CLINICAL STUDY PROTOCOL

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
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
IND No.:	106739
EudraCT Number:	2014-004674-42
Clinical Trials.gov Identifier:	NCT02510300
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-334-1113
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404, USA

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
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	106739 2014-004674-42 NCT02510300
Study Centers Planned:	Study centers with at least one adolescent or pediatric subject who received treatment with at least one Gilead HCV direct acting antiviral (DAA) while participating in a Gilead-sponsored chronic hepatitis C study.
Objectives:	The primary objective of this Registry is: • To determine the long-term safety of anti-HCV regimens in the pediatric population as determined by assessments of growth and development. The secondary objectives of this Registry are: • To determine whether subsequent detection of HCV RNA in subjects 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 subjects who did not achieve SVR The exploratory objective of this Registry is: P [redacted]

Study Design:	This Registry will enroll adolescent and pediatric subjects who received at least one Gilead HCV direct acting antiviral (DAA) while participating in Gilead-sponsored chronic hepatitis C clinical trials. Once enrolled, subjects will be followed for up to 5 years. The Day 1 visit will be documented as the last visit of the previous Gilead-sponsored treatment protocol. Subsequent visits will occur at Weeks 24, 48, 72, 96, 144, 192, and 240. At each visit, subjects will have blood drawn for plasma HCV RNA quantification and viral sequencing (archive). In addition, a symptom-directed physical examination, body height and weight measurements, and Tanner Pubertal Stage Assessment (when appropriate) will be performed. A quality-of-life survey will be completed. If a subject tests positive for HCV RNA after non-detectable levels at Day 1 or any time throughout the study, the subject will have a repeat blood sample drawn for confirmation. Subjects who begin a new treatment course for HCV infection will discontinue participation in the Registry.
Target Population:	Adolescent and pediatric subjects who received at least one Gilead HCV direct acting antiviral (DAA) while participating in a Gilead-sponsored chronic hepatitis C study.
Duration of Study Participation:	This observational Registry will follow subjects every 6 months for the first 2 years followed by every 12 months for up to five years.
Diagnosis and Main Eligibility Criteria:	Inclusion Criteria: To be eligible for participation, a subject must: • Have previously participated in a Gilead-sponsored chronic hepatitis C study as an adolescent or pediatric subject and received at least one Gilead HCV direct acting antiviral (DAA); • Parent or legal guardian able to provide written informed consent OR subject able to provide written informed consent and willing to comply with study requirements, as determined by IRB/IEC/local requirements and Investigator's discretion. • 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 Exclusion Criteria: • 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.

	• History of clinically-significant illness or any other major medical disorder that may interfere with the subject follow-up, assessments or compliance with the protocol.
Study Procedures/ Frequency:	The subject and/or the subject's parent or legal guardian must provide written consent within 168 days from the last visit of the previous Gilead-sponsored treatment protocol. Subjects will be assessed at Day1 and at Week 24, 48, 72, 96, 144, 192, and 240. At each visit blood will be collected for HCV RNA and viral sequencing (archive), and a quality-of-life survey will be completed. Symptom-directed physical exams, body height and weight measurements, and Tanner Pubertal Stage Assessment (if applicable) will be performed. Only AEs and SAEs considered to be related to study procedures mandated by the Registry protocol will be reported under this Registry. Any treatment related SAEs will be reported within the previous Gilead-sponsored treatment protocol.
Test Product, Dose, and Mode of Administration:	No test product will be administered in this Registry.
Reference Therapy, Dose, and Mode of Administration:	None.
Criteria for Evaluation:	None. This is an observational Registry.
Statistical Methods:	Data from this Registry study will be summarized descriptively. Statistical hypothesis testing will not be conducted. All continuous variables will be summarized using an 8-number descriptive summary (n, mean, standard deviation, and median, Q1, Q3, minimum, maximum) by visit. All categorical variables will be summarized by number and percentage of subjects in each categorical definition.

This study will be conducted in accordance with the guidelines of Good Clinical Practices (GCPs) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CRF	Case report form(s)
CRO	Contract (or clinical) research organization
DAA	Direct acting antiviral
DSPH	Drug Safety and Public Health
eCRF	Electronic case report form(s)
EC	European Commission
EU	European Union
EudraCT	European clinical trials database
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice (Guidelines)
GT	Genotype
HCV	Hepatitis C virus
HLT	High level term
HLGT	High level group term
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IL28B	IL28B gene
IND	Investigational New Drug (Application)
IRB	Institutional review board
IU	International unit
LLT	Low level term
LLoQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
N	Number
OAV	Oral antiviral
PEG	Pegylated interferon
PI	Protease inhibitor or principal investigator
PT	Prothrombin time or Preferred term
Q1, Q3	Quartiles 1 and 3
RBV	Ribavirin
RNA	Ribonucleic acid
SADR	Serious Adverse Drug Reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SAS	Statistical Analysis Software
SGPT	Alanine aminotransferase
SOC	System Organ Class or Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
TBD	To be determined
USA	United States

1. INTRODUCTION

1.1. Background

Hepatitis C virus (HCV) is responsible for a large proportion of chronic liver disease worldwide and accounts for 70% of cases of chronic hepatitis in industrialized countries. The global prevalence of chronic hepatitis C is estimated to average 3% {Esteban et al 2008}.

The natural history of chronic HCV infection in children differs from that in adults since HCV infection in children is relatively benign. Most children chronically infected with HCV are asymptomatic or have mild nonspecific symptoms. Clinical symptoms are present in approximately 20% of children in the first 4 years of life, with hepatomegaly being the most frequent sign (10%). Many, but not all, perinatally infected children will have intermittently or persistently abnormal alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, particularly in the first 2 years of life. In children with vertical HCV-infection who have undergone liver biopsy, the histological spectrum is usually mild, although severe liver disease is encountered {Mohan et al 2010}. Despite the overall more favorable prognosis compared to adults, approximately 4% to 6% of children with chronic HCV infection have evidence of advanced fibrosis or cirrhosis and some children eventually require liver transplantation for end-stage liver disease as a consequence of HCV infection {Hu et al 2010}.

Per the 2010 European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guideline, the primary goal of treatment in children is to eradicate the infection to prevent late complications {Wirth et al 2010}. Pediatric treatment of HCV is controversial as the current treatment options are limited, efficacy is variable and severe side effects and tolerability can significantly limit or preclude their use. PEG and weight-based RBV are currently considered the standard of care for the treatment of HCV infection in children. Current recommendations are that patients with GT-2 or GT-3 be treated with PEG+RBV for 24 weeks and those with GT-1 or GT-4 should receive 48 weeks of therapy. A number of pediatric studies have reported that despite 48 weeks of treatment, sustained virologic response (SVR24) was observed in only 36% to 53% of subjects with GT-1, while response rates were > 80% in subjects with GT-2 or GT-3 {Wirth 2012}.Additionally, the concern for growth and development in this age group and the role that both PEG and RBV potentially play in reducing growth rates has initiated significant debate among pediatric hepatologists as to whether these treatments should even be considered in the pediatric population {Serranti et al 2011}.

Novel HCV treatments under study are directed against a variety of viral molecular targets. Sofosbuvir (SOF) is a potent nucleotide analogue that inhibits HCV RNA replication in vitro and has demonstrated high rates of sustained viral response (SVR) when given with RBV +/- PEG to adult subjects with chronic GT- 1, 2, 3 or 4 HCV infection {Gilead Sciences Inc 2013}, {Gane et al 2013}, {Jacobson et al 2013}, {Lawitz et al 2013}. SOF (Sovaldi®) has been approved in the United States by the Food and Drug Administration (FDA) for the treatment of HCV infection GT- 1, 2, 3 and 4 including treatment naïve and experienced patients and HIV/HCV co-infected patients. Sovaldi™ is also approved in the EU and 34 additional countries. Based on its observed safety and efficacy in adult patients with HCV, SOF with RBV or other directly-acting antiviral

agents has the potential to be a safe, tolerable, and effective treatment for HCV infection in the pediatric population.

Ledipasvir/Sofosbuvir fixed-dose combination (LDV/SOF FDC) combines two HCV specific direct acting antiviral (DAA) agents into a single tablet for the treatment of chronic HCV infection. SOF is a nucleotide analog that is a potent and selective inhibitor of NS5B directed HCV replication with demonstrated activity against GT 1-6 HCV-infection. Ledipasvir (LDV) is a novel HCV NS5A inhibitor that has demonstrated potent anti HCV activity, with the highest activity against GT1 HCV-infection. Harvoni® (LDV/SOF FDC) has been approved in the United States by the Food and Drug Administration (FDA) for treatment of HCV infection GT-1 adult patients. Harvoni® is also approved in the EU for treatment of HCV infection GT-1, 4, 5, and 6 adult patients and for GT-3 treatment-experienced adults with cirrhosis and/or prior treatment failure subjects for 24 weeks treatment duration with ribavirin (RBV).

1.2. Rationale for the Registry Study

Gilead Sciences is developing a number of novel antiviral agents targeting various components of the hepatitis C virus replication cycle and the Registry Study will provide long-term assessment of safety and durability in pediatric subjects. Given the concern of the effect of current standard of care treatments (PEG and RBV) may have on growth and development in the pediatric population, the registry study will specifically determine the effect of investigational anti-HCV regimens in the pediatric population as determined by assessments of growth and development. It will also measure the effect of treatment on quality of life. Lastly, the Registry is designed to provide long term clinical and virologic follow-up in subjects who have achieved SVR while participating in a previous Gilead-sponsored HCV study. This Registry will also provide long-term follow-up to evaluate HCV viral sequences, and the persistence or evolution of viral mutations in subjects who did not achieve an SVR in a previous Gilead-sponsored chronic hepatitis C trial.

2. OBJECTIVES

The primary objective of this Registry is:

- To determine the long-term safety of anti-HCV regimens in the pediatric population as determined by assessments of growth and development.

The secondary objectives of this Registry are:

- To determine whether subsequent detection of HCV RNA in subjects who relapse following 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 subjects who did not achieve SVR;

The exploratory objective of this Registry is:

P
P

3. STUDY DESIGN

3.1. Study Design

This Registry will enroll adolescent and pediatric subjects who received at least one Gilead HCV direct acting antiviral (DAA) while participating in a Gilead-sponsored chronic hepatitis C clinical trial.

3.2. Visit Schedule

Once enrolled, subjects will be followed for up to 5 years. The subject and/or the subject's parent or legal guardian must provide written consent within 168 days from the last visit of the previous Gilead-sponsored treatment protocol. The Day 1 visit will be documented as the last visit of the previous Gilead-sponsored treatment protocol. Subsequent study visits will occur at Weeks 24, 48, 72, 96, 144, 192, and 240. At each subsequent visit, subjects will have blood drawn for plasma HCV RNA quantification and viral sequencing (archive). In addition, a symptom-directed physical examination, body height and weight measurements, and Tanner Pubertal Stage Assessment (when appropriate) will be performed. A quality-of-life survey will be completed. Reminder phone calls to subjects will be conducted by the site staff at 1-2 months prior to each study visit following the subject's Day 1 visit date.

While participating in the Registry, if a subject tests positive for HCV RNA after non-detectable levels at Day 1 (defined as HCV RNA ≥ LLoQ) or any time throughout the study, they will be asked to return to the clinic for collection of a repeat blood sample for HCV RNA quantitation.

The assessments to be performed at each visit are described in Section 6.

3.3. Discontinuations

While participating in the Registry, subjects will be discontinued for the following instances:

- Subjects who initiate a new course of hepatitis C therapy (including approved products and investigational agents);
- Subjects or parents/legal guardians who request to discontinue for any reason; it is important to clearly determine and document the specific reason for withdrawal of consent;
- Discontinuation of the Registry and/or subjects at the request of Gilead, regulatory agency or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

If a subject meets withdrawal criteria or discontinues participation for any reason, the subject should complete an Early Termination visit.

4. SUBJECT POPULATION

4.1. Inclusion Criteria

Subjects must meet *all* of the following inclusion criteria to be eligible for participation in this Registry.

Have previously participated in a Gilead-sponsored chronic hepatitis C study as an adolescent or pediatric subject and received at least one Gilead HCV direct acting antiviral (DAA);

Parent or legal guardian able to provide written informed consent OR subject able to provide written informed consent prior to any study procedures and willing to comply with study requirements as determined by IRB/IEC/local requirements and Investigator's discretion.

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

4.2. 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.

2. History of clinically-significant illness or any other major medical disorder that may interfere with the subject follow-up, assessments, or compliance with the protocol.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Investigational Medicinal Product

This is a long-term observational follow-up Registry study. No investigational medicinal product will be administered in this trial.

5.2. Prohibited Concomitant Medications

Any new course of hepatitis C therapy including any investigational drug or device will be prohibited while participating in this Registry. If a subject requires any new treatment course for HCV infection during the Registry, the subject will be discontinued from the Registry. There are no other concomitant medications which would preclude subjects from participating in this Registry.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment

The duration of study participation will be up to 5 years. For each child or adolescent participating within the study, subject's parent or legal guardian must sign an Informed Consent Form. Subject's eligibility will be determined and the Informed Consent Form must be signed prior to the conduct of any study procedures and within 168 days from the subject's last visit in the Gilead-sponsored treatment protocol. Each child or adolescent participating within the study who has the ability to read and write must sign an Assent Form, as required by IRB/IEC/local requirements, prior to the conduct of any study procedures. Subjects considered adults as per the IRB/IEC/local requirements may consent themselves without the subject's parent or legal guardian.

6.2. Day 1 Assessments

If a Tanner Pubertal Stage Assessment determined the subject was at a Tanner 5 in the Gilead-sponsored treatment protocol, no further Tanner Pubertal Stage Assessments are to be completed.

The Day 1 visit will be documented as the last visit of the previous Gilead-sponsored treatment protocol. The following procedures will be performed (if applicable) and documented:

- Written informed consent from parent or legal guardian and assent from subject OR informed consent from subject themselves, if applicable as described above (may be obtained prior to the Day 1 visit)
- Review eligibility criteria (Section 4)
- Perform symptom-directed physical examination
- Body height and weight measurements
- Tanner Pubertal Stage Assessment
- Complete quality-of-life survey
- Obtain blood samples for:
  - Plasma HCV RNA
  - Viral sequencing (archive)
- Assessment of procedure-related adverse events

6.3. Follow-Up Assessments

Follow-up assessment visits will be scheduled based on the Day 1 visit date.

6.3.1. Weeks 24, 48, 72, 96, 144, 192, and 240 (+/- 30 days)

A Tanner Pubertal Stage assessment will be performed at all study visits until a Tanner Stage 5 has been reached. Reminder phone calls to subjects will be conducted by the site staff at 1-2 months prior to each study visit following the subject's Day 1 visit date.

The following procedures will be performed and documented:

- Perform symptom-directed physical examination
- Body height and weight measurements
- Tanner Pubertal Stage Assessment (if applicable)
- Complete quality-of-life survey
- Obtain blood samples for:
  - Plasma HCV RNA (If HCV RNA is detected after non-detectable levels at Day 1 or any time throughout the study, the subject will have a repeat blood sample drawn for confirmation)
  - Viral sequencing, (archive)
- Assessment of procedure-related AEs

Subjects discontinuing participation for any reason should complete an Early Termination Visit.

6.3.2. Early Termination Visit

Subjects discontinuing the Registry for any reason should undergo the following procedures:

- Perform symptom-directed physical examination
- Body height and weight measurements
- Tanner Pubertal Stage Assessment (if applicable)
- Complete quality-of-life survey
- Obtain blood samples for:
  - Plasma HCV RNA (If HCV RNA is detected after non-detectable levels at Day 1 or any time throughout the study, the subject will have a repeat blood sample drawn for confirmation)
  - Viral sequencing, (archive)
- Assessment of procedure-related AEs

6.4. Procedures and Specifications

6.4.1. Clinical Laboratory Analytes

Virological Tests: Plasma HCV RNA and viral sequence analysis

A portion of the blood samples drawn at all study visits will be frozen and stored. The stored blood samples may be used by the Sponsor or its research partners for HCV genotyping/phenotyping assays (as applicable) or their development, for retesting the amount of HCV in the blood, and/or for future testing to learn more about how the study drug (received in the Gilead-sponsored treatment protocol) has worked against HCV or clinical laboratory testing to provide additional clinical data. No human genetic testing will be performed without the written consent of the parent or legal guardian. At the conclusion of this Registry, these samples may be retained in storage by Gilead Sciences, Inc. for a period up to 15 years.

6.4.2. HCV Sequence Analysis

HCV sequencing will be performed if confirmed HCV RNA is ≥1000 IU/mL at any time during the Registry. The specific HCV genes to be sequenced will be based on the specific oral anti-viral (OAV) agent(s) administered to the subject in the initial Gilead-sponsored treatment protocol.

6.4.3. Tanner Pubertal Stage Assessment

The Tanner Stage scale is available in Appendix 3. A Tanner Pubertal Stage assessment will be performed at all study visits until a Tanner Stage 5 has been reached. If the assessment within the Gilead-sponsored treatment protocol determined the subject was at a Tanner 5, no further Tanner Pubertal Stage Assessments are to be completed.

6.4.4. Body Height & Weight Measurement

Body height and weight measurements will be collected at each visit. The difference in body weight and height measurements between baseline and each visit will be calculated.

6.4.5. Quality of Life Survey

The PedsQL™ Pediatric Quality of Life Inventory V4.0 Short Form (SF15) will be completed at each visit. Subjects who are >18 years old will complete the PedsQL™ Pediatric Quality of Life Inventory V4.0.

The PedsQL™ has separate survey instruments administered by age group, including the Young Adult Report (ages >18), Teen Report (ages 13-18), Child Report (ages 8-12), Young Child Report (ages 5-7), and Toddlers (ages 2-4). Each survey accompanied by the respective parent proxy survey will be administered to the subject and their parent/legal guardian (with the exception of the Toddlers Report which will only be completed by the parent/legal guardian and the Young Adult Report which will only be complete by the subject) for the current age group at the time of survey administration.

7. ADVERSE EVENTS MANAGEMENT

7.1. Adverse Events

This study is a long-term observational Registry in which no study medication will be administered. Adverse events related to the initial Gilead-sponsored treatment protocol will be followed in accordance with that initial protocol.

As a consequence adverse event reporting in this Registry will be restricted to the following:

- Any adverse event occurring as a consequence of procedures required by this Registry protocol will be followed and documented in accordance with provisions outlined below.

For the purposes of this Registry an AE is any untoward medical occurrence in a clinical study subject associated with procedures mandated by this Registry protocol. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with procedures mandated by this Registry (e.g., hematoma following venipuncture).

An AE does not include the following for this Registry:

- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed is not an AE.

- Any medical condition or clinically significant laboratory abnormality occurring after the consent form is signed and is related to the initial Gilead-sponsored treatment protocol. Any events related to the initial treatment protocol will be followed according to that treatment protocol.

7.2. Serious Adverse Events

Any SAEs occurring during the initial Gilead-sponsored treatment protocol will be followed, documented and reported under that treatment protocol. Similarly any new SAEs occurring while the subject is participating in the Registry that are considered to be related to study drugs administered or procedures in the initial Gilead-sponsored treatment protocol will be followed, documented and reported under the initial Gilead-sponsored treatment protocol.

The only SAEs which will be reported under this Registry are events considered to be related to procedures mandated by the Registry protocol.

Serious adverse event (SAE) is defined as any adverse event that results in any of the following outcomes:

- Death

- Life-threatening situation (subject is at **immediate** risk of death)

- In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs)

- Persistent or significant disability/incapacity

- Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product. All pregnancy events will be followed to resolution/outcome in the initial Gilead-sponsored treatment protocol

- Other: medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself.

- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.

- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

The relationship to study procedures (e.g., invasive procedures such as venipuncture) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.

- **Yes:** The AE occurred as a result of protocol-mandated procedures such as venipuncture.

7.3. Serious Adverse Event Reporting Requirements

7.3.1. All Serious Adverse Events

Gilead Sciences may be required to expedite to worldwide regulatory authorities reports of SAEs, Serious Adverse Drug Reactions (SADRs) or Suspected Unexpected Serious Adverse Reactions (SUSARs) in line with relevant legislation, including the applicable US FDA Code of Federal Regulations, the European Commission Clinical Trials Directive (2001/20/EC); therefore, Gilead Sciences (or the CRO on the behalf of Gilead Sciences) must be notified immediately regarding the occurrence of any SAE or SADR that occurs after the subject consents to participate in the Registry, including SAEs/SADRs resulting from protocol-mandated procedures. The procedure for reporting SAEs is as follows:

- All SAEs will be recorded in the eCRF database within 24 hours of the investigator's knowledge.

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead Drug Safety and Public Health (DSPH) within 24 hours of the investigator's knowledge of the event. Detailed instructions for how to record SAE data in the eCRF database can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically (i.e. the eCRF database is not functioning) record the SAE on the paper SAE reporting form and submit within 24 hours by emailing or faxing the report form to the attention of Gilead DSPH:

Gilead Sciences	Fax:	+1 (650) 522-5477
DSPH:	E-mail:	safety_fc@gilead.com

- As soon as it is possible to do so, any SAE reported on paper via email or fax must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, also e-mail or fax copies of hospital case reports, autopsy reports, and other documents when requested and applicable. Transmission of such documents should occur with Personal Subject Details de-identified, without losing the traceability of a document to the Subject Identifiers.

- Gilead Sciences may request additional information from the investigator to ensure the timely completion of accurate safety reports.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded in the event description section of the SAE form.

Follow-up of SAEs will continue through the last day on the Registry and/or until a conclusive outcome (e.g., resolved, resolved with sequelae, lost to follow-up, fatal) is achieved.

For SAEs related to the previous Gilead-sponsored treatment protocol once the treatment protocols eCRF database has been locked, the SAE should be reported via a paper form specific to the previous Gilead-sponsored treatment protocol. Submit the paper SAE report form within 24 hours by emailing or faxing the report form to the attention of Gilead DSPH:

Gilead Sciences	Fax:	+1 (650) 522-5477
DSPH:	E-mail:	safety_fc@gilead.com

7.3.2. Investigator and Sponsor Reporting Requirements for SAEs

Any SAE deemed by the investigator to be related to a protocol-mandated procedure should be collected and reported throughout the Registry study and reported to Gilead Sciences DSPH using the SAE report form.

An SAE may qualify for reporting to regulatory authorities. All Investigators will receive a safety letter notifying them of relevant SUSAR reports. The Investigator should notify the IRB as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead will notify worldwide regulatory authorities and the relevant Ethics Committees in concerned Member States of applicable SUSARs.

7.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs or Serious AEs

Laboratory abnormalities are usually not recorded as AEs or SAEs. Laboratory abnormalities will only be recorded as an AE/SAE if they are related to a protocol-mandated procedure and require medical or surgical intervention or discontinuation from the study.

7.5. Procedures to be followed in the Event of Pregnancy

Procedures to be followed in the event of pregnancy occurring on the initial treatment protocol are detailed in the Gilead-sponsored treatment protocol. No additional pregnancy reporting requirements are included in this Registry protocol.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives

Treatment regimen is defined as treatment regimen in the initial Gilead-sponsored treatment protocol.

8.1.1. Primary Objective

The primary objective of this study is to assess the long-term safety of anti-HCV regimens in the pediatric population as determined by assessment of growth and development.

8.1.2. Secondary Objectives

The secondary objectives of this study are:

- To determine whether subsequent detection of HCV RNA in subjects who relapse following 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 subjects who did not achieve SVR;

8.1.3. Exploratory Objective

PPD

8.2. Primary Safety Endpoints

The primary safety endpoints are:

- Growth data by visit grouped by age and gender;
- Development by Tanner Pubertal Stage Assessment;

8.3. Other Endpoints of Interest

PPD

8.4. Methods of Analysis

All individual data will be listed as measured. All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

8.4.1. Analysis Sets

8.4.1.1. Safety Analysis Set

The safety analysis set is defined as all enrolled subjects.

8.4.1.2. Efficacy Analysis Set

Efficacy Analysis Set is the same as safety analysis set.

8.4.2. Data Handling Conventions

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed.

All available data for subjects who do not complete the study will be included in data listings.

HCV RNA values below the LLoQ for the assay will be set to the lower limit minus 1 for calculation of summary statistics for the actual HCV RNA values and the change from baseline values by study visit. The reported values will be provided in the HCV RNA listing.

For selected analyses, HCV RNA data (IU/mL) will be transformed to the logarithmic (base 10) scale ($\log_{10}$ IU/mL).

8.4.3. Interim Analyses

Interim analyses may be performed on an ad hoc basis, approximately every year throughout the duration of the Registry. All endpoints will be summarized by visit.

8.5. Demographic Data and Enrollment Characteristics

Demographic and enrollment measurements will be summarized using standard descriptive methods.

Demographic summaries will include gender, race (with Asian-Oriental, Asian-Indian, Asian-Other combined to Asian), ethnicity (Hispanic or non-Hispanic), and age.

Enrollment data will include a summary of HCV RNA levels, HCV genotype and IL28B genotype, Tanner Pubertal Stage Assessment, and growth data.

8.6. Safety Analyses

Analysis of safety measures will be descriptive and will include subjects in the Safety analysis set. All safety data collected on or after the date of enrollment through the end of the study will be summarized.

8.6.1. Extent of Exposure

This is a Registry study with no active treatment; hence, extent of exposure to study drug is not applicable.

8.6.2. Adverse Events

Clinical adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the data of onset for the event. An adverse event is defined as an event that begins or worsens on or after the date the ICF is signed through study completion or study discontinuation and is classified as related to a study procedure.

Summaries (number and percent of subjects) of adverse events and serious adverse events will be provided.

Data listings will be provided for subjects who discontinued the study due to an adverse event.

8.6.3. Other Safety Evaluations

8.6.3.1. Tanner Pubertal Stage Assessment

Tanner Stages (Appendix 3) will be summarized by baseline Tanner Stage using descriptive statistics.

8.6.3.2. Growth Data

For each subject, body height, body weight, and Z-scores at baseline and at each visit will be calculated based on sex and age.

The changes in body height and weight measurements for all subjects will be examined to determine, for example, if the majority of subjects increased, decreased or stayed the same at each visit. The baseline measurements will be examined to show where the subjects were before the study, in terms of their height and weight, compared to the population. Summary statistics will be calculated for the measurements and the changes in measurements at each visit by sex and overall. Depending on the distribution of the data, either a Wilcoxon signed rank test, or a one-sample t-test will be done to evaluate if the mean or median change from baseline is different from zero.

The number of subjects whose change increases, decreases, and stays the same will be tabulated at each visit. Due to the precise nature of the calculations, the "stays the same" category may be broadened to include changes other than zero, which are negligible (i.e. 0.5).

Z-scores for body weight and height and change from baseline in Z-scores for body weight and height will be summarized by visit. Figures for the median and IQR in height and weight Z-score by visit will be displayed.

In addition, summary statistics of the absolute value and change from baseline in both height and weight will be tabulated by visit.

8.7. Quality of Life Analysis

The data from PedsQL™ Pediatric Quality-of-life survey will be summarized with descriptive statistics at each visit by visit and age group and overall.

8.8. Other Analyses

In general, all continuous endpoints will be summarized using an 8-number descriptive summary (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum). All categorical endpoints will be summarized by the number and percent of subjects meeting the endpoint.

The proportion of subjects maintaining SVR, proportion of subjects with detectable HCV RNA due to re-emergence of pre-existing virus, proportion of subjects with detectable HCV resistance mutations, proportion of subjects with detectable HCV RNA due to re-infection, and the corresponding 95% confidence interval for each proportion will be computed by visit.

The proportion of subjects administered a Gilead OAV-containing regimen that maintain an SVR through end of study will also be estimated using a Kaplan-Meier model, allowing for censored observations due to early discontinuation from the Registry.

8.9. Sample Size

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

8.10. Additional Considerations

Any additional statistical analyses and/or methods for this study will be described in the Statistical Analysis Plan (SAP).

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this Registry is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a United States IND, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to.

Since this is a "covered" clinical trial, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all subinvestigators must provide documentation of their financial interest or arrangements with Gilead Sciences, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any subinvestigator. The investigator and subinvestigator agree to notify Gilead Sciences of any change to reportable interests during the Registry and for one year following completion of the Registry. Registry completion is defined as the date that the last subject has completed the protocol defined activities.

This Registry is also subject to and will be conducted in accordance with 21 CFR, part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB (for studies conducted in the United States) or IEC (for studies conducted outside of the United States). Approval from the IRB or IEC must be obtained **before** starting the Registry and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

9.1.3. Informed Consent/Assent

The investigator is responsible for obtaining written informed consent from the parent/legal guardian of the subject participating in this Registry after adequate explanation to the parent/legal guardian and subject of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. Written assent should be obtained from children and adolescent subjects as required by IRB/IEC/local requirements for this age population. The investigator must utilize an IRB- or IEC-approved consent form/assent form for documenting written informed consent/assent. Each informed consent/assent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent/assent. Subjects considered adults as per the IRB/IEC/local requirements may consent themselves without the subject's parent/legal guardian.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The investigator agrees that all information received from Gilead Sciences, including but not limited to the Investigator Brochure, this protocol, CRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of Gilead Sciences during the conduct of the Registry and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead Sciences. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the Registry to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data are listed in the Source Data verification Plan, and should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);

- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Participation in trial (including trial number);
- Trial discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date of Registry participation;
- Record of all AEs and other safety parameters (start and end date, and intensity);
- Date of trial completion and reason for early discontinuation, if applicable.

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with Gilead Sciences. The investigator must notify Gilead Sciences before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead Sciences must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead Sciences to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this Registry may be retained in storage by the Sponsor for a period up to 10 years for purposes of this Registry.

9.1.6. Case Report Forms

For each subject enrolled, a CRF (or eCRF) must be completed and signed by the principal investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. If a subject withdraws from the Registry, the reason must be noted on the CRF.

9.1.7. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Gilead Sciences or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

9.1.8. Protocol Compliance

The investigator is responsible for ensuring the Registry is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead Sciences. All protocol modifications must be submitted to the IRB, IEC, or competent authorities in accordance with local requirements. Approval must be obtained before changes can be implemented.

9.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies).
Gilead Sciences will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the Registry and without prior written approval from Gilead Sciences, investigators in this Registry may communicate, orally present, or publish in scientific journals or other scholarly media ***only after the following conditions have been met:***

- the results of the Registry in their entirety have been publicly disclosed by or with the consent of Gilead Sciences in an abstract, manuscript, or presentation form; or

- the Registry has been completed at all study sites for at least 2 years.

No such communication, presentation, or publication will include Gilead Sciences' confidential information (see Section 9.1.4).

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with Gilead Sciences' request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Access to Information for Monitoring

In accordance with ICH Good Clinical Practice (ICH GCP) guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for remote review of the CRFs at regular intervals throughout the Registry to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them.

Ad hoc site monitoring visits may occur and the monitor should have access to any subject records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

9.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead Sciences may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead Sciences medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead Sciences access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.3. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the Registry at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the Registry, Gilead Sciences and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

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

GS-US-334-1113, Protocol Amendment 3.0, 09 February 2016

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

PPD

Theo Brandt-Sarif MD

Theo Brandt-Sarif, MD
Clinical Research

Sig

09 Feb 2016

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this Registry as described. I will conduct this Registry as outlined herein and will make a reasonable effort to complete the Registry within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the Registry.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures

Appendix Table 1. Baseline and Follow-up Visits

Clinical Assessments	Day 1 (Baseline)[a]	Visit identified by study week							
		24	48	72	96	144	192	240	Early Termination
Quality of Life Survey [b]	X	X	X	X	X	X	X	X	X
Adverse events related to study procedures	X	X	X	X	X	X	X	X	X
Symptom-directed physical exam and body height/weight measurements	X	X	X	X	X	X	X	X	X
Tanner Pubertal Stage Assessment [c] (if applicable)	X	X	X	X	X	X	X	X	X
Laboratory Assessments									
HCV RNA[d]	X	X	X	X	X	X	X	X	X
Viral sequencing (archive)	X	X	X	X	X	X	X	X	X

a Day 1 visit will be documented from the last visit in the initial Gilead-sponsored treatment protocol
b Quality of life survey will be completed at all study visits if a site is approved to use the survey.
c Tanner Pubertal Stage Assessment will be performed at all study visits until a Tanner Stage 5 has been reached.
d If HCV RNA is detected after non-detectable levels at Day 1 or any time throughout the study, the subject will have a repeat blood sample drawn for confirmation.

Appendix 3. Tanner Stages

1. Pubic hair (male and female)	
Tanner I	no pubic hair at all (pre-pubertal Dominic state)
Tanner II	small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females)
Tanner III	hair becomes more coarse and curly, and begins to extend laterally
Tanner IV	adult-like hair quality, extending across pubis but sparing medial thighs
Tanner V	hair extends to medial surface of the thighs
2. Genitals (male) (One standard deviation around mean age)	
Tanner I	Testes, scrotum, and penis about same size and proportion as in early childhood
Tanner II	Enlargement of scrotum and testes; skin of scrotum reddens and changes in texture; little or no enlargement of penis (10.5-12.5)
Tanner III	Enlargement of penis, first mainly in length; further growth of testes and scrotum (11.5-14)
Tanner IV	Increased size of penis with growth in breadth and development of glans; further enlargement of testes and scrotum and increased darkening of scrotal skin (13.5-15)
Tanner V	Genitalia adult in size and shape
3. Breasts (female)	
Tanner I	no glandular tissue: areola follows the skin contours of the chest
Tanner II	breast bud forms, with small area of surrounding glandular tissue; areola begins to widen
Tanner III	breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast
Tanner IV	increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast
Tanner V	breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla.

Chart referenced from Marshall WA, Tanner JM, variations in the pattern of pubertal changes in boys and girls {Marshall et al 1970}, {Marshall et al 1969}.