14 September 2023
EMA/412280/2023
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Harvoni

ledipasvir / sofosbuvir

Procedure no: EMEA/H/C/003850/P46/023

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	2023-07-17	2023-07-14
☐	CHMP Rapporteur Assessment Report	2023-08-21	2023-08-18
☐	CHMP members comments	2023-09-04	2023-09-04
☐	Updated CHMP Rapporteur Assessment Report	2023-09-07	n.a.
☒	CHMP adoption of conclusions:	2023-09-14	2023-09-14

Table of contents

1. Introduction 4

2. Scientific discussion 4

2.1. Information on the development program 4
2.2. Information on the pharmaceutical formulation used in the study 4
2.3. Clinical aspects 4
2.3.1. Introduction 4
2.3.2. Clinical study 5
2.3.3. Discussion on clinical aspects 22

3. Rapporteur's overall conclusion and recommendation 22

Fulfilled: 22

1. Introduction

On 29-JUN-2023, the MAH submitted a completed paediatric study for Sovaldi (sofosbuvir [SOF]), Harvoni (ledipasvir/sofosbuvir [LDV/SOF]), Epclusa (sofosbuvir/velpatasvir [SOF/VEL] and Vosevi (sofosbuvir/ velpatasvir/ voxilaprevir [SOF/VEL/VOX]), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study GS-US-334-1113: *A Long Term Follow-up Registry for Adolescent and Pediatric Subjects Who Received a Gilead Hepatitis C Virus Direct Acting Antiviral (DAA) in Gilead-Sponsored Chronic Hepatitis C Infection Trials* is a standalone study.

2.2. Information on the pharmaceutical formulation used in the study

No study drug was administered during the study. This was a long-term observational follow-up registry.

Available formulations for paediatric patients

Sovaldi (SOF): 400 mg and 200 mg tablets; 150 mg and 200 mg oral granules in sachets.

Harvoni (LDV/SOF): 90 mg/400 mg and 45 mg/200 mg fixed dose combination (FDC) tablets; 33.75 mg/150 mg and 45 mg/200 mg oral granules in sachets.

Epclusa (SOF/VEL): 400 mg/100 mg and 200 mg/50 mg FDC tablets; 200 mg/50 mg and 150 mg/37.5 mg granules in sachets.

Vosevi (SOF/VEL/VOX): 400 mg/100 mg/100 mg and 200 mg/50 mg/50 mg FDC tablets

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

The phase 4 study GS-US-334-1113: *A Long Term Follow-up Registry for Adolescent and Pediatric Subjects Who Received a Gilead Hepatitis C Virus Direct Acting Antiviral (DAA) in Gilead-Sponsored Chronic Hepatitis C Infection Trials*

2.3.2. Clinical study

Study GS-US-334-1113

Description

This study enrolled adolescent and paediatric participants who received at least 1 of 4 of the MAH's hepatitis C virus (HCV) direct acting antivirals (DAAs) SOF, LDV/SOF, SOF/VEL and SOF/VEL/VOX while participating in MAH-sponsored chronic hepatitis C clinical studies regardless of whether the participant achieved a sustained virologic response (SVR). Once enrolled, participants were followed for up to 5 years.

Methods

Study participants

Inclusion Criteria

Subjects met all of the following inclusion criteria to be eligible for participation in the registry:

1. Have previously participated in a MAH-sponsored chronic hepatitis C study as an adolescent or paediatric subject and received at least one of MAH's HCV DAAs;
2. Parent or legal guardian able to provide written, informed consent and willing to comply with the visit schedule and subject able to provide written assent, if they have the ability to read and write, as determined by IRB/IEC/local requirements and Investigator's discretion, OR subject either able to provide written assent, if they have the ability to read and write, as determined by IRB/IEC/local requirements and Investigator's discretion.

Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in this registry.

1. Subject is currently receiving or plans to initiate a new course of hepatitis C therapy including any investigational drug or device during the course of the follow-up registry.

Treatments

This was a long-term follow-up registry study and no investigational medicinal product was administered. The HCV regimens prior received in the parent studies was used as treatment groups for analysis purpose. All the parent studies included in this registry are GS-US-334-1112, GS-US-337-1116, GS-US-342-1143, and GS-US-367-1175.

Objectives and outcomes/endpoints

Primary Objective	Primary Endpoints
• To determine the long-term safety of anti-hepatitis C virus (HCV) regimens in the pediatric population as determined by assessments of growth and development	• Growth data by visit grouped by age and gender • Development by Tanner Pubertal Stage assessment
Secondary Objectives	**Secondary Endpoints**
• To determine whether subsequent detection of HCV RNA in participants who relapse following a sustained virologic response (SVR) represents the re-emergence of pre-existing virus, the development of resistance mutations, or whether it is due to re-infection • To characterize resistance mutations and the persistence of resistance mutations in pediatric participants who did not achieve SVR	• The proportion of participants maintaining SVR at each visit • The proportion of participants with detectable HCV RNA due to re-emergence of pre-existing virus through each visit • The proportion of participants with detectable HCV resistance mutations through each visit • The proportion of participants with detectable HCV RNA due to re-infection through each visit
Exploratory Objective	**Exploratory Endpoint**
• To assess quality of life (QOL) following treatment in a Gilead Sciences (Gilead)–sponsored chronic hepatitis C (CHC) study	• Quality of life following treatment in a Gilead-sponsored CHC study

This observational registry followed participants for up to 5 years, or until early discontinuation from the study. The Day 1 visit was documented as the last visit of the previous MAH-sponsored treatment protocol. Subsequent visits occurred at Weeks 24, 48, 72, 96, 144, 192, and 240.

Assessments included (collected at each visit):

- Perform symptom-directed physical examination
- Body height and weight measurements
- Tanner Pubertal Stage assessment (if applicable)
- Complete QOL survey
- Obtain blood samples for:
    - Plasma HCV RNA (if HCV RNA is detected after nondetectable levels at Day 1 or any time throughout the study, the participant will have a repeat blood sample drawn for confirmation)
    - Viral sequencing (archive); for analysis if a participant who achieved SVR in the parent study has confirmed quantifiable HCV RNA after Day 1 and for persistence in participants who were viremic at the time of study enrollment
- Assessment of procedure-related adverse events (AEs)

Only AEs and serious adverse events (SAEs) considered to be related to study procedures as assessed by the investigator and mandated by the study protocol were reported under this study. Any treatment related SAEs were reported within the previous Gilead-sponsored treatment protocol.

Participants who began a new treatment course for HCV infection discontinued participation in this study.

Sample size

Due to the observational nature of this study, no formal power, or sample size calculations were used.

Randomisation and blinding (masking)

Not applicable

Statistical Methods

Data from this study were summarized descriptively and statistical hypothesis testing was not conducted. All continuous variables were summarized using an 8-number descriptive summary (n, mean, standard deviation, and median, first quartile (Q1), third quartile (Q3), minimum, maximum) by visit. All categorical variables were summarized by number and percentage of participants in each categorical definition.

The Full Analysis Set (FAS) included all enrolled participants who met all the study entry eligibility criteria and with at least 1 post-Day 1 (Day 1 was documented from the last visit in the initial MAH-sponsored treatment protocol, referred to as 'parent study') visit measurement available. The FAS was the primary analysis set for all analyses. Safety Analysis Set was the same as FAS in this study.

Sustained virologic response duration in days = SVR end date in registry (for participants who did not maintain SVR) or last day of registry (for participants who maintained SVR) − SVR12 date in parent study + 1.

Virologic failure was defined as having 2 consecutive blood samples (at least one week apart) with HCV RNA more than the lower limit of quantitation (LLOQ), or last available HCV RNA more than the LLOQ with no subsequent follow-up values.

Primary Endpoints

Body weight, height, body mass index (BMI), and the corresponding percentiles and Z-scores at each visit and change from baseline at each visit were summarized for the Safety Analysis Set by prior treatment group, sex, prior age group (based on the age at the entry of the parent treatment studies), and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum). A Wilcoxon signed-rank test was performed to evaluate if the median change from baseline for weight, height, BMI, and the corresponding percentiles and Z-scores at each postbaseline visit was different from zero.

A categorical frequency table of weight/height/BMI Z-scores at each visit by prior treatment group, sex, and prior age group was summarized by 6 categories (< -2, ≥ -2 to < -1, ≥ -1 to < 0, ≥ 0 to < 1, ≥ 1 to < 2, or ≥ 2). A categorical frequency table of weight/height/BMI percentile at each visit by prior treatment group, sex, and prior age group was also summarized by 3 categories (< fifth percentile, ≥ fifth to < 95th percentile, ≥ 95th percentile).

A shift table of Tanner Stages at each postbaseline visit from baseline was provided by prior treatment group, sex, and prior age group. If the assessment within the MAH-sponsored parent protocol determined the participant was at a Tanner Stage 5 or once a participant reached Tanner Stage 5 in the registry study, no further Tanner Pubertal Stage assessments were completed, and the stage was counted as Stage 5 for all the following visits in analyses.

Secondary Endpoints

The proportion of participants maintaining SVR, proportions of participants with detectable HCV RNA following SVR due to re-emergence of pre-existing virus/development of resistance mutations/re-infection, and proportion of participants with detectable HCV resistance mutations among participants who had not achieved SVR in parent study were summarized based on the plasma HCV RNA and viral sequence analysis results.

Exploratory Endpoint

The scores from Pediatric Quality of Life Inventory (PedsQL™) Version 4.0 Short Form (SF-15) were summarized with descriptive statistics at each visit by prior treatment group and prior age group.

Safety

Safety analyses were based on the Safety Analysis Set and all safety data collected on or after the enrolment through the remainder of the study were included. As there was no study treatment in this study, only AEs related to the required procedures by this study protocol were reported under this study. All deaths, regardless of relatedness to study procedures were recorded when available.

Due to disruption in study conduct as a result of the COVID-19 pandemic, some assessments were not conducted.

Results

Participant flow

- There were 461 participants enrolled in the study.
    - Four hundred twenty-six (92.4%) participants met the eligibility criteria and had available post-Day 1 visit measurements and were included in the FAS and Safety Analysis Sets (the primary analysis sets for endpoint analyses).
    - Thirty-five participants were enrolled, met all the eligibility criteria, but did not have available post-Day 1 visit measurements and thus were excluded from the FAS and Safety Analysis Set.
- Among 426 participants analysed in FAS, 253 (59.4%) participants prematurely discontinued the study, while 173 (40.6%) participants completed the study through Week 240. Of these, 65.9% (58/88 participants) from the SOF+ribavirin (RBV) treatment group, 56.2% (100/178 participants) from the LDV/SOF±RBV treatment group, 10.6% (15/142 participants) from the SOF/VEL treatment group, and 0% (0/18 participants) from the SOF/VEL/VOX treatment group completed the study.
- The most common reason for premature discontinuation from the study was "Lost to Follow Up" for participants in SOF+RBV (15.9% [14/88 participants]) and LDV/SOF±RBV (28.7% [51/178

participants]) treatment groups, and "Study Terminated by Sponsor" for participants in the SOF/VEL (48.6% [69/142 participants]) and SOF/VEL/VOX (77.8% [14/18 participants]) treatment groups.

This study is a Postmarketing Requirement (PMR) from the US Food and Drug Administration (FDA) for SOF and LDV/SOF, which requires at least 3 years of follow-up data for paediatric subjects who were treated with SOF or LDV/SOF. In addition, this study was included in the EU Risk Management Plan (RMP) as a category 'missing information' for SOF, SOF/VEL, and SOF/VEL/VOX. The MAH determined that the scientific objectives of the study would be met when all participants reached 3 years of follow-up as required in the US PMRs for SOF and LDV/SOF or had discontinued early. Consequently, when study closure occurred on 06th January 2023, not all participants had reached up to 5 years of follow-up offered in the study, and clinical sites were instructed to follow the standardized eCRF Completion guidelines to mark the subject completion reason as "Study Terminated by Sponsor" for these participants. Overall, out of the 426 study participants in the safety analysis set, 302 (70.9%) completed Week 144, or 3 years, of follow-up. The table below shows the total number of participants that reached Week 144 by treatment received in the parent study.

Duration on Registry Study by Treatment Group

	SOF+RBV	LDV/SOF +/- RBV	SOF/VEL	SOF/VEL VOX
Baseline	88 (100.0%)	178 (100.0%)	142 (100.0%)	18 (100.0%)
>=24 weeks	88 (100.0%)	172 (96.6%)	136 (95.8%)	18 (100.0%)
>=48 weeks	85 (96.6%)	163 (91.6%)	123 (86.6%)	18 (100.0%)
>=72 weeks	82 (93.2%)	158 (88.8%)	113 (79.6%)	18 (100.0%)
>=96 weeks	78 (88.6%)	147 (82.6%)	105 (73.9%)	17 (94.4%)
>=144 weeks	73 (83%)	131 (73.6%)	91 (64.1%)	7 (38.9%)
>=192 weeks	64 (72.7%)	114 (64.0%)	42 (29.6%)	0
>=240 weeks	41 (46.6%)	82 (46.1%)	9 (6.3%)	0

Table 15.8.1.3.1.1: Participant Disposition by HCV Treatment and Age Group
All Enrolled Analysis Set

	GS-US-334-1112 (SOF+RBV)				GS-US-337-1116 (LDV/SOF+/-RBV)			
	12 to < 18 years old (N=45)	6 to < 12 years old (N=38)	3 to < 6 years old (N=10)	Total (N=93)	12 to < 18 years old (N=86)	6 to < 12 years old (N=79)	3 to < 6 years old (N=27)	Total (N=192)
Participants Enrolled	45	38	10	93	86	79	27	192
Participants in Safety Analysis Set	42	36	10	88	75	77	26	178
Participants in Full Analysis Set	42	36	10	88	75	77	26	178
Study Status								
Discontinued Study	17 (40.5%)	8 (22.2%)	5 (50.0%)	30 (34.1%)	27 (36.0%)	34 (44.2%)	17 (65.4%)	78 (43.8%)
Completed Study	25 (59.5%)	28 (77.8%)	5 (50.0%)	58 (65.9%)	48 (64.0%)	43 (55.8%)	9 (34.6%)	100 (56.2%)
Reason for Premature Discontinuation of Study								
Lost to Follow-Up	7 (16.7%)	3 (8.3%)	4 (40.0%)	14 (15.9%)	23 (30.7%)	19 (24.7%)	9 (34.6%)	51 (28.7%)
Study Terminated by Sponsor	1 (2.4%)	1 (2.8%)	0	2 (2.3%)	0	1 (1.3%)	6 (23.1%)	7 (3.9%)
Withdrew Consent	4 (9.5%)	3 (8.3%)	1 (10.0%)	8 (9.1%)	4 (5.3%)	12 (15.6%)	2 (7.7%)	18 (10.1%)
Investigator's Discretion	5 (11.9%)	0	0	5 (5.7%)	0	1 (1.3%)	0	1 (0.6%)
Death	0	0	0	0	0	1 (1.3%)	0	1 (0.6%)
Protocol Violation	0	1 (2.8%)	0	1 (1.1%)	0	0	0	0
Progressive Disease	0	0	0	0	0	0	0	0

(Continued)	GS-US-342-1143 (SOF/VEL)				GS-US-367-1175 (SOF/VEL/VOX)			
	12 to < 18 years old (N=76)	6 to < 12 years old (N=55)	3 to < 6 years old (N=27)	Total (N=158)	12 to < 18 years old (N=18)	6 to < 12 years old (N=0)	3 to < 6 years old (N=0)	Total (N=18)
Participants Enrolled	76	55	27	158	18	0	0	18
Participants in Safety Analysis Set	70	51	21	142	18	0	0	18
Participants in Full Analysis Set	70	51	21	142	18	0	0	18
Study Status								
Discontinued Study	57 (81.4%)	49 (96.1%)	21 (100.0%)	127 (89.4%)	18 (100.0%)	0	0	18 (100.0%)
Completed Study	13 (18.6%)	2 (3.9%)	0	15 (10.6%)	0	0	0	0
Reason for Premature Discontinuation of Study								
Lost to Follow-Up	24 (34.3%)	11 (21.6%)	7 (33.3%)	42 (29.6%)	3 (16.7%)	0	0	3 (16.7%)
Study Terminated by Sponsor	23 (32.9%)	33 (64.7%)	13 (61.9%)	69 (48.6%)	14 (77.8%)	0	0	14 (77.8%)
Withdrew Consent	10 (14.3%)	5 (9.8%)	1 (4.8%)	16 (11.3%)	1 (5.6%)	0	0	1 (5.6%)
Investigator's Discretion	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0
Protocol Violation	0	0	0	0	0	0	0	0
Progressive Disease	0	0	0	0	0	0	0	0

(Continued)	Overall (N=461)
Participants Enrolled	461
Participants in Safety Analysis Set	426
Participants in Full Analysis Set	426
Study Status	
Discontinued Study	253 (59.4%)
Completed Study	173 (40.6%)
Reason for Premature Discontinuation of Study	
Lost to Follow-Up	110 (25.8%)
Study Terminated by Sponsor	92 (21.6%)
Withdrew Consent	43 (10.1%)
Investigator's Discretion	6 (1.4%)
Death	1 (0.2%)
Protocol Violation	1 (0.2%)
Progressive Disease	0

Protocol deviation

The majority of important protocol deviations were categorized as related to eligibility criteria and informed consent. None of the COVID-19 pandemic-related protocol deviations affected the overall quality or interpretation of the study data.

Recruitment

Study Period:

21 October 2015 (first participant enrolled)

06 January 2023 (last participant last visit for the primary endpoint and for this report)

Baseline data

Among 426 participants analysed in FAS, the majority of participants were female (58.0%) and White (80.3%). Based on the age at the entry of this registry study, among 426 participants analysed in FAS:

- 35 (8.2%) participants were in the 3 to < 6 years age group
- 162 (38.0%) participants were in the 6 to < 12 years age group
- 229 (53.8%) participants were in the 12 to ≤ 18 years age group

Table 2. Demographics and Baseline Characteristics by Treatment Group and Age Group (Safety Analysis Set)

	GS-US-334-1112 (SOF+RBV)	GS-US-337-1116 (LDV/SOF±RBV)	GS-US-342-1143 (SOF/VEL)	GS-US-367-1175 (SOF/VEL/VOX)
Age (Median [Q1, Q3]) on Parent Study Day 1 (Years)				
3 to < 6 years	5 (3, 5) N = 10	5 (4, 5) N = 26	5 (4, 5) N = 21	N = 0
6 to < 12 years	8 (7, 10) N = 36	9 (7, 10) N = 77	8 (7, 10) N = 51	N = 0
12 to < 18 years	15 (13, 17) N = 42	14 (13, 16) N = 75	14 (13, 16) N = 70	14 (13, 14) N = 18
Sex at Birth Male (N [%])				
3 to < 6 years	2 (20.0%) N = 10	7 (26.9%) N = 26	8 (38.1%) N = 21	N = 0
6 to < 12 years	8 (22.2%) N = 36	42 (54.5%) N = 77	19 (37.3%) N = 51	N = 0
12 to < 18 years	26 (61.9%) N = 42	29 (38.7%) N = 75	31 (44.3%) N = 70	7 (38.9%) N = 18
Sex at Birth Female (N [%])				
3 to < 6 years	8 (80.0%) N = 10	19 (73.1%) N = 26	13 (61.9%) N = 21	N = 0
6 to < 12 years	28 (77.8%) N = 36	35 (45.5%) N = 77	32 (62.7%) N = 51	N = 0
12 to < 18 years	16 (38.1%) N = 42	46 (61.3%) N = 75	39 (55.7%) N = 70	11 (61.1%) N = 18
Weight (Median [Q1, Q3]) at Baseline (kg)				
3 to < 6 years	18.7 (16.8, 20.5) N = 10	19.1 (16.2, 24.2) N = 26	21.0 (16.6, 22.0) N = 21	N = 0
6 to < 12 years	31.7 (24.7, 46.2) N = 36	34.0 (28.2, 43.2) N = 77	32.6 (26.3, 41.3) N = 51	N = 0
12 to < 18 years	61.1 (53.0, 73.4) N = 42	57.0 (49.4, 74.3) N = 75	57.7 (49.0, 65.4) N = 70	55.9 (46.5, 59.9) N = 18
Height (Median [Q1, Q3]) at Baseline (cm)				
3 to < 6 years	113.6 (104.0, 118.0) N = 10	111.4 (105.0, 116.0) N = 26	113.8 (103.4, 116.6) N = 21	N = 0
6 to < 12 years	133.9 (123.9, 148.3) N = 36	135.1 (128.8, 147.2) N = 77	132.7 (126.5, 143.0) N = 51	N = 0
12 to < 18 years	167.3 (158.7, 171.5) N = 42	163.3 (159.2, 170.7) N = 75	161.7 (157.0, 169.0) N = 70	162.8 (160.0, 168.0) N = 18
BMI (Median [Q1, Q3]) at Baseline (kg/m^2)				
3 to < 6 years	15.1 (14.5, 15.5) N = 10	16.0 (14.3, 18.5) N = 26	16.3 (15.4, 17.8) N = 21	N = 0
6 to < 12 years	17.0 (15.3, 21.2) N = 36	18.0 (16.3, 20.6) N = 77	17.4 (15.4, 20.4) N = 51	N = 0
12 to < 18 years	22.5 (19.8, 25.0) N = 42	21.3 (19.1, 26.4) N = 75	20.9 (19.1, 24.3) N = 70	19.7 (18.0, 22.0) N = 18

BMI = body mass index; Gilead = Gilead Sciences; HCV = hepatitis C virus; LDV/SOF = ledipasvir/sofosbuvir (coformulated; Harvoni®); Q1 = first quartile; Q3 = third quartile; RBV = ribavirin; SD = standard deviation; SOF = sofosbuvir (Sovaldi®); SOF/VEL = sofosbuvir/velpatasvir (coformulated; Epclusa®); SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir (coformulated; Vosevi®)
BMI = weight (kg)/height (m)^2
Treatment groups are based on the HCV treatment received in the parent Gilead study.
Age groups in rows are based on the age on Day 1 of the parent treatment study.
In Study GS-US-337-1116, all participants received LDV/SOF for 12 weeks except 3 participants in the 6 to < 12 year age group: 1 participant had LDV/SOF for 24 weeks, 2 participants had LDV/SOF+RBV for 24 weeks.
Source: Table 15.8.3.1 and Table 15.8.3.3

A majority (99.5%) of participants had no HCV RNA detected on Day 1 of the registry study (all but 2

participants achieved SVR24 in parent study), and a majority of participants had either HCV Genotype 1 (66.0%) or Genotype 3 (20.7%).

Number analysed

The number of enrolled and analysed participants is summarized in the table below.

Table 1. Total Number of Participants (Enrolled and Analyzed)

Participants	SOF+RBV	LDV/SOF±RBV	SOF/VEL	SOF/VEL/VOX	Total
Enrolled	93	192	158	18	461
SAS	88	178	142	18	426
FAS	88	178	142	18	426

FAS = Full Analysis Set; Gilead = Gilead Sciences; HCV = hepatitis C virus; LDV/SOF = ledipasvir/sofosbuvir (coformulated; Harvoni®); RBV = ribavirin; SAS = Safety Analysis Set; SOF = sofosbuvir (Sovaldi®); SOF/VEL = sofosbuvir/velpatasvir (coformulated; Epclusa®); SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir (coformulated; Vosevi®)
Treatment groups are based on the HCV treatment received in the parent Gilead study.
SAS/FAS include participants who met all inclusion criteria and did not meet any of the exclusion criteria, and with at least 1 post-Day 1 visit measurement available.

Safety and Efficacy results

Duration of participants in study

Overall, the median (Q1, Q3) duration of participants in this study was 192.9 (139.1, 241.1) weeks. Participants from the SOF+RBV and LDV/SOF±RBV treatment groups had median (Q1, Q3) duration of 239.1 (179.0, 243.6) weeks and 238.6 (142.6, 244.1) weeks, respectively and participants in the SOF/VEL and SOF/VEL/VOX treatment groups had median (Q1, Q3) duration of 168.5 (80.1, 193.7) weeks and 143.1 (142.1, 144.0) weeks, respectively.

Primary endpoint

Growth Data by Visit, Grouped by Age

Table 3. Body Weight Percentile and Median (Q1, Q3) Change From Baseline at Weeks 144 and 240 by Treatment Group and Age Group (Full Analysis Set)

	GS-US-334-1112 (SOF+RBV)	GS-US-337-1116 (LDV/SOF±RBV)	GS-US-342-1143 (SOF/VEL)	GS-US-367-1175 (SOF/VEL/VOX)	Overall
Baseline					
3 to < 6 years	43.8 (18.1, 72.5) N = 10	61.5 (16.0, 88.7) N = 26	57.6 (35.7, 70.3) N = 21	N = 0	57.6 (23.9, 74.9) N = 57
6 to < 12 years	45.9 (20.5, 84.3) N = 36	60.6 (30.5, 83.1) N = 77	63.2 (26.6, 86.5) N = 51	N = 0	60.3 (25.6, 84.5) N = 164
12 to < 18 years	68.1 (42.9, 86.3) N = 42	64.8 (38.6, 88.3) N = 75	59.7 (34.5, 84.2) N = 70	54.5 (24.1, 69.5) N = 18	62.7 (37.2, 84.2) N = 205
Change at Week 144					
3 to < 6 years	15.2 (0.4, 29.1) N = 4	0.0 (−5.1, 1.2) N = 18	−0.9 (−9.8, 5.5) N = 12	N = 0	0.0 (−7.0, 4.6) N = 34
6 to < 12 years	3.4 (−2.2, 15.9) N = 26	2.9 (−2.5, 9.8) N = 52	3.5 (−0.2, 11.6) N = 33	N = 0	3.5 (−1.6, 12.2) N = 111
12 to < 18 years	0.4 (−7.3, 6.5) N = 35	−0.6 (−11.0, 3.9) N = 61	0.0 (−13.4, 5.0) N = 43	−9.9 (−16.6, −1.5) N = 14	−0.8 (−11.6, 4.1) N = 153
Change at Week 240					
3 to < 6 years	15.4 (5.3, 32.8) N = 5	0.3 (−14.0, 4.4) N = 11	N = 0	N = 0	2.8 (−6.0, 12.7) N = 16
6 to < 12 years	3.9 (−4.4, 27.1) N = 28	1.8 (−1.1, 7.8) N = 43	19.6 (19.6, 19.6) N = 1	N = 0	2.4 (−1.5, 12.4) N = 72
12 to < 18 years	5.0 (−12.3, 15.6) N = 25	−0.2 (−16.0, 6.8) N = 47	0.5 (−12.4, 9.7) N = 14	N = 0	0.3 (−13.3, 10.0) N = 86

HCV = hepatitis C virus; LDV/SOF = ledipasvir/sofosbuvir (coformulated; Harvoni®); Q1 = first quartile; Q3 = third quartile; RBV = ribavirin; SOF = sofosbuvir (Sovaldi®); SOF/VEL = sofosbuvir/velpatasvir (coformulated; Epclusa®); SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir (coformulated; Vosevi®)
Participants older than 239 months are considered 239 months old for the purpose of determining the percentile. Treatment groups are based on the HCV treatment received in the parent Gilead study.
Age groups in columns are based on the age on Day 1 of the parent treatment study.

Results based on change in Z-scores were similar and did not identify any impact of prior treatment with SOF-based regimen on weight.

Table 5. BMI Percentile and Median (Q1, Q3) Change From Baseline at Weeks 144 and 240 by Treatment Group and Age Group (Full Analysis Set)

	GS-US-334-1112 (SOF+RBV)	GS-US-337-1116 (LDV/SOF±RBV)	GS-US-342-1143 (SOF/VEL)	GS-US-367-1175 (SOF/VEL/VOX)	Overall
Baseline					
3 to < 6 years	41.8 (21.0, 55.6) N = 10	68.7 (14.7, 94.2) N = 26	75.2 (50.3, 88.5) N = 21	N = 0	66.6 (39.2, 84.8) N = 57
6 to < 12 years	57.8 (31.7, 87.2) N = 36	67.1 (45.1, 89.8) N = 77	66.8 (32.1, 90.1) N = 51	N = 0	66.4 (35.1, 89.8) N = 164
12 to < 18 years	68.7 (40.1, 89.2) N = 42	64.2 (40.7, 91.3) N = 75	65.6 (33.0, 84.3) N = 70	54.5 (23.5, 69.6) N = 18	64.2 (38.1, 88.0) N = 205
Change at Week 144					
3 to < 6 years	26.7 (5.4, 42.8) N = 4	−0.3 (−13.3, 5.9) N = 18	−5.3 (−27.5, 5.1) N = 12	N = 0	−0.8 (−13.3, 10.4) N = 34
6 to < 12 years	1.7 (−3.3, 9.4) N = 26	−0.2 (−6.0, 3.2) N = 52	1.2 (−2.9, 11.1) N = 32	N = 0	0.5 (−5.0, 8.3) N = 110
12 to < 18 years	−1.3 (−8.2, 7.1) N = 35	−1.0 (−8.1, 3.3) N = 61	−0.1 (−9.0, 6.5) N = 43	−7.4 (−11.8, 0.4) N = 14	−1.1 (−9.6, 5.7) N = 153
Change at Week 240					
3 to < 6 years	34.4 (1.1, 38.2) N = 5	−1.9 (−24.7, 5.4) N = 11	N = 0	N = 0	1.2 (−12.5, 25.0) N = 16
6 to < 12 years	3.1 (−1.9, 18.6) N = 28	0.6 (−7.0, 2.9) N = 43	9.7 (9.7, 9.7) N = 1	N = 0	1.5 (−2.3, 6.0) N = 72
12 to < 18 years	3.6 (−10.1, 16.2) N = 25	0.0 (−14.2, 6.7) N = 47	2.0 (−17.9, 13.5) N = 14	N = 0	1.1 (−13.6, 9.7) N = 86

BMI = body mass index; HCV = hepatitis C virus; LDV/SOF = ledipasvir/sofosbuvir (coformulated; Harvoni®); Q1 = first quartile; Q3 = third quartile; RBV = ribavirin; SOF = sofosbuvir (Sovaldi®); SOF/VEL = sofosbuvir/velpatasvir (coformulated; Epclusa®); SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir (coformulated; Vosevi®)
BMI = weight (kg)/height $(m)^2$
Participants older than 239 months are considered 239 months old for the purpose of determining the percentile.
Treatment groups are based on the HCV treatment received in the parent Gilead study.
Age groups in columns are based on the age on Day 1 of the parent treatment study.

Results based on change in Z-scores were similar and did not identify any impact of prior treatment with SOF-based regimen on BMI.

Table 4. Body Height Percentile and Median (Q1, Q3) Change From Baseline at Weeks 144 and 240 by Treatment Group and Age Group (Full Analysis Set)

	GS-US-334-1112 (SOF+RBV)	GS-US-337-1116 (LDV/SOF±RBV)	GS-US-342-1143 (SOF/VEL)	GS-US-367-1175 (SOF/VEL/VOX)	Overall
Baseline					
3 to < 6 years	56.0 (33.6, 65.0) N = 10	48.4 (12,4, 65.8) N = 26	30.7 (19.9, 62.0) N = 21	N = 0	49.6 (19.0, 63.7) N = 57
6 to < 12 years	46.4 (15.8, 75.9) N = 36	39.8 (16.4, 70.9) N = 77	44.4 (24.2, 70.3) N = 51	N = 0	42.7 (17.5, 73.5) N = 164
12 to < 18 years	45.9 (19.3, 75.5) N = 42	42.5 (19.1, 74.4) N = 75	42.7 (17.9, 69.1) N = 70	49.9 (31.8, 64.2) N = 18	43.5 (19.6, 69.1) N = 205
Change at Week 144					
3 to < 6 years	2.5 (−5.1, 7.7) N = 4	0.9 (−3.4, 3.4) N = 18	1.1 (−6.3, 3.1) N = 12	N = 0	0.9 (−4.8, 3.4) N = 34
6 to < 12 years	−1.2 (−9.3, 13.9) N = 26	2.2 (−3.4,13.8) N = 52	3.9 (−0.8, 9.9) N = 32	N = 0	2.6 (−4.0, 13.2) N = 110
12 to < 18 years	−0.9 (−10.9, 1.5) N = 35	−0.2 (−4.1, 3.5) N = 61	−1.5 (−4.2, 2.0) N = 43	−5.7 (−12.5, −1.4) N = 14	−1.0 (−6.4, 2.4) N = 153
Change at Week 240					
3 to < 6 years	18.1 (−7.9, 19.6) N = 5	2.4 (−1.5, 3.9) N = 11	N = 0	N = 0	2.4 (−4.7, 11.8) N = 16
6 to < 12 years	0.4 (−22.5, 17.3) N = 28	0.3 (−13.1, 13.3) N = 43	20.2 (20.2, 20.2) N = 1	N = 0	0.5 (−13.2, 15.2) N = 72
12 to < 18 years	−0.5 (−6.5, 2.0) N = 25	−1.0 (−5.8, 5.0) N = 47	−2.4 (−5.4, 2.2) N = 14	N = 0	−1.0 (−5.8, 3.2) N = 86

HCV = hepatitis C virus; N = number of participants; LDV/SOF = ledipasvir/sofosbuvir (coformulated; Harvoni®); Q1 = first quartile; Q3 = third quartile; RBV = ribavirin; SOF = sofosbuvir (Sovaldi®); SOF/VEL = sofosbuvir/velpatasvir (coformulated; Epclusa®); SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir (coformulated; Vosevi®)
Participants older than 239 months are considered 239 months old for the purpose of determining the percentile. Treatment groups are based on the HCV treatment received in the parent Gilead study.
Age groups in columns are based on the age on Day 1 of the parent treatment study.

Results based on change in Z-scores were similar and did not identify any impact of prior treatment with SOF-based regimen on height.

Assessor's comment:

No major changes from baseline in the weight, BMI or height percentiles were observed during the follow up study. Thus, treatment with DAAs (SOF+RBV, LDV/SOF±RBV, SOF/VEL, SOF/VEL/VOX) does not seem to notably affect long-term growth parameters.

Tanner Stages to Assess Sexual Maturation

Study GS-US-334-1112 (SOF+RBV)

3 to < 6 years old

Males

There were 2 participants with pubic hair and genitalia tanner assessments at baseline and Week 240. At baseline, both participants were at Stage 1 and had no change or an increase from baseline in their Tanner stage for pubic hair and genitalia development at Week 240.

Females

There were 3 participants with pubic hair and breast development assessments at baseline and Week 240.

Pubic hair: At baseline, all 3 participants were at Stage 1 for pubic hair assessment. At Week 240, 1 participant each were at Stage 1, 2, and 3, respectively.

Breast development: At baseline, all 3 participants were at Stage 1 for breast development assessment. At Week 240, 2 and 1 participants were at Stage 1 and 3, respectively.

6 to < 12 years old

Males

There were 5 participants with pubic hair and genitalia development assessments at baseline and Week 240.

Pubic hair: At baseline, 4 and 1 participants were at Stage 1 and 2, respectively for pubic hair assessment. At Week 240, 1 participant remained at Stage 1 at Week 240, 2 participant each were at Stage 2 and 3, respectively.

Genitalia development: At baseline, 4 and 1 participants were at Stage 1 and 2, respectively for genitalia development assessment. At Week 240, 2, 1, and 1 participants were at Stage 3, 4, and 5, respectively. One participant remained at Stage 1.

Females

There were 22 participants with pubic hair and breast development assessments at baseline and Week 240.

Pubic hair: At baseline, 12, 5, 3, and 2 participants were at Stage 1, 2, 3, and 4, respectively for pubic hair assessment. At Week 240, 1, 2, 4, 6, and 9 participants were at Stage 1, 2, 3, 4, and 5, respectively. Only 1 participant with Stage 1 at baseline remained at Stage 1 at Week 240, all the rest 21 participants developed into higher stage at Week 240.

Breast development: At baseline, 10, 7, 3, and 2 participants were at Stage 1, 2, 3, and 4, respectively for breast development assessment. At Week 240, 1, 7, 5, and 9 participants were at Stage 1, 3, 4, and 5, respectively. One participant with Stage 1 at baseline and 1 participant with Stage 3 at baseline remained at Stage 1 and 3 at Week 240, respectively. All the rest 20 participants developed into higher stage at Week 240.

12 to < 18 years old

Males

There were 14 participants with pubic hair and genitalia development assessments at baseline and Week 240.

Pubic hair: At baseline, 1, 4, 3, and 6 participants were at Stage 1, 3, 4, and 5, respectively for pubic hair assessment. At Week 240, 1 participant with Stage 1 at baseline developed into Stage 4 and all rest 13 participants were at Stage 5.

Genitalia development: At baseline, 1, 4, 3, and 6 participants were at Stage 1, 3, 4, and 5, respectively for genitalia development assessment. At Week 240, 1 participant with Stage 1 at baseline developed into Stage 4 and all rest 13 participants were at Stage 5.

Females

There were 11 participants with pubic hair and breast development assessments at baseline and Week 240.

Pubic hair: At baseline, 1, 4, 4, and 2 participants were at Stage 1, 3, 4, and 5, respectively for pubic hair assessment. At Week 240, 1 and 10 participants were at Stage 4 and 5, respectively. At Week 240, all 11 participants either developed into higher stage or remained at Stage 5.

Breast development: At baseline, 5, 2, and 4 participants were at Stage 3, 4, and 5, respectively for breast development assessment. At Week 240, all 11 participants either developed into higher stage or remained at Stage 5.

Study GS-US-337-1116 (LDV/SOF±RBV)

3 to < 6 years old

Males

There were 3 participants with pubic hair and genitalia tanner assessments at baseline and Week 240. At baseline, all 3 participants were at Stage 1 and had no change or an increase from baseline in their Tanner stage for pubic hair and genitalia development at Week 240.

Females

There were 8 participants with pubic hair and breast development assessments at baseline and Week 240. At baseline, all 8 participants were at Stage 1 pubic hair and breast development assessments. At Week 240, 5 participants remained at Stage 1 and 1 participant each were at Stage 2, 3, and 5, respectively for both pubic hair and breast development assessments.

6 to < 12 years old

Males

There were 26 participants with pubic hair and genitalia development assessments at baseline and Week 240.

Pubic hair: At baseline, 21, 4, and 1 participants were at Stage 1, 2, and 4, respectively for pubic hair assessment. At Week 240, 3, 5, 3, 6, and 9 participants were at Stage 1, 2, 3, 4, and 5, respectively. At Week 240, 3 participants with Stage 1 at baseline remained at Stage 1, all the rest 23 participants developed into higher stage.

Genitalia development: At baseline, 21, 4, and 1 participants were at Stage 1, 2, and 3, respectively for genitalia development assessment. At Week 240, 1, 6, 4, 7, and 8 participants were at Stage 1, 2, 3, 4, and 5, respectively. At Week 240, 1 participant with Stage 1 at baseline remained at Stage 1, all the rest 25 participants developed into higher stage.

Females

There were 15 participants with pubic hair and breast development assessments at baseline and Week 240.

Pubic hair: At baseline, 10, 2, 2, and 1 participants were at Stage 1, 2, 3, and 5, respectively for pubic hair assessment. At Week 240, 1, 3, 1, and 10 participants were at Stage 2, 3, 4, and 5, respectively. At Week 240, all 15 participants developed into higher stage or remained at Stage 5.

Breast development: At baseline, 7, 3, 4, and 1 participants were at Stage 1, 2, 3, and 5, respectively for breast development assessment. At Week 240, 1, 3, 1, and 10 participants were at Stage 2, 3, 4, and 5, respectively. At Week 240, all 15 participants developed into higher stage or remained at Stage 5.

12 to < 18 years old

Males

There were 18 participants with pubic hair and genitalia development assessments at baseline and Week 240.

Pubic hair: At baseline, 2, 3, 4, and 9 participants were at Stage 2, 3, 4, and 5, respectively for pubic hair assessment. At Week 240, all 18 participants were at Stage 5.

Genitalia development: At baseline, 2, 3, 5, and 8 participants were at Stage 2, 3, 4, and 5, respectively for genitalia development assessment. At Week 240, all 18 participants were at Stage 5.

Females

There were 30 participants with pubic hair and breast development assessments at baseline and Week 240.

Pubic hair: At baseline, 1, 3, 7, and 19 participants were at Stage 2, 3, 4, and 5, respectively for pubic hair assessment. At Week 240, all 30 participants were at Stage 5.

Breast development: At baseline, 1, 3, 9, and 17 participants were at Stage 1, 3, 4, and 5, respectively for breast development assessment. At Week 240, all 30 participants were at Stage 5.

Study GS-US-342-1143 (SOF/VEL)

3 to < 6 years old

No male or female participant had Week 240 assessments.

6 to < 12 years old

Males

No male participant had Week 240 assessments.

Females

There was 1 participant with pubic hair and breast development assessments at baseline and Week 240. At baseline, this participant was at Stage 1 for pubic hair and breast development assessments and moved to Stage 4 for pubic hair and Stage 3 for breast development assessments at Week 240.

12 to < 18 years old

Males

There were 7 participants with pubic hair and genitalia development assessments at baseline and Week 240.

Pubic hair: At baseline, 2, 1, and 4 participants were at Stage 2, 4, and 5, respectively for pubic hair assessment. At Week 240, all 7 participants were at Stage 5.

Genitalia development: At baseline, 1 participant each were at Stage 2 and 3, and 5 participants were at Stage 5 for genitalia development assessment. At Week 240, all 7 participants were at Stage 5.

Females

There were 7 participants with pubic hair and breast development assessments at baseline and Week 240.

Pubic hair: At baseline, 2 and 5 participants were at Stage 4 and 5, respectively for pubic hair assessment. At Week 240, all 7 participants were at Stage 5.

Breast development: At baseline, 1 and 6 participants were at Stage 4 and 5, respectively for breast development assessment. At Week 240, all 7 participants were at Stage 5.

Study GS-US-367-1175 (SOF/VEL/VOX)

12 to < 18 years old

No male or female participant had Week 240 assessments.

Assessor's comment:

The development and sexual maturation as assessed by changes from baseline through end of study in Tanner pubertal stages did not seem to be affected by treatment with DAAs.

Secondary endpoints

Proportion of participants maintaining SVR

Out of 424 participants who had achieved SVR in their parent treatment study, all (100%) participants maintained SVR during this registry study.

Two participants did not achieve SVR in their parent treatment studies and hence, no SVR duration was calculated. Hepatitis C virus sequencing was performed with blood samples collected during this registry study for these 2 participants (both with HCV Genotype 1a) in the FAS who had not achieved SVR in their parent treatment study.

One participant treated with LDV/SOF for 12 weeks in the parent Study GS-US-337-1116 had the NS5A resistance-associate variant (RAV) Y93H which developed at Week 4 posttreatment. The Y93H RAV was maintained through Week 144. One participant treated with SOF/VEL for 12 weeks in the parent Study GS-US-342-1143 had the NS5A RAV L31V which developed at Week 8 on treatment. The L31V RAV was not detected at Week 24 and Week 48, was detected as a mixture (L31L/V) at Week 72, then not detected at Week 96, 144, and 192. Both participants were tested for the presence of NS5B RAVs during the parent and registry study. No NS5B RAVs were detected in either participant during the parent or registry study at all tested visits.

Table 6 summarizes the SVR duration of participants who achieved SVR in the parent study by treatment group. Overall, the mean (SD) SVR duration was 1359.0 (510.82) days.

Table 6. Summary of SVR Duration for Participants Who Achieved SVR12 in Parent Study by Treatment Group (Full Analysis Set)

	GS-US-334-1112 (SOF+RBV)	GS-US-337-1116 (LDV/SOF±RBV)	GS-US-342-1143 (SOF/VEL)	GS-US-367-1175 (SOF/VEL/VOX)	Total
SVR Duration (Days)					
N	88	177	141	18	424
Mean (SD)	1544.3 (450.11)	1467.7 (538.16)	1147.7 (449.08)	1040.4 (135.04)	1359.0 (510.82)
Median	1761.5	1762.0	1282.0	1086.0	1450.0
Q1, Q3	1422.5, 1791.0	1110.0, 1797.0	778.0, 1444.0	1080.0, 1101.0	1080.5, 1776.5
Min, max	260.0, 2261.0	221.0, 2389.0	211.0, 1879.0	636.0, 1132.0	211.0, 2389.0

HCV = hepatitis C virus; LDV/SOF = ledipasvir/sofosbuvir (coformulated; Harvoni®); max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; RBV = ribavirin; SD = standard deviation; SOF = sofosbuvir (Sovaldi®); SOF/VEL = sofosbuvir/velpatasvir (coformulated; Epclusa®); SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir (coformulated; Vosevi®); SVR = sustained virologic response
Treatment groups are based on the HCV treatment received in the parent Gilead study.
Sustained virologic response duration = last day of registry (for participants who maintained SVR)–SVR12 date in parent study + 1.
Two participants did not achieve SVR in their parent treatment studies and no SVR duration calculated.
All 424 participants who had achieved SVR in parent treatment studies maintained SVR during the registry study.

Assessor's comment:

Of the 424 participants with SVR24 in the parent study all maintained SVR during the follow up registry study. Two participants did not achieve SVR in the parent study and thus SVR was not calculated for the registry study.

Exploratory endpoint

Quality of life results

Participant-reported outcomes were assessed using the PedsQL™ Version 4.0 Short Form (SF15). No clinically significant changes were observed from the registry baseline throughout the study.

Adverse Events

As there was no study treatment in this study, only adverse events (AEs) related to the required procedures by the study protocol were reported under this study. During the registry study, 1 participant experienced a Grade 1 nonserious AE of presyncope that was resolved on the day of onset without any corrective treatment. The AE was considered related to study procedures. No action was taken due to the AE.

*Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Event*s

No participant experienced a serious adverse event or an AE leading to premature study discontinuation.

One participant died during the study due to progressive cerebellar glioblastoma and the death was not considered related to study procedures.

Postmarketing Experience

Based on postmarketing experience to date, the safety profile of SOF, LDV/SOF, SOF/VEL, and SOF/VEL/VOX, in the paediatric population is consistent with their safety profile in adults. No new adverse drug reactions related to SOF, LDV/SOF, SOF/VEL, and SOF/VEL/VOX have been observed in paediatric patients in the postmarketing setting. No postmarketing data are submitted with this application.

2.3.3. Discussion on clinical aspects

This long-term follow up registry assessed safety data of growth and development in paediatric patients previously treated with SOF+RBV, LDV/SOF±RBV, SOF/VEL or SOF/VEL/VOX.

The median (Q1, Q3) of duration on this registry study was 239.1 (179.0, 243.6) weeks for SOF+RBV, 238.6 (142.6, 244.1) weeks for LDV/SOF±RBV, 168.5 (80.1, 193.7) weeks for SOF/VEL, and 143.1 (142.1, 144.0) weeks for SOF/VEL/VOX. No long-term effects of treatment on height, weight, BMI, Tanner pubertal stage, and SF15 scores were observed.

For those participants with SVR in the parent study all maintained SVR during the follow up in the registry.

No clinically significant safety signals have been identified in this long-term follow-up study.

3. Rapporteur's overall conclusion and recommendation

A favourable long-term safety profile was observed with SOF+RBV, LDV/SOF±RBV, SOF/VEL, SOF/VEL/VOX treatment in paediatric and adolescent participants with HCV infection in the follow up registry.

No label update is proposed which is endorsed.

☒ **Fulfilled:**

No regulatory action required.