FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	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
Name of Test Drug:	Not Applicable
Dose and Formulation:	Not Applicable
Indication:	Hepatitis C Virus Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-334-1113
Phase of Development:	Phase 4
IND No.: **EudraCT No.:**	106739 2014-004674-42
ClinicalTrials.gov Identifier:	NCT02510300
Study Start Date:	21 October 2015 (first participant enrolled)
Study End Date:	06 January 2023 (last participant last visit for the primary endpoint and for this report)
Principal Investigator:	Name: PPD Affiliation: Advent Health Orlando
Sponsor Responsible Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD
Report Date:	16 June 2023

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Study GS-US-334-1113
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: 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

Investigators: Multicenter study

Further details are provided in Appendix 16.1.4.

Study Centers: 52 sites in Australia (3 sites), Belgium (1 site), Germany (2 sites), Italy (8 sites), New Zealand (1 site), Poland (2 sites), Russian Federation (4 sites), United Kingdom (4 sites), and United States (27 sites).

Publications:

Wen, J., et al. (2022). Long-term Follow-up of Safety and Efficacy of Sofosbuvir-Based Treatment for Chronic HCV Infection in Pediatric Patients [Presentation]. ESPGHAN, Copenhagen, Denmark

Wen, J., et al. (2020). Long-term Follow-up of Safety and Efficacy of Sofosbuvir-Based HCV DAAs in Pediatric Patients [Poster]. AASLD, Virtual

Study Period:

21 October 2015 (first participant enrolled)
06 January 2023 (last participant last visit for the primary endpoint and for this report)

Phase of Development: Phase 4

Study Objectives and 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**
[redacted]	[redacted]

Methodology: This study enrolled adolescent and pediatric participants who received at least 1 of 4 Gilead HCV DAAs (sofosbuvir [SOF, Sovaldi®], ledipasvir/sofosbuvir [LDV/SOF, coformulated; Harvoni®], sofosbuvir/velpatasvir [SOF/VEL, coformulated; Epclusa®], and sofosbuvir/velpatasvir/voxilaprevir [SOF/VEL/VOX, coformulated; Vosevi®]) while participating in Gilead-sponsored CHC clinical studies regardless of whether the participant achieved a SVR. Once enrolled, participants were followed for up to 5 years. The Day 1 visit was documented as the last visit of the previous Gilead-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.

Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 pandemic control measures are described in the study's investigator memo COVID-19 (Appendix 16.1.1).

Number of participants (Planned and Analyzed):
Planned: Due to the observational nature of this study, no formal power, or sample size calculations were used.
Analyzed: The number of enrolled and analyzed participants is summarized in Table 1.

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.
Source: Table 15.8.1.3.1.1

Diagnosis and Main Criteria for Inclusion:

- Participants had previously participated in a Gilead-sponsored CHC study as an adolescent or child and received at least 1 Gilead HCV DAA.
- Participant had a parent or legal guardian able to provide written informed consent or participant was able to provide written informed consent prior to any study procedures and was willing to comply with study requirements.

Duration of Treatment:

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

This observational registry followed participants every 6 months for the first 2 years followed by every 12 months for up to 5 years, or until early discontinuation from the study.

Test Product, Dose, Mode of Administration, and Batch No.: Not applicable

Reference Therapy, Dose, Mode of Administration, and Batch No.: Not applicable

Criteria for Evaluation: Not applicable. This was an observational registry to follow the long-term safety (growth and development), SVR duration, and QOL of adolescent and pediatric participants treated with Gilead HCV DAA.

Statistical Methods: Section 15.1 and Appendix 16.2 **i**nclude all tables, figures, and listings produced for this study. Appendix 16.1.9 includes documentation of 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 Gilead-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 (Appendix 3 of study protocol Appendix 16.1.1) at each postbaseline visit from baseline was provided by prior treatment group, sex, and prior age group. If the assessment within the Gilead-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.

CCI [redacted]

SUMMARY OF RESULTS:

Participant Disposition and Demographics:

Table 15.8.1.3.1.1 includes a summary of participant disposition, including the reasons for premature discontinuation of the study.

- 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 (see Section 4 of the protocol for a list of inclusion and exclusion criteria, Appendix 16.1.1).

- Among 426 participants analyzed 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.
- 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 (Table 15.9.1).
- Among 426 participants analyzed in the FAS, the majority of participants were female (58.0%) and White (80.3%).

Listing 16.2.1.3.2 includes a by-participant listing of study discontinuations due to COVID-19 pandemic-related matters. None of these discontinuations affected the overall quality or interpretation of the study data.

Listing 16.2.1.3.3 includes a by-participant listing of missed study visits due to COVID-19. None of these missed study visits affected the overall quality or interpretation of the study data.

Baseline Characteristics:

Table 2 includes a summary of demographics and baseline characteristics:

- The majority of participants had no HCV RNA detected (99.5% [424/426 participants]).
- The majority of participants had either HCV Genotype 1 (66.0% [281/426 participants]) or Genotype 3 (20.7% [88/426 participants]) (Table 15.8.3.3).

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

Protocol Deviations:

Listing 16.2.2.2.1 provides a by-participant list of important protocol deviations (IPDs). The majority of IPDs were categorized as related to eligibility criteria and informed consent. Listings 16.2.2.2.2 and 16.2.2.2.3 provide by-participant listings of important and nonimportant protocol deviations due to COVID-19 pandemic-related study disruptions, respectively. None of these pandemic-related protocol deviations affected the overall quality or interpretation of the study data.

Primary Endpoints:

Growth Data by Visit Grouped by Age and Gender

Weight

Table 15.10.1.1 summarizes body weight values and changes from baseline by visit and by prior treatment group, sex, and prior age group.

Table 3 summarizes body weight percentiles and changes from baseline at Weeks 144 and 240 by treatment group and age group.

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.
Source: Table 15.10.2.1

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 15.10.3.1).

Height

Table 15.10.1.2 summarizes body height values and changes from baseline by visit and by prior treatment group, sex, and prior age group.

Table 4 summarizes body height percentiles and changes from baseline at Weeks 144 and 240 by treatment group and age group.

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.
Source: Table 15.10.2.2

Results based on change in Z-scores were similar and did not identify any impact of prior treatment with SOF-based regimen on height (Table 15.10.3.2).

Body Mass Index

Table 15.10.1.3 summarizes BMI values and changes from baseline by visit and by prior treatment group, sex, and prior age group.

Table 5 summarizes BMI percentiles and changes from baseline at Weeks 144 and 240 by treatment group and age group.

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.
Source: Table 15.10.2.3

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 15.10.3.3).

Tanner Stages to Assess Sexual Maturation

Tanner stages shift from baseline to Week 240 by treatment group, sex and age group are presented below (Table 15.10.6).

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.

Other Endpoints of Interest:

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.
Source: Table 15.10.8.2

CCI [redacted]

CONCLUSIONS: the conclusions for this study are as follows:

- 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.
- No notable effects of Gilead HCV DAA (SOF+RBV, LDV/SOF±RBV, SOF/VEL, SOF/VEL/VOX) were observed during the follow-up on growth of participants as assessed by changes from baseline through end of study on height, weight, and BMI percentiles and Z-scores for any age group or on the development and sexual maturation of participants as assessed by changes from baseline through end of study in Tanner pubertal stages.
- All participants who were enrolled in the study and had achieved SVR12 in the parent study maintained SVR through end of the registry.