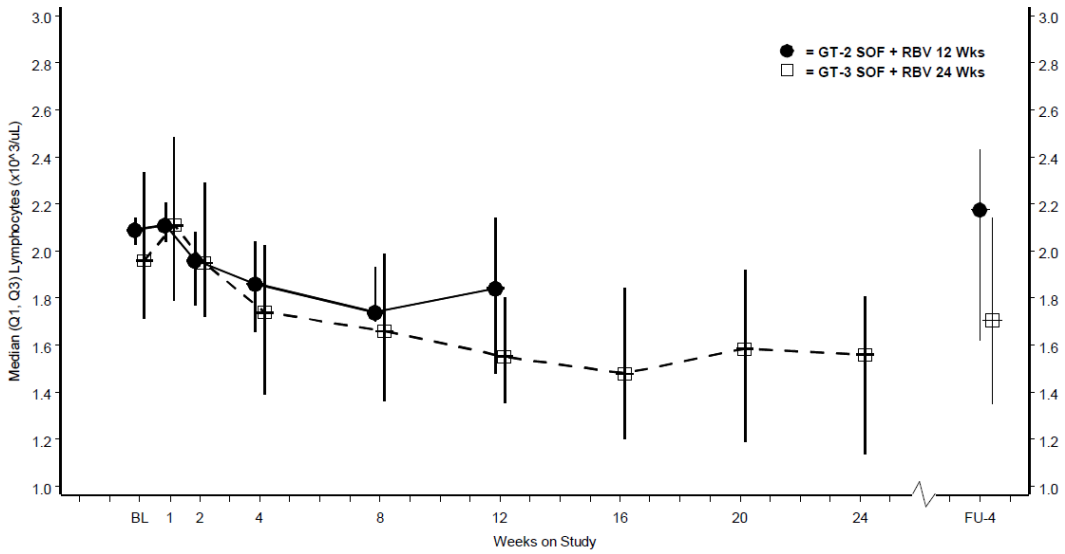
BL = baseline; FU-x = follow-up visit at x weeks after discontinuing treatment

Baseline values were the last available value on or prior to the first dose date of any study drug.

Data included to last dose date of any study drug + 30 days.

Offsets were applied to treatment groups.

Figure 6. GS-US-334-1112: Median (Q1, Q3) Lymphocytes (x103/µL) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)



GT-2 SOF + RBV 12 Wks (n=):	13	13	13	12	13	13				12
GT-3 SOF + RBV 24 Wks (n=):	37	37	37	37	36	36	33	34	32	26

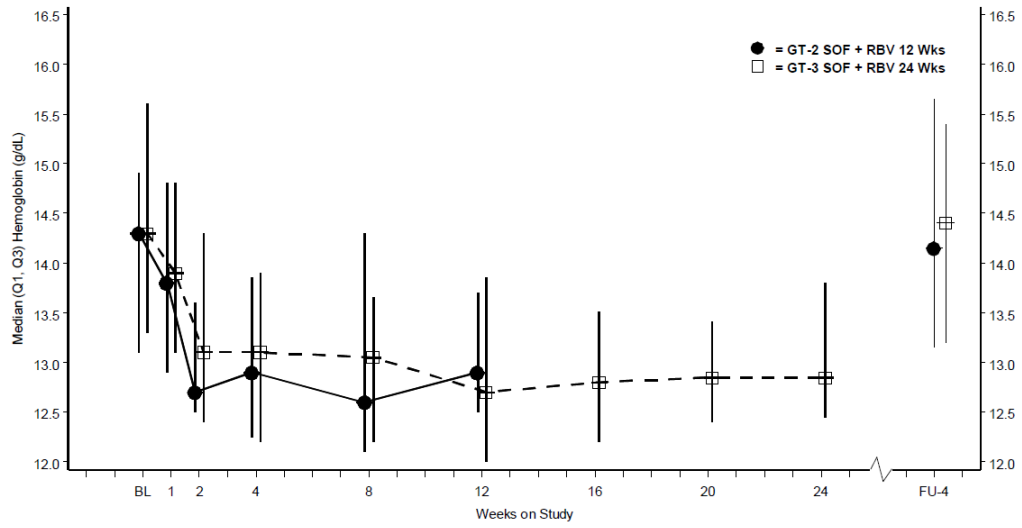
BL = baseline; FU-x = follow-up visit at x weeks after discontinuing treatment

Baseline values were the last available value on or prior to the first dose date of any study drug.

Data included to last dose date of any study drug + 30 days.

Offsets were applied to treatment groups.

Figure 7. GS-US-334-1112: Median (Q1, Q3) Haemoglobin (g/dL) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)



GT-2 SOF + RBV 12 Wks (n=):	13	13	13	12	13	13				12
GT-3 SOF + RBV 24 Wks (n=):	37	37	37	37	36	36	33	34	32	26

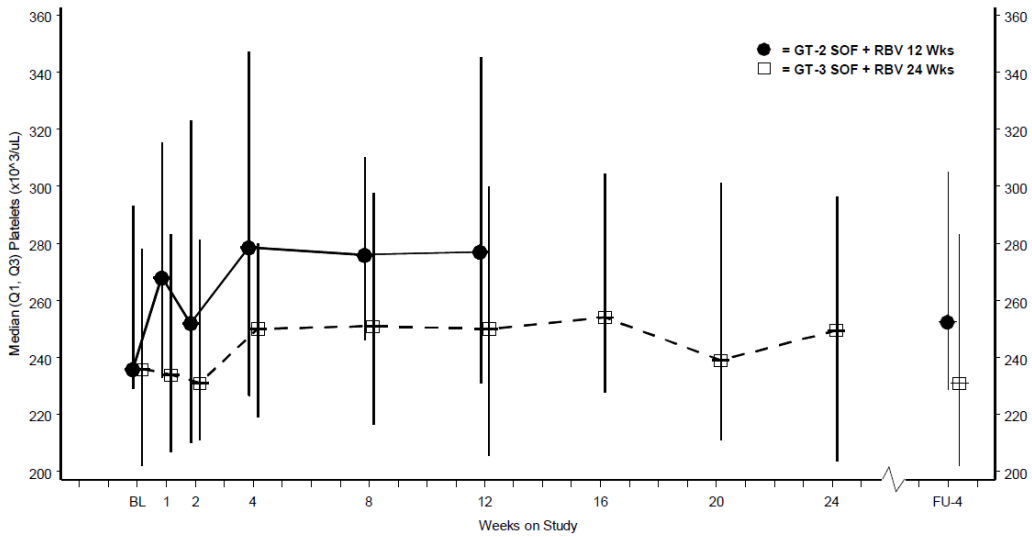
BL = baseline; FU-x = follow-up visit at x weeks after discontinuing treatment

Baseline values were the last available value on or prior to the first dose date of any study drug.

Data included to last dose date of any study drug + 30 days.

Offsets were applied to treatment groups.

Figure 8. GS-US-334-1112: Median (Q1, Q3) Platelets (x103/µL) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)



GT-2 SOF + RBV 12 Wks (n=):	13	13	13	12	13	13				12
GT-3 SOF + RBV 24 Wks (n=):	37	37	37	37	36	36	33	34	32	26

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

Baseline values were the last available value on or prior to the first dose date of any study drug.

Data included to last dose date of any study drug + 30 days.

Offsets were applied to treatment groups.

Chemistry

Grade 3 chemistry laboratory abnormalities for INR and total bilirubin were reported, and 1 Grade 4 laboratory abnormality of increased INR was reported. All Grade 3 or 4 coagulation or chemistry

laboratory abnormalities occurred in subjects treated with SOF+RBV for 24 weeks. All but 1 Grade 3 and Grade 4 chemistry laboratory abnormalities were isolated incidents and did not remain at Grade 3 or 4 for more than one assessment. One subject, with a medical history of Gilbert's syndrome and jaundice from screening, had a Grade 3 increased total bilirubin at Weeks 1 and 2, and Weeks 8 through 20. The subject had a Grade 2 increased total bilirubin level at baseline. This subject had an AE of blood bilirubin increase of Grade 2 severity with an onset on study Day 7 which was resolved by posttreatment Day 29. The AE of bilirubin increase was considered not related to study drug by the investigator and did not result in a change in dosing regimen.

Table 13. GS-US-334-1112: Grade 3 or 4 Coagulation or Chemistry Laboratory Abnormalities for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)

	SOF+RBV 12 Weeks (N = 13)	SOF+RBV 24 Weeks (N = 37)
Coagulation		
INR		
Grade 3	0	1 (2.7%)
Grade 4	0	1 (2.7%)
Chemistry		
Total Bilirubin (Hyperbilirubinemia)		
Grade 3	0	2 (5.4%)

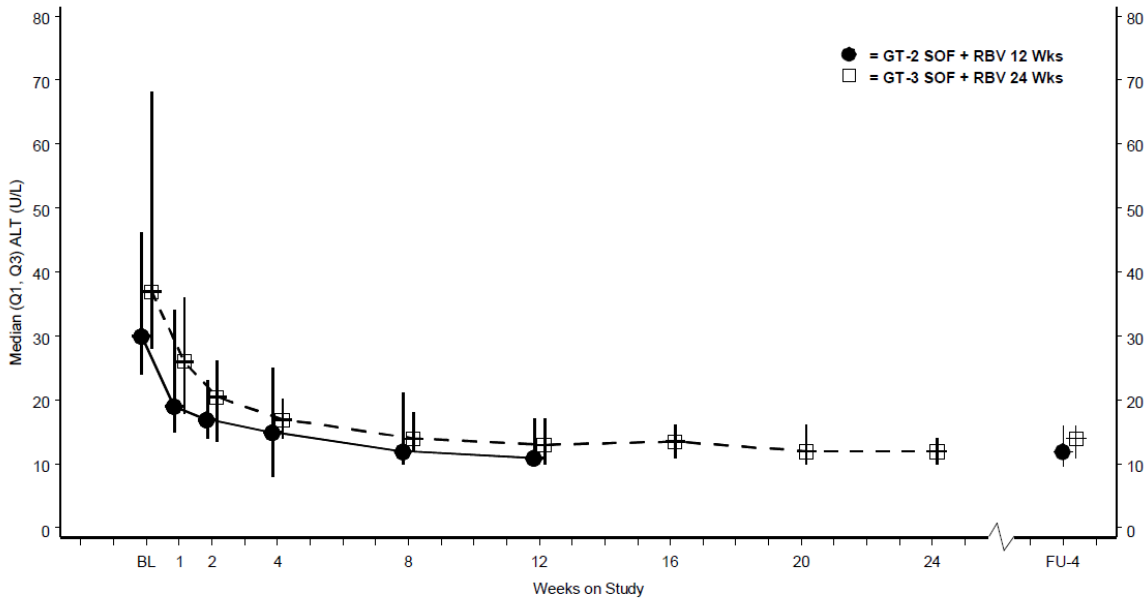
Laboratory abnormalities were graded using GSI Grading Scale, 1 April 2015 version.

Toxicity grade must have increased at least 1 toxicity grade from baseline value (missing was considered grade 0) to be included.

Subjects counted once at maximum toxicity grade (hyper [+] and hypo [-] when applicable) for each laboratory test.

Data included up to the last dose date of any study drug + 30 days.

Figure 9. GS-US-334-1112: Median (Q1, Q3) ALT (U/L) by Visit for Subjects in Group 1 (12 to < 18 Years Old) (Safety Analysis Set)



	BL	1	2	4	8	12	16	20	24	FU-4
GT-2 SOF + RBV 12 Wks (n=):	13	13	13	11	13	13				12
GT-3 SOF + RBV 24 Wks (n=):	37	37	36	37	37	37	36	37	34	26

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

Baseline values were the last available value on or prior to the first dose date of any study drug.

Data included to last dose date of any study drug + 30 days.

Offsets were applied to treatment groups.

The mean (SD) height at baseline for subjects treated with SOF+RBV for 12 and 24 weeks was 161.8 (13.53) and 165.6 (9.20) cm, respectively. No clinically relevant changes from baseline in body height or body height percentiles were observed during the study. At posttreatment Week 12, the mean (SD) change from baseline in body height was 1.4 (1.65) and 1.1 (1.75) cm, respectively. The mean (SD) body height percentile at baseline for subjects treated with SOF+RBV for 12 and 24 weeks was 40.36 (34.596) and 50.00 (25.904), respectively. At posttreatment Week 12, the mean (SD) body height percentile was 41.14 (32.960) and 48.24 (26.705), respectively.

2.5.1. Discussion on clinical safety

In this limited safety dataset, there are no signs that the safety profile of SOF in adolescent patients differs from what is previously established for adults. The adverse events related to haematology are well-known effects of RBV treatment.

2.5.2. Conclusions on clinical safety

The safety profile of SOF in adolescents is favourable, given that exposure is similar to that of adult pivotal studies.

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 5.2 is acceptable.

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.

Safety concerns

Changes are highlighted in bold.

Table 14. Safety concerns

Important Identified Risks	Cardiac arrhythmia (bradycardia) when sofosbuvir and other DAAs are used concomitantly with amiodarone
Important Potential Risks	Cardiac arrhythmia (bradycardia), in particular when concomitantly used with daclatasvir and other bradycardic medicines
	Drug-drug interaction with potent intestinal Pgp inducers
Missing Information	Safety in children **(<12 years of age)**
	Safety in pregnant or breastfeeding women
	Safety in patients with severe renal impairment or end-stage renal disease

Pharmacovigilance plan

Only the below study was modified as follows:

Table 15. Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan (Categories 1-3)

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-334-1112 – A Phase 2, Open-Label, Multicenter, Multi-Cohort, Single-Arm Study to Investigate the Safety and Efficacy of Sofosbuvir Plus Ribavirin in Adolescents and Children with	To evaluate the PK, efficacy, and safety of SOF+RBV for ***12*** or 24 weeks in adolescents and children	*Missing information*: Safety in children **(<12 years of age)**	Started	**Interim study report September 2016** Final study report Q3 2018

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Chronic Genotype 2 or 3 HCV Infection				

Risk minimisation measures

Only the missing information “safety in children” was modified as follows:

Table 16. Summary Table of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Missing information		
Safety in children **(<12 years of age)**	The EU SmPC (Sections 4.2, 4.4, 4.8, and 5.2) states that the safety, efficacy, and PK of SOF in pediatric ~~subjects~~**patients <12 years of age** have not been established and that SOF is not recommended for use in children**pediatric patients <12 years of age.** ~~and adolescents < 18 years of age~~. Study GS-US-334-1112 is ongoing and will investigate the safety and efficacy of SOF+RBV in adolescents and children with chronic genotype 2 or 3 HCV infection. **Further information on the safety in children (<12 years of age) will be obtained at the conclusion of study GS-US-334-1112.** A PIP for SOF has been agreed with the PDCO.	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, Sovaldi (sofosbuvir) 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.

The treatment regimens with DAAs available for adults with HCV infection have created an opportunity to address this unmet medical need in the paediatric population. SOF has shown a favourable safety profile and high efficacy in adults with chronic HCV across a range of genotypes, treatment experience, and disease status.

3.1.3. Main clinical studies

The purpose of Study GS-US-334-1112 is to demonstrate the safety and tolerability of SOF+RBV in children and adolescents (3 to < 18 years old), and to assess the efficacy of SOF+RBV in this population.

In addition, all paediatric subjects previously treated with a Gilead HCV DAA in a company-sponsored study fulfilling the entry criteria, will be eligible to enrol into a registry study (Study GS-US-334-1113) to be followed for a total of 5 years for assessments of growth, quality of life, and long-term viral suppression.

3.2. Favourable effects

Sofosbuvir 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 adolescents. Only GT2 and GT3 non-cirrhotic patients were included in the study, and were treated with SOF+RBV 12 or 24 weeks, in accordance with adult recommendations.

3.3. Uncertainties and limitations about favourable effects

There are no identified uncertainties of regulatory importance.

3.4. Unfavourable effects

The safety profile and tolerability of sofosbuvir is favourable in adults, and there are no indications in this limited safety dataset that the safety profile is any different in adolescents. The safety profile of ribavirin is as anticipated based on extensive clinical trial and real life experience.

3.5. Uncertainties and limitations about unfavourable effects

There are no identified uncertainties of regulatory importance.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Sofosbuvir provides an important addition to the pharmacological armamentarium in adolescents, as the currently approved treatment options (pegylated interferon in combination with ribavirin) has a less favourable efficacy and safety profile.

Unfavourable effects are generally few and in line with the safety profile in observed adults.

3.6.2. Balance of benefits and risks

There are no a priori reasons to anticipate that the 400 mg dose of sofosbuvir, approved for adults, would yield different exposure in adolescents aged 12 to <18 years. Indeed, the high efficacy and tolerability seen in this limited experience in adolescents are as anticipated. It is recognised that drug exposure is similar in adolescents and adults.

In the general case, for direct acting antiviral therapy against HCV, a demonstration of similar exposure in a paediatric patient stratum would allow for bridging to the full set of clinical situations for which the drug is recommended in adults. In this case, however, it is notable that sofosbuvir is recommended in combination with interferon and ribavirin for genotypes 1, 4 and 5, whereas interferon-free therapy is recommended in genotypes 2 and 3. As stated, interferon therapy has an unfavourable safety profile and

is no longer recommended per treatment guidelines. In patients that are not fully grown, a 48 week course of interferon has been associated with permanent loss of adult stature, and this risk is considered highest when treating during the pubertal growth spurt. While it is recognised that the interferon course when using sofosbuvir would be only of 12 weeks duration, it still does not seem presently relevant to provide a recommendation in 4.2 on the use of interferon-based therapy in adolescents. Therefore, the CHMP only recommend interferon-free therapy in GTs 2 and 3 where this is relevant.

3.7. Conclusions

The overall B/R of sofosbuvir 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, II, IIIA 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 5.2) are updated in accordance.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.
Furthermore, the Product Information is brought in line with the latest QRD template version 10.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0178/2014 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 5.2) are updated in accordance.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.
Furthermore, the Product Information is brought in line with the latest QRD template version 10.

Summary

Please refer to the Scientific Discussion Sovaldi EMEA/H/C/002798/II/0036.