Clinical trial results:
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

Summary

EudraCT number	2014-004674-42
Trial protocol	GB DE BE PL IT
Global end of trial date	06 January 2023

Results information

Result version number	v1 (current)
This version publication date	21 June 2023
First version publication date	21 June 2023

Trial information

Trial identification

Sponsor protocol code	GS-US-334-1113

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02510300
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 January 2023
Global end of trial reached?	Yes
Global end of trial date	06 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this registry was to evaluate the long-term safety of anti-HCV regimens in the pediatric population as determined by assessments of growth and development.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 38
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	United States: 336
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	New Zealand: 2
Worldwide total number of subjects	461
EEA total number of subjects	50

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	236
Adolescents (12-17 years)	225
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Australia, Belgium, Germany, Italy, New Zealand, Poland, Russia, the United Kingdom, and the United States.

Pre-assignment

Screening details:

461 participants were enrolled in the registry.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	SOF+RBV

Arm description:

Participants who were previously treated with sofosbuvir (SOF) along with ribavirin (RBV) were followed for up to 5 years.

Arm type	Observational
Investigational medicinal product name	Sofosbuvir
Investigational medicinal product code	
Other name	SOF, GS-7977, PSI-7977, Sovaldi®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

No treatment was administered in this study. Participants received SOF in a previous Gilead-sponsored chronic hepatitis C infection study.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	RBV
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No treatment was administered in this study. Participants received RBV in a previous Gilead-sponsored chronic hepatitis C infection study.

Arm title	LDV/SOF+/-RBV

Arm description:

Participants who were previously treated with ledipasvir (LDV)/SOF with or without RBV were followed for up to 5 years.

Arm type	Observational
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	
Other name	LDV/SOF; Harvoni®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

No treatment was administered in this study. Participants received LDV/SOF in a previous Gilead-sponsored chronic hepatitis C infection study.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	RBV
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No treatment was administered in this study. Participants received RBV in a previous Gilead-sponsored chronic hepatitis C infection study.

Arm title	SOF/VEL

Arm description:

Participants who were previously treated with SOF/velpatasvir (VEL) were followed for up to 5 years.

Arm type	Observational
Investigational medicinal product name	Sofosbuvir/velpatasvir
Investigational medicinal product code	
Other name	SOF/VEL; Epclusa®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

No treatment was administered in this study. Participants received SOF/VEL in a previous Gilead-sponsored chronic hepatitis C infection study.

Arm title	SOF/VEL/VOX

Arm description:

Participants who were previously treated with SOF/VEL/voxilaprevir (VOX) were followed for up to 5 years.

Arm type	Observational
Investigational medicinal product name	Sofosbuvir/velpatasvir/voxilaprevir
Investigational medicinal product code	
Other name	SOF/VEL/VOX; Vosevi®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

No treatment was administered in this study. Participants received SOF/VEL/VOX in a previous Gilead-sponsored chronic hepatitis C infection study.

Number of subjects in period 1[1]	SOF+RBV	LDV/SOF+/-RBV	SOF/VEL
Started	88	178	142
Completed	58	100	15
Not completed	30	78	127
Protocol violation	1	-	-
Death	-	1	-
Study terminated by sponsor	2	7	69
Lost to follow-up	14	51	42
Withdrew consent	8	18	16
Investigator's discretion	5	1	-

Number of subjects in period 1[1]	SOF/VEL/VOX
Started	18
Completed	0
Not completed	18
Protocol violation	-
Death	-
Study terminated by sponsor	14
Lost to follow-up	3
Withdrew consent	1
Investigator's discretion	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of the 461 participants who were enrolled, 426 participants who met eligibility criteria and had at least one post-Day 1 visit measurement available were included in the analysis.

Baseline characteristics

Reporting groups	
Reporting group title	SOF+RBV
Reporting group description:	
Participants who were previously treated with sofosbuvir (SOF) along with ribavirin (RBV) were followed for up to 5 years.	
Reporting group title	LDV/SOF+/-RBV
Reporting group description:	
Participants who were previously treated with ledipasvir (LDV)/SOF with or without RBV were followed for up to 5 years.	
Reporting group title	SOF/VEL
Reporting group description:	
Participants who were previously treated with SOF/velpatasvir (VEL) were followed for up to 5 years.	
Reporting group title	SOF/VEL/VOX
Reporting group description:	
Participants who were previously treated with SOF/VEL/voxilaprevir (VOX) were followed for up to 5 years.	

Reporting group values	SOF+RBV	LDV/SOF+/-RBV	SOF/VEL
Number of subjects	88	178	142
Age categorical Units: Subjects			
12 to < 18 years old	42	75	70
6 to < 12 years old	36	77	51
3 to < 6 years old	10	26	21
Gender categorical Units: Subjects			
Female	52	100	84
Male	36	78	58
Race Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	8	7	9
Black or African American	4	12	11
Native Hawaiian or Pacific Islander	1	1	1
White	69	152	108
Other	6	6	11
Not Reported	0	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	13	22	16
Not Hispanic or Latino	73	153	119
Not Reported	2	3	7

Reporting group values	SOF/VEL/VOX	Total	
Number of subjects	18	426	

Age categorical Units: Subjects			
12 to < 18 years old	18	205	
6 to < 12 years old	0	164	
3 to < 6 years old	0	57	
Gender categorical Units: Subjects			
Female	11	247	
Male	7	179	
Race Units: Subjects			
American Indian or Alaska Native	0	1	
Asian	2	26	
Black or African American	1	28	
Native Hawaiian or Pacific Islander	0	3	
White	13	342	
Other	2	25	
Not Reported	0	1	
Ethnicity Units: Subjects			
Hispanic or Latino	0	51	
Not Hispanic or Latino	18	363	
Not Reported	0	12	

End points

End points reporting groups

Reporting group title	SOF+RBV
Reporting group description:	
Participants who were previously treated with sofosbuvir (SOF) along with ribavirin (RBV) were followed for up to 5 years.	
Reporting group title	LDV/SOF+/-RBV
Reporting group description:	
Participants who were previously treated with ledipasvir (LDV)/SOF with or without RBV were followed for up to 5 years.	
Reporting group title	SOF/VEL
Reporting group description:	
Participants who were previously treated with SOF/velpatasvir (VEL) were followed for up to 5 years.	
Reporting group title	SOF/VEL/VOX
Reporting group description:	
Participants who were previously treated with SOF/VEL/voxilaprevir (VOX) were followed for up to 5 years.	
Subject analysis set title	12 to < 18 years old
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants within the age group of 12 to < 18 years old who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.	
Subject analysis set title	6 to < 12 years old
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants within the age group of 6 to < 12 years old who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.	
Subject analysis set title	3 to < 6 years old
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants within the age group of 3 to < 6 years old who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.	
Subject analysis set title	Male: Baseline Stage 1
Subject analysis set type	Full analysis
Subject analysis set description:	
Male participants who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.	
Subject analysis set title	Male: Baseline Stage 2
Subject analysis set type	Full analysis
Subject analysis set description:	
Male participants who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.	
Subject analysis set title	Male: Baseline Stage 3
Subject analysis set type	Full analysis
Subject analysis set description:	
Male participants who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.	
Subject analysis set title	Male: Baseline Stage 4
Subject analysis set type	Full analysis
Subject analysis set description:	
Male participants who were previously treated with SOF along with RBV, or LDV/SOF with or without	

RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.

Subject analysis set title	Male: Baseline Stage 5
Subject analysis set type	Full analysis

Subject analysis set description:

Male participants who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.

Subject analysis set title	Female: Baseline Stage 1
Subject analysis set type	Full analysis

Subject analysis set description:

Female participants who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.

Subject analysis set title	Female: Baseline Stage 2
Subject analysis set type	Full analysis

Subject analysis set description:

Female participants who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.

Subject analysis set title	Female: Baseline Stage 3
Subject analysis set type	Full analysis

Subject analysis set description:

Female participants who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.

Subject analysis set title	Female: Baseline Stage 4
Subject analysis set type	Full analysis

Subject analysis set description:

Female participants who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.

Subject analysis set title	Female: Baseline Stage 5
Subject analysis set type	Full analysis

Subject analysis set description:

Female participants who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.

Subject analysis set title	All participants
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who were previously treated with SOF along with RBV, or LDV/SOF with or without RBV, or SOF/VEL, or SOF/VEL/VOX were followed for up to 5 years.

Primary: Change From Baseline in Height Z-scores as a Measurement of Growth and Development

End point title	Change From Baseline in Height Z-scores as a Measurement of Growth and Development[1]

End point description:

An age- and sex-specific Z-score was derived for each weight, height and body mass index (BMI) measurement according to the downloadable SAS program available on the Centers for Disease Control (CDC) website using the year 2000 growth charts. The Full Analysis Set (all enrolled participants who met all the study entry eligibility criteria and with at least one post-Day 1 visit measurement available) with available data were analysed.

End point type	Primary

End point timeframe:

Baseline (Day 1); Weeks 24, 48, 72, 96, 144, 192, and 240

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed for the overall population between the age groups.

End point values	12 to < 18 years old	6 to < 12 years old	3 to < 6 years old	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	205	164	57	
Units: z-score				
median (inter-quartile range (Q1-Q3))				
Baseline	-0.2 (-0.9 to 0.5)	-0.2 (-0.9 to 0.6)	0.0 (-0.9 to 0.4)	
Change at Week 24 (N = 190, 163, 54)	0.0 (-0.1 to 0.1)	0.0 (-0.1 to 0.1)	-0.1 (-0.3 to 0.0)	
Change at Week 48 (N = 164, 136, 45)	0.0 (-0.2 to 0.2)	0.1 (-0.1 to 0.2)	0.0 (-0.3 to 0.1)	
Change at Week 72 (N = 170, 135, 38)	0.0 (-0.2 to 0.1)	0.1 (-0.1 to 0.3)	0.0 (-0.3 to 0.2)	
Change at Week 96 (N = 165, 123, 38)	-0.1 (-0.2 to 0.1)	0.1 (-0.1 to 0.4)	-0.1 (-0.3 to 0.1)	
Change at Week 144 (N = 153, 110, 34)	-0.1 (-0.2 to 0.1)	0.1 (-0.1 to 0.5)	0.1 (-0.3 to 0.2)	
Change at Week 192 (N = 117, 94, 24)	0.0 (-0.2 to 0.1)	0.1 (-0.2 to 0.6)	0.1 (-0.2 to 0.5)	
Change at Week 240 (N = 86, 72, 16)	0.0 (-0.2 to 0.1)	0.0 (-0.5 to 0.6)	0.2 (-0.3 to 0.6)	

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Weight Z-scores as a Measurement of Growth and Development

End point title	Change From Baseline in Weight Z-scores as a Measurement of Growth and Development[2]

End point description:

An age- and sex-specific Z-score was derived for each weight, height and BMI measurement according to the downloadable SAS program available on the CDC website using the year 2000 growth charts. Participants in the Full Analysis Set with available data were analysed.

End point type	Primary

End point timeframe:

Baseline (Day 1); Weeks 24, 48, 72, 96, 144, 192, and 240

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed for the overall population between the age groups.

End point values	12 to < 18 years old	6 to < 12 years old	3 to < 6 years old	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	205	164	57	
Units: z-score				
median (inter-quartile range (Q1-Q3))				
Baseline	0.3 (-0.3 to 1.0)	0.3 (-0.7 to 1.0)	0.2 (-0.7 to 0.7)	
Change at Week 24 (N = 191, 163, 54)	0.0 (-0.1 to 0.2)	0.0 (-0.1 to 0.2)	-0.1 (-0.2 to 0.1)	

Change at Week 48 (N = 165, 136, 45)	0.0 (-0.2 to 0.2)	0.1 (-0.1 to 0.3)	-0.1 (-0.2 to 0.1)	
Change at Week 72 (N = 170, 135, 39)	0.0 (-0.3 to 0.3)	0.0 (-0.2 to 0.3)	0.0 (-0.2 to 0.3)	
Change at Week 96 (N = 165, 123, 38)	0.0 (-0.4 to 0.3)	0.1 (-0.1 to 0.4)	0.1 (-0.1 to 0.3)	
Change at Week 144 (N = 153, 111, 34)	-0.1 (-0.4 to 0.3)	0.2 (-0.1 to 0.6)	0.0 (-0.3 to 0.3)	
Change at Week 192 (N = 117, 94, 24)	-0.1 (-0.4 to 0.5)	0.2 (-0.1 to 0.6)	0.2 (-0.1 to 0.5)	
Change at Week 240 (N = 86, 72, 16)	0.1 (-0.5 to 0.5)	0.3 (-0.1 to 0.5)	0.3 (-0.2 to 0.6)	

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Body Mass Index (BMI) Z-scores as a Measurement of Growth and Development

End point title	Change From Baseline in Body Mass Index (BMI) Z-scores as a Measurement of Growth and Development[3]

End point description:

An age- and sex-specific Z-score was derived for each weight, height and BMI measurement according to the downloadable SAS program available on the CDC website using the year 2000 growth charts. Participants in the Full Analysis Set with available data were analysed.

End point type	Primary

End point timeframe:

Baseline (Day 1); Weeks 24, 48, 72, 96, 144, 192, and 240

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed for the overall population between the age groups.

End point values	12 to < 18 years old	6 to < 12 years old	3 to < 6 years old	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	205	164	57	
Units: z-score				
median (inter-quartile range (Q1-Q3))				
Baseline	0.4 (-0.3 to 1.2)	0.4 (-0.4 to 1.3)	0.4 (-0.3 to 1.0)	
Change at Week 24 (N = 190, 163, 54)	0.0 (-0.1 to 0.2)	0.0 (-0.2 to 0.2)	0.0 (-0.3 to 0.2)	
Change at Week 48 (N = 164, 136, 45)	0.0 (-0.2 to 0.2)	0.0 (-0.2 to 0.2)	0.0 (-0.3 to 0.2)	
Change at Week 72 (N = 170, 135, 38)	0.0 (-0.3 to 0.3)	0.0 (-0.3 to 0.2)	0.1 (-0.2 to 0.3)	
Change at Week 96 (N = 165, 123, 38)	-0.1 (-0.4 to 0.3)	0.0 (-0.2 to 0.4)	0.0 (-0.2 to 0.4)	
Change at Week 144 (N = 153, 110, 34)	-0.1 (-0.4 to 0.3)	0.0 (-0.2 to 0.3)	0.0 (-0.5 to 0.6)	
Change at Week 192 (N = 117, 94, 24)	0.0 (-0.4 to 0.5)	0.1 (-0.2 to 0.5)	-0.1 (-0.4 to 0.4)	
Change at Week 240 (N = 86, 72, 16)	0.1 (-0.5 to 0.5)	0.1 (-0.2 to 0.4)	0.1 (-0.5 to 0.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Height Percentiles as a Measurement of Growth and Development

End point title	Change From Baseline in Height Percentiles as a Measurement of Growth and Development[4]

End point description:

An age- and sex-specific percentile was derived for each weight, height and BMI measurement according to the downloadable SAS program available on the Centers for Disease Control (CDC) website using the year 2000 growth charts. Participants in the Full Analysis Set with available data were analysed.

End point type	Primary

End point timeframe:

Baseline (Day 1); Weeks 24, 48, 72, 96, 144, 192, and 240

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed for the overall population between the age groups.

End point values	12 to < 18 years old	6 to < 12 years old	3 to < 6 years old	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	205	164	57	
Units: percentile				
median (inter-quartile range (Q1-Q3))				
Baseline	43.5 (19.6 to 69.1)	42.7 (17.5 to 73.5)	49.6 (19.0 to 63.7)	
Change at Week 24 (N = 190, 163, 54)	0.0 (-2.7 to 2.4)	0.5 (-1.7 to 3.7)	-1.5 (-8.3 to 1.0)	
Change at Week 48 (N = 164, 136, 45)	-0.2 (-3.6 to 3.9)	1.2 (-1.1 to 6.4)	-0.2 (-6.7 to 3.1)	
Change at Week 72 (N = 170, 135, 38)	-0.6 (-4.9 to 2.7)	2.1 (-1.7 to 6.4)	0.0 (-8.9 to 2.6)	
Change at Week 96 (N = 165, 123, 38)	-1.2 (-5.7 to 2.3)	2.2 (-2.3 to 7.9)	-2.6 (-9.1 to 1.2)	
Change at Week 144 (N = 153, 110, 34)	-1.0 (-6.4 to 2.4)	2.6 (-4.0 to 13.2)	0.9 (-4.8 to 3.4)	
Change at Week 192 (N = 117, 94, 24)	-0.6 (-6.7 to 2.6)	2.5 (-3.3 to 16.3)	2.5 (-6.3 to 13.8)	
Change at Week 240 (N = 86, 72, 16)	-1.0 (-5.8 to 3.2)	0.5 (-13.2 to 15.2)	2.4 (-4.7 to 11.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Weight Percentiles as a Measurement of Growth and Development

End point title	Change From Baseline in Weight Percentiles as a Measurement of Growth and Development[5]

End point description:

An age- and sex-specific percentile was derived for each weight, height and BMI measurement according to the downloadable SAS program available on the CDC website using the year 2000 growth charts. Participants in the Full Analysis Set with available data were analysed.

End point type	Primary

End point timeframe:

Baseline (Day 1); Weeks 24, 48, 72, 96, 144, 192, and 240

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed for the overall population between the age groups.

End point values	12 to < 18 years old	6 to < 12 years old	3 to < 6 years old	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	205	164	57	
Units: percentile				
median (inter-quartile range (Q1-Q3))				
Baseline	62.7 (37.2 to 84.2)	60.3 (25.6 to 84.5)	57.6 (23.9 to 74.9)	
Change at Week 24 (N = 191, 163, 54)	0.0 (-3.5 to 3.2)	0.3 (-2.3 to 3.8)	-0.6 (-5.9 to 1.7)	
Change at Week 48 (N = 165, 136, 45)	0.3 (-5.3 to 5.0)	0.6 (-2.7 to 7.0)	-0.8 (-6.0 to 1.5)	
Change at Week 72 (N = 170, 135, 39)	-0.3 (-8.0 to 4.0)	0.5 (-2.6 to 7.7)	-0.1 (-6.9 to 3.2)	
Change at Week 96 (N = 165, 123, 38)	0.0 (-12.4 to 5.6)	2.3 (-1.1 to 9.7)	1.0 (-4.7 to 2.6)	
Change at Week 144 (N = 153, 111, 34)	-0.8 (-11.6 to 4.1)	3.5 (-1.6 to 12.2)	0.0 (-7.0 to 4.6)	
Change at Week 192 (N = 117, 94, 24)	-0.1 (-13.0 to 6.3)	3.2 (-1.3 to 12.9)	0.5 (-3.9 to 5.6)	
Change at Week 240 (N = 86, 72, 16)	0.3 (-13.3 to 10.0)	2.4 (-1.5 to 12.4)	2.8 (-6.0 to 12.7)	

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in BMI Percentiles as a Measurement of Growth and Development

End point title	Change From Baseline in BMI Percentiles as a Measurement of Growth and Development[6]

End point description:

An age- and sex-specific percentile was derived for each weight, height and BMI measurement according to the downloadable SAS program available on the CDC website using the year 2000 growth charts. Participants in the Full Analysis Set with available data were analysed.

End point type	Primary

End point timeframe:

Baseline (Day 1); Weeks 24, 48, 72, 96, 144, 192, and 240

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed for the overall population between the age groups.

End point values	12 to < 18 years old	6 to < 12 years old	3 to < 6 years old	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	205	164	57	
Units: Percentile				
median (inter-quartile range (Q1-Q3))				
Baseline	64.2 (38.1 to 88.0)	66.4 (35.1 to 89.8)	66.6 (39.2 to 84.8)	
Change at Week 24 (N = 190, 163, 54)	0.1 (-4.2 to 3.9)	-0.2 (-4.1 to 3.9)	-0.1 (-7.4 to 5.1)	
Change at Week 48 (N = 164, 136, 45)	0.3 (-5.2 to 4.8)	0.3 (-5.5 to 4.6)	0.0 (-7.7 to 3.7)	
Change at Week 72 (N = 170, 135, 38)	-0.4 (-8.3 to 5.4)	0.4 (-4.8 to 5.5)	0.3 (-5.6 to 7.2)	
Change at Week 96 (N = 165, 123, 38)	-1.1 (-9.7 to 5.0)	0.1 (-4.3 to 6.9)	0.3 (-5.5 to 7.8)	
Change at Week 144 (N = 153, 110, 34)	-1.1 (-9.6 to 5.7)	0.5 (-5.0 to 8.3)	-0.8 (-13.3 to 10.4)	
Change at Week 192 (N = 117, 94, 24)	-0.2 (-11.9 to 7.1)	1.0 (-2.1 to 9.9)	-0.8 (-8.6 to 8.3)	
Change at Week 240 (N = 86, 72, 16)	1.1 (-13.6 to 9.7)	1.5 (-2.3 to 6.0)	1.2 (-12.5 to 25.0)	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Male Participants With a Change in Tanner Stage Assessment for Pubic Hair

End point title	Number of Male Participants With a Change in Tanner Stage Assessment for Pubic Hair[7]

End point description:

Tanner Pubertal Staging was assessed for pubic hair growth and genitalia development in males from stages 1 to 5. Tanner stages were used to evaluate the progression of pubertal changes from stage 1 (pre-pubertal) to stage 5 (adult). If a participant had reached Tanner stage 5, no further Tanner pubertal stage
assessments were to be completed. Pubic hair growth: Tanner stages (1: No hair, 2: Downy hair, 3: More coarse and curly hair, 4: Adult-like hair quality; 5: Hair extends to the medial surface of the thighs). Participants in the Full Analysis Set with available data were analysed.

End point type	Primary

End point timeframe:

Baseline (Day 1); Week 240

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified for this primary end point.

End point values	Male: Baseline Stage 1	Male: Baseline Stage 2	Male: Baseline Stage 3	Male: Baseline Stage 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	79	19	11	24
Units: participants				
number (not applicable)				
Week 240; Stage 1 (N = 75)	9	0	0	0
Week 240; Stage 2 (N = 75)	5	0	0	0
Week 240; Stage 3 (N = 75)	4	1	0	0
Week 240; Stage 4 (N = 75)	7	2	0	0
Week 240; Stage 5 (N = 75)	6	6	7	9
Not done	1	0	0	0
Visit not reached	47	10	4	15

End point values	Male: Baseline Stage 5			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: participants				
number (not applicable)				
Week 240; Stage 1 (N = 75)	0			
Week 240; Stage 2 (N = 75)	0			
Week 240; Stage 3 (N = 75)	0			
Week 240; Stage 4 (N = 75)	0			
Week 240; Stage 5 (N = 75)	19			
Not done	0			
Visit not reached	27			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Male Participants With a Change in Tanner Stage Assessment for Genitalia

End point title	Number of Male Participants With a Change in Tanner Stage Assessment for Genitalia[8]

End point description:

Tanner Pubertal Staging was assessed for pubic hair growth and genitalia development in males from stages 1 to 5. Tanner stages were used to evaluate the progression of pubertal changes from stage 1 (pre-pubertal) to stage 5 (adult). If a participant had reached Tanner stage 5, no further Tanner pubertal stage
assessments were to be completed. Genitalia development: Tanner stages (1: Testes, scrotum, and penis about same size, 2: Enlargement of scrotum, testes and penis, 3: Enlargement of penis, 4: Penis size enlargement, 5: Genitalia adult in size and shape). Participants in the Full Analysis Set with available data
were analysed.

End point type	Primary

End point timeframe:

Baseline (Day 1); Week 240

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified for this primary end point.

End point values	Male: Baseline Stage 1	Male: Baseline Stage 2	Male: Baseline Stage 3	Male: Baseline Stage 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	18	16	20
Units: participants				
number (not applicable)				
Week 240; Stage 1 (N = 75)	7	0	0	0
Week 240; Stage 2 (N = 75)	6	0	0	0
Week 240; Stage 3 (N = 75)	5	1	0	0
Week 240; Stage 4 (N = 75)	7	2	0	0
Week 240; Stage 5 (N = 75)	6	5	9	8
Not done	1	0	0	0
Visit not reached	45	10	7	12

End point values	Male: Baseline Stage 5			
Subject group type	Subject analysis set			
Number of subjects analysed	48			
Units: participants				
number (not applicable)				
Week 240; Stage 1 (N = 75)	0			
Week 240; Stage 2 (N = 75)	0			
Week 240; Stage 3 (N = 75)	0			
Week 240; Stage 4 (N = 75)	0			
Week 240; Stage 5 (N = 75)	19			
Not done	0			
Visit not reached	29			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Female Participants With a Change in Tanner Stage Assessment for Pubic Hair

End point title	Number of Female Participants With a Change in Tanner Stage Assessment for Pubic Hair[9]

End point description:

Tanner Pubertal Staging was assessed for pubic hair growth and breast development in females from stages 1 to 5. Tanner stages were used to evaluate the progression of pubertal changes from stage 1 (pre-pubertal) to stage 5 (adult). If a participant had reached Tanner stage 5, no further Tanner pubertal stage
assessments were to be completed. Pubic hair growth: Tanner stages (1: No hair, 2: Downy hair, 3: More coarse and curly hair, 4: Adult-like hair quality; 5: Hair extends to the medial surface of the thighs). Participants in the Full Analysis Set with available data were analysed.

End point type	Primary

End point timeframe:

Baseline (Day 1); Week 240

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified for this primary end point.

End point values	Female: Baseline Stage 1	Female: Baseline Stage 2	Female: Baseline Stage 3	Female: Baseline Stage 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	101	23	29	36
Units: participants				
number (not applicable)				
Week 240; Stage 1 (N = 97)	7	0	0	0
Week 240; Stage 2 (N = 97)	5	0	0	0
Week 240; Stage 3 (N = 97)	7	2	0	0
Week 240; Stage 4 (N = 97)	7	0	2	0
Week 240; Stage 5 (N = 97)	9	6	10	15
Not done	1	2	0	0
Visit not reached	65	13	17	21

End point values	Female: Baseline Stage 5			
Subject group type	Subject analysis set			
Number of subjects analysed	58			
Units: participants				
number (not applicable)				
Week 240; Stage 1 (N = 97)	0			
Week 240; Stage 2 (N = 97)	0			
Week 240; Stage 3 (N = 97)	0			
Week 240; Stage 4 (N = 97)	0			
Week 240; Stage 5 (N = 97)	27			
Not done	0			
Visit not reached	31			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Female Participants With a Change in Tanner Stage Assessment for Breast Development

End point title	Number of Female Participants With a Change in Tanner Stage Assessment for Breast Development[10]

End point description:

Tanner Pubertal Staging was assessed for pubic hair growth and breast development in females from stages 1 to 5. Tanner stages were used to evaluate the progression of pubertal changes from stage 1 (pre-pubertal) to stage 5 (adult). If a participant had reached Tanner stage 5, no further Tanner

pubertal stage
assessments were to be completed. Breast development: Tanner stages (1: No glandular tissue, 2: Breast bud forms,3: More elevated, outside areola, 4: Increased breast size,5: Final adult-size breasts). Participants in the Full Analysis Set with available data were analysed.

End point type	Primary

End point timeframe:

Baseline (Day 1); Week 240

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified for this primary end point.

End point values	Female: Baseline Stage 1	Female: Baseline Stage 2	Female: Baseline Stage 3	Female: Baseline Stage 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	86	33	31	40
Units: participants				
number (not applicable)				
Week 240; Stage 1 (N = 97)	8	0	0	0
Week 240; Stage 2 (N = 97)	2	0	0	0
Week 240; Stage 3 (N = 97)	8	4	1	0
Week 240; Stage 4 (N = 97)	4	1	2	0
Week 240; Stage 5 (N = 97)	8	5	12	14
Not done	1	2	0	0
Visit not reached	55	21	16	26

End point values	Female: Baseline Stage 5			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: participants				
number (not applicable)				
Week 240; Stage 1 (N = 97)	0			
Week 240; Stage 2 (N = 97)	0			
Week 240; Stage 3 (N = 97)	0			
Week 240; Stage 4 (N = 97)	0			
Week 240; Stage 5 (N = 97)	28			
Not done	0			
Visit not reached	29			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Maintained Sustained Virologic Response (SVR) During the Study

End point title	Percentage of Participants Who Maintained Sustained Virologic

	Response (SVR) During the Study

End point description:

A participant was considered to have achieved SVR if the hepatitis C virus (HCV) levels were less than the lower limit of quantification (LLOQ) [i.e 15 international units (IU)/millilitre (mL)] during the parent study. Virologic failure is defined as having 2 consecutive blood samples (at least one week apart) with HCV ribonucleic acid (RNA) > LLOQ, or last available HCV RNA> LLOQ with no subsequent follow-up values. Participants in the Full Analysis Set who achieved SVR in the parent study were analyzed.

End point type	Secondary

End point timeframe:

From enrollment up to maximum duration of 6.3 years

End point values	All participants			
Subject group type	Subject analysis set			
Number of subjects analysed	424			
Units: percentage				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-Cause Mortality and Adverse Events (AEs): From enrollment up to maximum duration of 6.3 years

Adverse event reporting additional description:

All-Cause Mortality: Included participants who signed informed consent and enrolled into study. AEs: Included all enrolled participants who met all inclusion criteria , and with at least one post-Day 1 visit measurement available.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	SOF+RBV

Reporting group description:

Participants who were previously treated with sofosbuvir (SOF) along with ribavirin (RBV) were followed for up to 5 years.

Reporting group title	LDV/SOF+/-RBV

Reporting group description:

Participants who were previously treated with ledipasvir (LDV)/SOF with or without RBV were followed for up to 5 years.

Reporting group title	SOF/VEL

Reporting group description:

Participants who were previously treated with SOF/velpatasvir (VEL) were followed for up to 5 years.

Reporting group title	SOF/VEL/VOX

Reporting group description:

Participants who were previously treated with SOF/VEL/voxilaprevir (VOX) were followed for up to 5 years.

Serious adverse events	SOF+RBV	LDV/SOF+/-RBV	SOF/VEL
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 88 (0.00%)	0 / 178 (0.00%)	0 / 142 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			

Serious adverse events	SOF/VEL/VOX		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	SOF+RBV	LDV/SOF+/-RBV	SOF/VEL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 88 (1.14%)	0 / 178 (0.00%)	0 / 142 (0.00%)
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 88 (1.14%)	0 / 178 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	SOF/VEL/VOX		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)		
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2014	- Quality of Life assessment was moved from a secondary objective/endpoint to an exploratory objective/endpoint. - Added exclusion criteria for subjects with history of clinically significant illness or any other major medical disorder that may interfere with the study - Modified discontinuation criteria to include subjects initiating any new course of hepatitis C therapy rather than only antiviral therapy. - Added Tanner Pubertal Stage Assessment as a baseline assessment - Modified the physical examination procedure performed at each study visit to a symptom-directed physical examination. - Modified inform consent procedures to align with parent pediatric procedures. - Added Tanner Pubertal Stage Assessment procedures and specifications. - Added Body Height & Weight Measurement procedures and specifications. - Added Quality of Life Surveys procedure and specifications. - Updated the SAE reporting procedure and requirements to align with Gilead Sciences Inc. (GSI) standard operating procedures.
22 May 2015	- Laboratory tests assessing liver function has been removed as a primary end point based on local standard of care and that the goal of the registry is to evaluate growth and development after therapy. - Each subject will not be required to complete the Day 1 assessments. These assessments will be documented as the last visit of the previous Gileadsponsored treatment protocol. - Study visits were reduced by fulfilling the minimum regulatory requirements. - Informed consent language was added to align with the Gilead-sponsored treatment protocols. - Since each subject's Day 1 assessments will be documented from the last visit of the previous Gilead-sponsored treatment protocol, the informed consent must be signed prior to conduct of any study assessment at the Week 24 visit and within 120 days from the subject's last visit in the Gileadsponsored treatment protocol. - The PedsQL™ Young Adult survey was added to the protocol for subjects who are >18 years old.
09 February 2016	- Additional language has been added for clarification on retesting procedures in the event of a positive HCV RNA result as requested by country-specific ethics committees. - Additional flexibility in the duration of time each subject and their parent/legal guardian has to sign the initial consent form(s) has been included within the Registry protocol. - Additional language was added to provide clarification on how SAEs related to the previous Gilead-sponsored study will be reported once the treatment protocols' database has been locked. - Reminder phone calls to the subject by the study site have been added to the study procedures in order to increase subject retention. - Language for consent requirements has been modified to be more generic due to the varying country-specific regulations on the age of an adult subject. - Date of first menses is not a required data point in order to conduct the Tanner Pubertal Stage Assessment and therefore has been removed. - Adverse events had been added to the primary safety endpoints in error and therefore have been removed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported