NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	**A Prospective cohort study on the use of Sofosbuvir-based regimens in HCV-infected patients in clinical practice in France** **HELIOS : HE**patitis C real-**LI**fe study for patients **O**n **S**ofosbuvir
Protocol ID	GS-FR-334-1530
Protocol Version/Date:	Original, version 2.0, 5 December 2014
EU PAS Register No	ENCEPP/SDPP/11074
Clinical Trials.gov Identifier	Study not registered
Active substance	Sofosbuvir (ATC code J05AX15), Ledipasvir/Sofosbuvir, and other anti HCV treatment authorized in France associated with sofosbuvir and/or Ledipasvir/Sofosbuvir.
Medicinal Product	Sofosbuvir and Ledipasvir/Sofosbuvir FDC and other anti HCV treatments authorized in France associated with sofosbuvir and/or Ledipasvir/Sofosbuvir.
Product reference	Sofosbuvir CIP Code: 34009 277 070 7 0
Procedure number	NA
Joint PASS	No
Research Question and Objectives	This cohort study will collect and evaluate information on safety and efficacy of sofosbuvir-based regimens in routine clinical practice in France. The primary objective of this study is to assess the efficacy of Sofosbuvir-based regimens in adult patients with chronic hepatitis C virus infection treated in routine clinical practice. The secondary objectives of this study are to assess: - The safety and tolerability of Sofosbuvir-based regimens and

	Ledipasvir/Sofosbuvir in adult patients with chronic HCV infection treated in routine clinical practice, - The characteristics of patients treated with Sofosbuvir-based regimens and Ledipasvir/Sofosbuvir in clinical practice: severity of the liver disease, history of treatment, HCV genotypes and sub-types, - The impact of treatment with Sofosbuvir-based regimens and Ledipasvir/Sofosbuvir on Quality of life - Patient adherence - Pharmaco-economic data, including work productivity and activity impairment, number of consultations/hospitalizations due to HCV and/or liver disease and/or HCV treatment during treatment and follow-up (2 years) and treatment occurrence for anemia, thrombopenia and/or neutropenia, - Long term follow-up (2 years post treatment).
Country (-ies) of study	France
Gilead Study Director / Author/Contact Person:	Nom : Olivier LIBERT, PharmD Téléphone : + 33 1 46 09 41 73 Fax : + 33 1 46 09 41 06 E-mail : Olivier.libert@gilead.com
Marketing Authorization Holder	Gilead Sciences International Limited Cambridge CB21 6GT, United Kingdom Sponsor: Gilead Sciences SAS 65 quai Georges Gorse 92100 Boulogne-Billancourt, France
MAH contact person	Name: Francesca Day Telephone : +44 (0)1223 897 476 E-mail : Francesca.day@gilead.com Granta Park, Cambridge, CB21 6GT, UK
Gilead Qualified Person Responsible for Pharmacovigilance:	Name: Anne-Ruth van Troostenburg de Bruyn Telephone: + 44 (0) 1223 897 500 Fax: + 44 (0) 1223 897 290 Mobile: +44 (0) 7887450620

1. TABLE OF CONTENTS

1.1. LIST OF IN-TEXT TABLES

1.2. LIST OF IN-TEXT FIGURES

NA

2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AASLD	American Association for the Study of Liver Disease
ADR	Adverse drug reaction
AE	Adverse event
AFEF	Association Française de l'Etude du Foie
ALD	*Affection Longue Durée* (a long-term condition for which the treatment qualifies for full reimbursement in the French healthcare system)
ALTANSM	Alanine Aminotransferase
AST	*Agence Nationale de Sécurité du Médicament et des produits de santé* (French competent authority)
BMI	Aspartate Aminotransferase
CA	Body Mass Index
CCTIRS	Competent Authority
CRF	*Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé* (Advisory Committee on Information Processing in in health research) Case report form
CDC	Centers for Disease Control
CNIL	*Commission Nationale de l'Informatique et des Libertés* (National Computers and Privacy Commission)
CPP	*Comité de Protection des Personnes* (Ethic Committee)
CRO	Contract Research Organization
CSR	Clinical Study Report
DAA	Directly Acting Agent
DAC	Daclatasvir
DSPH	Drug Safety & Public Health
EASL	European Association for the Study of the Liver
eCRF	Electronic Case report form
EDD	Estimated date of Delivery
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.
EQ5D	EuroQoL – 5 Dimensions (QoL: Quality of Life)
EU	European Union
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
FDC	Fixed Dose Combination
GGT	Gamma-Glutamyl Transferase
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GSI	Gilead Sciences, Inc.
GVP	Good Pharmacovigilance Practices (guidelines for)

HBV	Hepatitis B Virus
HCC	HepatoCellular_Carcinoma
HCV	Hepatitis C Virus
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional review board
JFHOD	*Journées Francophones d'Hépatologie et d'Oncologie Digestives* (Hepatology and Digestive Oncology Francophones days)
HCC	Hepatocellular Carcinoma
LDV	Ledipasvir
MELD	Model For End-Stage Liver Disease
NAFLD	Non Alcoholic Fatty Liver Disease
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
Peg-INF	Pegylated Interferon
PhRMA	Pharmaceutical Research and Manufacturers of America
PRAC	European Pharmacovigilance Risk Assessment Committee
RBV	Ribavirin
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SADR	Serious Adverse Drug Reaction
SIM	Simeprevir
SmPC	Summary of Product Characteristics
SOF	Sofosbuvir
SSR	Special situation report
STI	Sexually transmitted infection
SUSAR	Serious Unexpected Suspected Adverse Reaction
SVR	Sustained Virologic Response
US, USA	United States, United States of America
WPAI	Work Productivity and Activity Impairment (questionnaire)
Analytical dataset	The minimum set of data required to perform the statistical analyses leading to the results of the primary objective(s) of the study
Bias	Systemic error in the design, conduct or analysis of a study that results in a mistaken estimate
Cases	Group of individuals with the condition of interest
Cohort	Group of people characterized by a common experience (e.g., occurrence of a specified disease, exposure to a given medication)
Confounder	Extraneous factor that accounts for a difference in disease frequency between the exposure groups; associated factors serving as surrogates for these factors are also commonly called confounders

Confounding by indication	A patient characteristic that is related to the outcome of interest and which influences treatment choice (exposure)
Controls	Group of individuals without the condition of interest but are otherwise similar to cases, or unexposed to or not treated with the agent of interest
Date at which a study commences	Date of the start of data collection
Effect modifier	If an effect measure varies within categories or levels of a variable, that variable is described as an effect-measure modifier
End of data collection	The date from which the analytical dataset is completely available
Exposure	A variable whose effect is of interest and is being studied
External validity	Whether or not the results from the study can be generalized to other populations
Internal validity	Whether or not the study provides an unbiased estimate of what it claims to estimate
Odds	The ratio of the probability that an event will happen to the probability that it will not happen
Outcome	An event (such as disease occurrence or death) that is studied in relation to exposure
Prevalence	Proportion of persons with the exposure/outcome at a specific point in time
Rate	A measure of event occurrence, calculated by dividing the total number of events by the total amount of person-time within an exposure category
Relative Risk (RR)	A general term that can refer to the ratio of 2 risks or the ratio of 2 rates
Risk	The proportion of a fixed cohort in which an outcome occurs during a specified period of time
Start of data collection	Date from which information on the first study subject is first recorded in the study dataset

3. RESPONSIBLE PARTIES

Table 1: Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Medical Manager Gilead	Olivier Libert Sr Manager Hepatitis, Medical Affairs, Gilead Sciences Gilead Sciences, 65 quai Georges Gorse, 92100 Boulogne-Billancourt • FRANCE	Phone: +33 1 46 09 41 73 Fax: +33 1 46 09 41 27 Mobile: +33 6 24 06 42 18
Clinical Manager Gilead	Pascal Pétour Sr Manager, Clinical Operations Gilead Sciences, 65 quai Georges Gorse, 92100 Boulogne-Billancourt • FRANCE	Phone: +33 1 46 09 41 85 Fax: +33 1 46 09 41 72 Mobile: +33 6 19 07 04 91
Leading Investigator	Pr Stanislas Pol Hôpital Cochin Unité d'Hépatologie Médicale 27 rue du Faubourg Saint Jacques,75679 Paris, France	Phone: +33 1 58 41 30 01
Drug Safety	Marie Terrier Sr Manager, Drug Safety & Public Health, Gilead Sciences, 65 quai Georges Gorse, 92100 Boulogne-Billancourt • FRANCE	Phone: +33 1 46 09 41 95 Fax: +33 1 46 09 41 72 Mobile: +33 6 14 19 20 65

3.1. Scientific Committee

A Scientific Committee has been composed for this study.

Table 2: Scientific Committee

Name	Affiliation, Address
ASSELAH, Tarik	Hôpital Beaujon, Clichy
BAILLY, François	Hôpital de la Croix Rousse, Lyon
GUYADER, Dominique	Hôpital Pontchaillou, Rennes
OUZAN, Denis	Institut Arnault Tzanck, Saint-Laurent du Var
POL, Stanislas (Coordinator)	Hôpital Cochin, Paris
ROSA, Isabelle	Centre Hospitalier Inter Communal, Créteil

The role of this Committee is to validate the study protocol, monitor the study progress and review and approve the results of statistical analysis and the study report.

4. PROTOCOL SYNOPSIS/ABSTRACT

Gilead Sciences
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

Title:	**A Prospective cohort study on the use of Sofosbuvir-based regimens in HCV-infected patients in clinical practice in France** **HELIOS : HE**patitis C real-**LI**fe study for patients **O**n **S**ofosbuvir
Rationale and Background:	Hepatitis C Virus (HCV) infection is a global health challenge with an estimated 180 million individuals infected worldwide {13693}. It is a leading cause of chronic hepatitis, cirrhosis and liver cancer and a primary indication for liver transplantation in the Western world. The efficacy and safety profiles of Sofosbuvir and Ledipasvir/Sofosbuvir FDC have been established in phase III clinical trials {24713, 24715, 40001, 40002, 40003, 40009}. However, patients are included in phase III clinical trials according to strict, selective inclusion and exclusion criteria. The characteristics of patients treated in routine clinical practice after marketing authorization of the products may therefore differ from those on which the product was primarily evaluated. Special subpopulations are under evaluated and most of the time excluded from clinical studies. Further evaluations are still needed in these populations like elderly patients, patients with comorbidities such as hypertension, diabetes, alcohol consumption, pregnant and breastfeeding women, patients with severe renal impairment or end-stage renal disease for which data are missing. The present study is therefore designed to assess Sofosbuvir-based regimens in routine clinical practice in adult patients with chronic hepatitis C virus in France, when used in accordance with the approved SmPC for SOF or LDV/SOF.
Research Question and Objectives:	The primary objective of this study is to assess the efficacy of Sofosbuvir-based regimens in adult patients with chronic hepatitis C virus infection treated in routine clinical practice. The secondary objective(s) of this study are to assess: - The safety and tolerability of Sofosbuvir-based regimens and ledipasvir/sofosbuvir in adult patients with chronic HCV infection treated in routine clinical practice,

- The characteristics of patients treated with Sofosbuvir based regimens and Ledipasvir/Sofosbuvir in clinical practice: severity of the liver disease, history of treatment, HCV genotypes and sub-types,

- The impact of treatment with Sofosbuvir-based regimens and Ledipasvir/Sofosbuvir on Quality of life,

- The patient adherence,

- Pharmaco-economic data, including work productivity and activity impairment, number of consultations/hospitalizations due to HCV and/or liver disease and/or HCV treatment during treatment and follow-up (2 years) and treatment occurrence for anemia, thrombopenia and/or neutropenia,

- Long term follow-up (2 years post treatment).

Study Design:

This is a multi-centre, prospective, non interventional cohort study on the use of Sofosbuvir-based regimens or Ledipasvir/Sofosbuvir in adult patients with HCV infection in clinical practice.

Population:

Adult patients with HCV infection initiating a treatment with Sofosbuvir-based regimen or Ledipasvir/Sofosbuvir.

Inclusion Criteria:

- Age ≥ 18 years
- HCV-infected patients (HCV RNA positive)
- Patient initiating treatment on Sofosbuvir-based therapy or Ledipasvir/Sofosbuvir*
- Signed Patient Information Form

Exclusion Criteria:

- Concurrent participation in a HCV clinical trial (except trials not testing investigational medicinal product)
- Patients presenting a risk of not being able to be followed during 2 years (patients planning to move home, or leave the country in a foreseeable future)

* please refer to respective SmPC

Variables:

Patients characteristics

Medical History

Addictions

Extra hepatic manifestations

HCV Treatment

Laboratory tests

Quality of Life (EQ-5D)

Individual productivity (WPAI)

Resources consumption

Safety (ADR, SADR, SSR and fatal AEs)

Data Sources:

Clinical data is collected from the subject medical records that are closest to the treatment initiation and pre-specified follow up time points (Baseline, end of treatment, 12 weeks, 1 year and 2 years after end of treatment). Primary data sources are defined as paper and/or electronic medical records. Study related data will be captured in an electronic CRF. Paper Patient Questionnaires (EQ-5D, WPAI and Treatment Adherence) will be completed by the subjects, collected by site staff and forwarded to the CRO for data capture in the clinical database

Study Size:

600 subjects will be recruited during 2 periods of approximately 6 months as follows:

Cohort 1: 300 subjects initiating a treatment with Sofosbuvir-based regimen

Cohort 2: 300 subjects initiating a treatment with Ledipasvir/Sofosbuvir

NB: as a non-interventional PASS, the second cohort is subject to FDC of Ledipasvir/Sofosbuvir Market Authorisation.

Data Analysis:

Descriptive analysis

Binary, categorical and ordinal variables will be described by counts and frequencies of each modality (over the total number of responses), and comparisons between groups will be tested using chi square tests and/or Fisher's exact tests.

Continuous variables will be described by means, standard errors, 95% confidence intervals, medians, minima, and maxima. Differences in means and medians between groups will be tested using t-tests and non-parametric tests, respectively.

When deemed necessary, sub-group comparisons and/or between time point comparisons may be implemented.

Multivariable analysis

As part of the secondary objectives of this study, rates of events per person-time of exposure will be computed using Poisson regression, after adjusting for potential confounding factors. These events include medication switching, medication discontinuation, co-medication use, ADRs and SADRs.

Milestones:

Start of data collection (first patient in):	Q2 2015
End of data collection (last patient out):	Q4 2018*
Final report cohort 2:	Q1 2019*

* depending on and subject to FDC full availability on the French market of Ledipasvir/Sofosbuvir.

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

5. AMENDMENTS AND UPDATES

Table 3: Amendment and updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
None				

- **Protocol Modifications**

Protocol modifications may only be made by Gilead Sciences. Approval must be obtained before changes can be implemented.

6. MILESTONES

Table 4: Milestones

Milestone	Planned Date
Cohort 1: Start of data collection (first patient in)	Q2 2015
Cohort 1: Last patient in	Q4 2015
Cohort 2: Start of data collection (first patient in)	Q4 2015*
Cohort 2: Last patient in	Q2 2016*
End of data collection (last patient out)	Q4 2018*
Registration in the EU PAS register	Q2 2015
<Interim report 1> SVR12 cohort 1	Q4 2016
<Interim report 2> SVR12 cohort 2	Q2 2017*
<Interim report 3> 1 year follow-up cohort 1	Q3 2017
<Interim report 4> 1 year follow-up cohort 2	Q1 2018*
<Final report cohort 1	Q3 2018
<Final report cohort 2	Q1 2019*

* depending on and subject to FDC full availability on the French market of Ledipasvir/Sofosbuvir.

7. RATIONALE AND BACKGROUND

7.1. Background

Hepatitis C Virus (HCV) infection is a global health challenge with an estimated 180 million individuals infected worldwide {13693}. It is a leading cause of chronic hepatitis, cirrhosis and liver cancer and a primary indication for liver transplantation in the Western world.
Up to 85% of individuals infected with HCV fail to clear the virus and progress to chronic infection; over the ensuing 20 years, as many as 20% of patients with chronic HCV infection are estimated to develop complications, including cirrhosis, end-stage liver disease, and hepatocellular carcinoma.
Chronic HCV infection leads to approximately 16,000 deaths each year in the US {27167}. In Europe, an estimated 7.3 to 8.8 million people have chronic HCV infection leading to approximately 86,000 deaths each year {19055}, {16473}. In France chronic hepatitis C is the second cause of cirrhosis and hepatocellular carcinoma, after excess alcohol consumption. It is the second cause of liver transplantation (cirrhosis and hepatocellular carcinoma combined). HCV infection is the cause of 2 600 deaths per year {40006}.

Hepatitis C virus has significant genetic (ribonucleic acid [RNA] sequence) variability and is classified on this basis into at least 6 genotypes. The most common HCV genotype in the US and Europe is genotype 1 {25891}; genotypes 2 and 3 HCV infection represent the majority of the remaining cases of chronic HCV infection in the US and Europe {8074}, {14093}, {19705},{25896},{25892}, {25891}. Genotype 4, 5, and 6 HCV infections are most prevalent in the Middle East, South Africa, and Southeast Asia, respectively {22111}.

7.2. General Information on Study drugs

7.2.1. Sofosbuvir (SOF)

Sofosbuvir (Sovaldi® or 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 Peg-IFN and/or RBV to subjects with chronic genotype 1-6 HCV infection {27503}, {23275}, {24713}, {24715}. Sofosbuvir has been approved in the United States by the Food and Drug Administration (FDA) for the treatment of HCV infection genotype 1, 2, 3 and 4 including treatment-naïve and experienced patients and HIV-1/HCV co-infected patients. In Europe Sofosbuvir has also been approved for the treatment of HCV infection genotype 1, 2, 3, 4, 5 and 6.
For further information on the, indication, posology, clinical pharmacology, virology, safety and efficacy of sofosbuvir (SOF), please refer to the current version of Sovaldi® EMA SmPC. {40004}

7.2.2. Ledipasvir/Sofosbuvir (LDV/SOF) Fixed Dose Combination (FDC)

Ledipasvir/Sofosbuvir fixed-dose combination (Harvoni® or LDV/SOF FDC) combines two HCV specific direct acting antiviral (DAA) agents into a single tablet for the treatment of

chronic HCV infection. Ledipasvir is a novel HCV NS5A inhibitor that has demonstrated potent anti HCV activity against genotypes 1 and 4 HCV infection. Sofosbuvir is a nucleotide analog that is a potent and selective inhibitor of NS5B directed HCV replication, irrespective of HCV genotype.
A fixed-dose combination tablet (FDC) of LDV 400 mg / SOF 90 mg with or without RBV has demonstrated favorable safety and efficacy profiles in over 3000 HCV-infected subjects across different patient populations in Phase 2 and 3 trials. {40001}, {40002}, {40003}. These doses represent the proposed marketed doses of LDV and SOF. LDV/SOF has been administered to more than 3,000 subjects with HCV infection in clinical trials. No safety issues related to LDV/SOF administration have been identified to date.
Overall, LDV/SOF has been well tolerated. The most frequently reported adverse events (AEs) for LDV/SOF were fatigue, headache, and nausea.
Please refer to Harvoni® EMA SmPC {40005}, for further information on LDV/SOF.
A new Drug Application has been submitted to FDA and EMA for approval of Ledipasvir/Sofosbuvir FDC.

7.3. Rationale for the Current Study

The efficacy and safety profiles of Sofosbuvir and Ledipasvir/Sofosbuvir FDC have been established in phase III clinical trials{24713, 24715, 40001, 40002, 40003, 40009}. However, patients are included in phase III clinical trials according to strict, selective inclusion and exclusion criteria. The characteristics of patients treated in routine clinical practice after marketing authorization of the products may therefore differ from those on which the product was primarily evaluated. Special subpopulations are under evaluated and most of the time excluded from clinical studies. Further evaluations are still needed in these populations like elderly patients, patients with comorbidities such as hypertension, diabetes, alcohol consumption, pregnant and breastfeeding women, patients with severe renal impairment or end-stage renal disease for which data are missing[1].
The present study is therefore designed to assess Sofosbuvir-based regimens in routine clinical practice in adult patients with chronic hepatitis C virus in France, when used in accordance with the approved SmPC for Sovaldi® or Harvoni®.

[1] * Sovaldi® Risk Management Plan – version 2.0

8. RESEARCH QUESTIONS AND OBJECTIVES

This cohort study will collect and evaluate information on the safety and efficacy of sofosbuvir-based regimens and Ledipasvir/Sofosbuvir in routine clinical practice in France.

The primary objective of this study is to assess the efficacy of Sofosbuvir-based regimens in adult patients with chronic hepatitis C virus infection treated in routine clinical practice.

The secondary objectives of this study are to assess:

- The safety and tolerability of Sofosbuvir-based regimens or Ledipasvir/Sofosbuvir in adult patients with chronic HCV infection treated in routine clinical practice,

- The characteristics of patients treated with Sofosbuvir-based regimens or Ledipasvir/Sofosbuvir in clinical practice: severity of the liver disease, history of treatment, HCV genotypes and sub-types,

- The impact of treatment with Sofosbuvir-based regimens or Ledipasvir/Sofosbuvir on Quality of life,

- The patient adherence,

- Pharmaco-economic data, including work productivity and activity impairment, number of consultations/hospitalizations due to HCV and/or liver disease and/or HCV treatment during treatment and follow-up (2 years) and treatment occurrence for anemia, thrombopenia and/or neutropenia,

- Long term follow-up (2 years post treatment).

9. RESEARCH METHODS

9.1. Study Design

9.1.1. General Outline

This is a multi-centre, prospective, non interventional cohort study on the use of Sofosbuvir-based regimens in adult patients with HCV infection in clinical practice.

Data shall be collected from available information in medical records. The decision to initiate or not to initiate patient treatment with Sofosbuvir or Ledipasvir/Sofosbuvir FDC will be based on the prescribing doctor's own judgement, and will not be influenced in any manner by the present study.

600 subjects will be recruited during 2 periods of approximately 6 months as follow:
Cohort 1: 300 subjects initiating a treatment with Sofosbuvir-based regimen.
Cohort 2: 300 subjects initiating a treatment with Ledipasvir/Sofosbuvir (FDC)

NB: as a non-interventional PASS, the second cohort is subject to FDC of Ledipasvir/Sofosbuvir Market Authorisation.

9.1.2. Observation period

Data will be collected when treatment with Sofosbuvir-based regimen or Ledipasvir/Sofosbuvir is initiated and at the usual patient follow-up consultations. Patients will be monitored during their treatment period and until 2 years after the end of their treatment. During the post treatment follow-up period, any patient that would initiate a new HCV treatment will not be followed-up anymore within this study (except for safety information occurring within 30 days after study HCV treatment discontinuation, refer to section 11.5).

9.1.3. Endpoints

The endpoints are:

- Primary Endpoint

- The primary endpoint is the proportion of subjects with sustained virologic response 12 weeks after discontinuation of therapy (SVR12).

  Virologic response is defined as HCV RNA < 25 UI/mL (lower limit of quantification, LLOQ).

- Secondary Endpoints

- Safety endpoints include any Adverse Drug Reaction (ADR) leading to permanent discontinuation of treatment with sofosbuvir-based regimen or ledipasvir/sofosbuvir, the number and percentage of subjects with ADR or laboratory abnormalities.
- Secondary efficacy endpoints include the proportion of subjects with virologic response at 24 weeks post treatment (SVR24), viral breakthrough, relapse, clinical outcomes during follow-up including but not limited to diagnosis of hepatocellular carcinoma, liver fibrosis, signs of decompensated cirrhosis.
- Quality of life assessed with EQ-5D questionnaire during therapy and long-term follow-up (2 years).
- Patient adherence to HCV treatment assessed with patient questionnaire during therapy period
- Work Productivity and Activity Impairment assessed with WPAI questionnaire during therapy and long-term follow-up (2 years).
- Number of consultations/hospitalizations due to HCV and/or liver disease and/or HCV treatment during treatment and follow-up (2 years).
- Treatment occurrence for anemia, thrombopenia and/or neutropenia during treatment and follow-up (2 years).

9.2. Setting

Conducting a non-interventional study (NIS) presupposes, according to definition of a "non-interventional study" in terms of the EU-guideline 2001/20/EC that the documentation plan does not stipulate or dictate the diagnosis, therapeutic decision and follow-up. It is at the discretion of the respective physician if a specific subject will be treated and what regimen will be used according to routine clinical practice. Only after these decisions have been made can the subject be agreed to be included in the present study.

9.2.1. Patient recruitment

Patients will be recruited prospectively.

In order to have a good representativeness of current practice in France:

- Around 60 sites will be selected all around France, primarily in departments of Hepato-Gastro-Enterology, Infectious Diseases, Internal Medicine.
- Each site will have the opportunity to enroll up to 10 patients (5 patients in cohort 1 and 5 patients in cohort 2).

For both cohorts the recruitment periods will be split as follows in order to allow all sites to enroll patients:

- Non competitive enrolment at the enrollment launch (i.e. study initiation of the first site). During this period the sites will be allowed to enroll up to 5 patients per cohort.
- Competitive enrollment during a second phase if needed. All sites will be allowed to enroll patients without limitation until reaching 300 patients per cohort.

9.2.2. Eligibility criteria

Inclusion Criteria

- Age ≥ 18 years
- HCV-infected patients(HCV RNA positive)
- Patient initiating treatment on Sofosbuvir-based therapy or Ledipasvir/Sofosbuvir therapy*
- Patient Information Form signed

Exclusion Criteria

- Concurrent participation in a HCV clinical trial (except trials not testing investigational medicinal product)
- Patients presenting a risk of not being able to be followed during 2 years (patients planning to move home or leave the country in a foreseeable future)

* please refer to respective SmPC

9.2.3. Patient premature discontinuation

During the post treatment follow-up period, any patient that would initiate a new HCV treatment won't be followed-up anymore within this study (except for safety information occurring within 30 days after study HCV treatment discontinuation, refer to section 11.5).

9.3. Variables

Data will be collected from the medical records using electronic case report form (eCRF), with questionnaires completed by the patients, where indicated.

At baseline: prior to initiation of treatment with Sofosbuvir-based regimen or Ledipasvir/Sofosbuvir (V1)

The following variables will be collected at baseline, where available:

- Patients characteristics
    - Demographic factors : year of birth, gender, ethnic origin

  - Body size measures : weight, height, waist circumference, Body Mass Index (BMI)

- Medical history :

  - Addictions : alcohol consumption (consumption in the past, current consumption), tobacco, recreational drugs abuse (in the past and at present)

  - Non alcoholic fatty liver disease (NAFLD), renal insufficiency, dialysis, diabetes, arterial hypertension, renal transplantation,

  - Liver transplantation , listed on liver transplant waiting list

  - Fibrosis/cirrhosis evaluation: evaluation method (biopsy : METAVIR Score, Fibroscan, Fibrotest, Fibrometer) and scores

  - Child-Pugh score

  - MELD score,

  - History of ascitis, bleeding esophageal varices, jaundice, or hepatic encephalopathy (grade)

  - HCC

- Extrahepatic manifestations : cryoglobulinemia, lymphoma, arthralgia, depressive syndrome

- Virus : HCV genotype/sub-type, HIV co-infection, HBV co-infection

- HCV treatment history: drugs, associated response (non-response, relapse, breakthrough, intolerance) and dates.

- Laboratory tests

  - HCV-RNA

  - Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) Gammaglutamyl Transferase (GGT), Alkaline Phosphatase, Serum albumin,Total bilirubin, Alpha foetoprotein, Serum creatinine

  - Hematology test: hemoglobin, platelet count, red blood cell count and white blood cell count with differential, Prothrombin time, INR

- Quality of Life: EQ-5D questionnaire

- Individual productivity: WPAI questionnaire, professional status, “ALD” status, sick leave status and duration

- HCV treatment prescribed and duration

At the end of treatment with sofosbuvir-based regimen or Ledipasvir/Sofosbuvir (V2)

The following variables will be collected at the end of treatment with sofosbuvir-based regimen or Ledipasvir/Sofosbuvir, where available:

- Patients characteristics
    - Body size measures : weight, Body Mass Index
- Addictions : alcohol consumption, tabacco, drugs abuse
- Extrahepatic manifestations : cryoglobulinemia, lymphoma, arthralgia, depressive syndrome
- Liver disease status:
    - Fibrosis/cirrhosis evaluation: evaluation method (biopsy: METAVIR Score, Fibroscan, Fibrotest, Fibrometer) and scores,
    - Child-Pugh score
    - MELD score,
    - Ascitis, bleeding esophageal varices, jaundice, hepatic encephalopathy (grade)
    - HCC
    - Liver transplantation , listed on liver transplant waiting list
- Sofosbuvir-based regimen
    - Sofosbuvir or Ledipasvir/Sofosbuvir start and stop dates, premature discontinuation
    - Concomitant HCV-treatment (Ribavirin, Peg-IFN, Simeprevir, Daclatasvir), start and stop dates, premature discontinuation
    - Adherence to treatment : Questionnaire completed at week 4, week 12 and week 24 (if applicable)
- Concomitant Medication
- Significant event or concomitant diseases ((including dialysis and renal transplantation)

- Safety
    - Adverse drug reactions (serious and non-serious) related to HCV treatment
    - adverse events with fatal outcome (i.e. cause of death)
- Laboratory tests
    - HCV-RNA at week 1, 2; 4, 8, 12 and at the end of treatment
    - ALT, AST, GGT, Alkaline Phosphatase, Serum albumin, Total bilirubin, Alpha foetoprotein, Serum creatinine
    - Hematology test: hemoglobin, platelet count, red blood cell count and white blood cell count with differential, Prothrombin time, INR
- Quality of Life: EQ-5D questionnaire
- Individual productivity: WPAI questionnaire, professional status, “ALD” status, number and duration of sick leaves
- Resources consumption
    - Number of consultations at hospital, number of hospitalizations and number of nurse visits at home due to HCV and/or liver disease and/or HCV treatment
    - Drug resources for anemia (e.g. EPO, transfusions, others), neutropenia (e.g. filgrastim) and/or thrombopenia (e.g. eltrombopag)

At 12 weeks post treatment with sofosbuvir-based regimen or Lediopasvir/Sofosbuvir (V3)

The following variables will be collected 12 weeks after the end of treatment with sofosbuvir-based regimen or Ledipasvir/Sofosbuvir, where available:

- Patients characteristics
    - Body size measures : weight, Body Mass Index
- Addictions : alcohol consumption, tabacco, drugs abuse
- Extrahepatic manifestations : cryoglobulinemia, lymphoma, arthralgia, depressive syndrome
- Liver disease status:

  - Fibrosis/cirrhosis evaluation: evaluation method (biopsy: METAVIR Score, Fibroscan, Fibrotest, Fibrometer) and scores,
  - Child-Pugh score
  - MELD score,
  - Ascitis, bleeding esophageal varices, jaundice, hepatic encephalopathy (grade)
  - HCC
  - Liver transplantation , listed on liver transplant waiting list
- Significant event or concomitant diseases (including dialysis and renal transplantation)
- Safety
  - Adverse drug reactions (serious and non-serious) related to HCV treatment and adverse event with fatal outcome (i.e. cause of death).
- Laboratory tests
  - HCV-RNA
  - ALT, AST, GGT, Alkaline Phosphatase, serum albumin,Total bilirubin, Alpha foetoprotein, Serum creatinine
  - Hematology test: hemoglobin, platelet count, red blood cell count and white blood cell count with differential, Prothrombin time, INR
- Quality of Life: EQ-5D questionnaire
- Individual productivity: WPAI questionnaire, professional status, “ALD” status, number and duration of sick leaves
- Resources consumption
  - Number of consultations at hospital, number of hospitalizations and number of nurse visits at home due to HCV and/or liver disease and/or HCV treatment
  - Drug resources for anemia (e.g. EPO, transfusions, others), neutropenia (e.g. filgrastim) and/or thrombopenia (e.g. eltrombopag)

At 48 weeks post treatment with sofosbuvir-based regimen or Ledipasvir/Sofosbuvir (V4)

The following variables will be collected 48 weeks after the end of treatment with sofosbuvir-based regimen or Ledipasvir/Sofosbuvir, where available:

- Patients characteristics
    - Body size measures : weight, Body Mass Index
- Addictions : alcohol consumption, tabacco, drugs abuse
- Extrahepatic manifestations : cryoglobulinemia, lymphoma, arthralgia, depressive syndrome
- Liver disease status
    - Fibrosis/cirrhosis evaluation: evaluation method (biopsy: METAVIR Score, Fibroscan, Fibrotest, Fibrometer) and scores,
    - Child-Pugh score,
    - MELD score,
    - Ascitis, bleeding esophageal varices, jaundice, hepatic encephalopathy (grade)
    - HCC
    - Liver transplantation , listed on liver transplant waiting list
- Significant event or concomitant diseases (including dialysis and renal transplantation)
- Safety
    - Adverse drug reactions (serious and non-serious) related to HCV treatment and adverse event with fatal outcome (i.e. cause of death).
- Laboratory tests
    - HCV-RNA
    - ALT, AST, GGT, Alkaline Phosphatase, Serum albumin,Total bilirubin, Alpha foetoprotein, Serum creatinine
    - Hematology test: hemoglobin, platelet count, red blood cell count and white blood cell count with differential, Prothrombin time, INR
- Quality of Life: EQ-5D questionnaire

- Individual productivity: WPAI questionnaire, professional status, “ALD” status, number and duration of sick leaves

- Resources consumption

    - Number of consultations at hospital, number of hospitalizations and number of nurse visits at home due to HCV and/or liver disease and/or HCV treatment

    - Drug resources for anemia (e.g. EPO, transfusions, others), neutropenia (e.g. filgrastim) and/or thrombopenia (e.g. eltrombopag)

At 96 weeks post treatment with sofosbuvir-based regimen or Ledipasvir/Sofosbuvir (V5)

The following variables will be collected 96 weeks after the end of treatment with sofosbuvir-based regimen or Ledipasvir/Sofosbuvir, where available:

- Patients characteristics

    - Body size measures : weight, Body Mass Index

- Addictions : alcohol consumption, tabacco, drugs abuse

- Extrahepatic manifestations : cryoglobulinemia, lymphoma, arthralgia, depressive syndrome

- Liver disease status

    - Fibrosis/cirrhosis evaluation: evaluation method (biopsy: METAVIR Score, Fibroscan, Fibrotest, Fibrometer) and scores,

    - Child-Pugh score

    - MELD score,

    - Ascitis, bleeding esophageal varices, jaundice, hepatic encephalopathy (grade)

    - HCC

    - Liver transplantation , listed on liver transplant waiting list

- Significant event or concomitant diseases ((including dialysis and renal transplantation)

- Safety

- Adverse drug reactions (serious and non-serious) related to HCV treatment and adverse event with fatal outcome (i.e. cause of death).

- Laboratory tests
  - HCV-RNA ALT, AST, GGT, Alkaline Phosphatase, Serum albumin,Total bilirubin, Alpha foetoprotein, Serum creatinine
  - Hematology test: hemoglobin, platelet count, red blood cell count and white blood cell count with differential, Prothrombin time, INR
- Quality of Life: EQ-5D questionnaire
- Individual productivity: WPAI questionnaire, professional status, “ALD” status, number and duration of sick leaves
- Resources consumption
  - Number of consultations at hospital, number of hospitalizations, number of nurse visits at home due to HCV and/or liver disease and/or HCV treatment
  - Drug resources for anemia (EPO, transfusions, others), neutropenia (e.g. filgrastim) and/or thrombopenia (e.g. eltrombopag)

9.4. Data Sources

The conduct of a non-interventional study (NIS) requires, according to definition of a ”non-interventional study“ in terms of Guideline on Good Pharmacovigilance Practices (GVP) – Module VIII (Rev 1), that the protocol does not stipulate or dictate the diagnosis, therapeutic decisions and follow-up of the individual subject. This study only observes and collects the use of Sofosbuvir based therapy or Ledipasvir/Sofosbuvir therapy and the corresponding descriptive and clinical outcome by the treating physician.

Clinical data is collected from the physician’s documentation of the subject’s visit in subject medical records that are closest to the pre-specified follow up time points (approximately end of treatment, 12 weeks, 1 year and 2 years after treatment). Primary data sources are paper and/or electronic medical records. Questionnaires (EQ-5D, WPAI and Treatment Adherence) will be filled in by the subjects in paper form and collected by site staff. Data from medical records will be manually transcribed by the investigator or site staff into electronic case record forms (eCRF) within the week following the patient visit.
Questionnaires will be sent by sites to the CRO. The CRO will be in charge of their data entry into the eCRF.

9.5. Study Size

- Cohort 1: 300 subjects initiating a treatment with Sofosbuvir-based regimen (see table 5 below)
- Cohort 2: 300 subjects initiating a treatment with Ledipasvir-Sofosbuvir FDC
- Total for the whole study : 600 subjects

In an observational study, the necessary sample size is based on the expected precision of estimations of the variables collected, i.e. confidence intervals (CI) of the proportions observed.

The confidence interval of a proportion is calculated by using the approximation of the Normal law.

$$CI_{95\%} = p \pm 1{,}96\sqrt{\frac{p \times q}{n}}$$

The number of patients to be included is therefore: $n = 1{,}96^2 \times \frac{P(1-P)}{precision^2}$

Assuming a percentage of 85% of SVR12 with estimation of this percentage with a confidence interval of ± 3% (i.e. a precision of 3%), the number of patients to be included must be 545. Table 5 indicates the confidence intervals for various proportions. It is estimated that less than 10% of the patients will have stopped the study prior to SVR12 evaluation. So the number of patients to be included in this study is 600.

Table 5: Confidence intervals for the various proportions for a sample of 600 subjects

Proportion	Confidence interval	
95%	92.9%	97.1%
90%	87.1%	92.9%
80%	76.1%	83.9%
70%	65.5%	74.5%
60%	55.2%	64.8%
50%	45.1%	54.9%

•

In the first cohort, the patients will be distributed regarding their treatment regimen according to the table 6.

Table 6: Specific regimens to be collected in the cohort

Corhort	Arms	Regimen	Total
1	a	SOF + R ± P	220
	b	SOF + DAA ± R	80*
2	/	LDV/SOF ± R	300

* maximum 40 SOF+SIM±R and 40 SOF+DAC±R

Justification: according to Sofosbuvir (Sovaldi®) label in Europe {40004}, EASL Recommendations on Treatment of Hepatitis C 2014 {40007} and French guidelines 2014 {40006} it is anticipated that Sofosbuvir-based regimen could differ according to HCV genotype and physician decision. Genotype prevalence in France is estimated to be GT1 60%, GT2 10%, GT3 20%, GT4/5/6 10%. To ensure representativeness of current practice in France, we propose to collect data on a maximum of :

- 220 patients treated with Sofosbuvir + Ribavirin +/-Peg-IFN
- 40 patients treated with Sofosbuvir + Simeprevir +/- Ribavirin
- 40 patients treated with Sofosbuvir + Daclatasvir +/- Ribavirin.

9.6. Data Management

The study will use an electronic data entry system (EDC, eCRF). All users will receive their own username and password to enable them to log into the EDC system'.

Patients questionnaires will be completed by the subjects collected by site staff and forwarded to the CRO for data capture in the electronic data entry system.

Pathologies/events/reactions and drugs will be coded using the most recent version of MedDra and WhoDrug dictionaries.

For more details regarding the data entry, please refer to 9.4. Data Sources

A Data Management Unit will be responsible for designing and validating the web-based eCRFs. A detailed data validation plan that will identify missing data, out-of-range data, and other data inconsistencies will be implemented in the electronic platform prior to study start.
Once all information is introduced in the database, data will be reviewed. Queries will be prepared in case data inconsistencies are found and will be resolved by each investigator. After

the data validation, the database will be locked and sent to a Statistics Unit in order to perform the statistical analysis and report.

9.7. Data Analysis

Descriptive analysis

Binary, categorical and ordinal variables will be described by counts and frequencies of each modality (over the total number of responses), and comparisons between groups will be tested using chi square tests and/or Fisher's exact tests.

Continuous variables will be described by means, standard errors, 95% confidence intervals, medians, minima, and maxima. Differences in means and medians between groups will be tested using t-tests and non-parametric tests, respectively. When deemed necessary, sub-group comparisons and/or between time point comparisons may be implemented.

Multivariable analysis

As part of the secondary objectives of this study, rates of events per person-time of exposure will be computed using Poisson regression, after adjusting for potential confounding factors. These events include medication switching, medication discontinuation, co-medication use, ADRs and SADRs and fatal AEs.

Deviations: patients with protocol deviation will be excluded from the analysis. For the avoidance of doubt, since this PASS is non-interventional, only wrong enrollment will be considered as protocol deviation.

9.8. Quality Control

The electronic data entry system will contain automatic checks for data completeness and to identify inconsistent data and respective queries will be generated when necessary. Data and queries will be remotely monitored for consistency and completeness.

Some monitoring visits could be performed on several sites. For more details please refer to the part 9.10.1.1.

9.9. Limitations of the Research Methods

In a non-interventional study all decisions on the management of the patient are made solely by the treating physician. As such, some data or visits can be missing and or visits delayed.

Additionally, selection bias for patient recruitment cannot completely be ruled out. Physicians in the recruiting sites might prefer to include one patient in comparison to another due to the small number of patients included per site. However, due to the high number of sites involved, no change in the overall results of the study are to be expected.

In order to get a good representation of the patient treated with Sofosbuvir in France, sites will be selected all over the French metropolitan territory, including both big hospitals and smaller ones. However, non-inclusion criteria de facto exclude some patients for the scope of the study. Indeed patients presenting a risk of not being able to be followed during 2 years won't be enrolled in this study.

9.10. Other Aspects

9.10.1. Joint Investigator/Sponsor Responsibilities

9.10.1.1. Access to Information for Monitoring

The involved CRO is responsible for routine online review of the eCRFs at regular intervals throughout the study to check the completeness, consistency, and accuracy of the data being entered on the forms. The investigator agrees to cooperate with the CRO to ensure that any problems detected in the course of this monitoring are resolved.

During monitoring visits the study monitor will review some CRFs to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on the forms. The investigator will provide the study monitor with access to any subject records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

9.10.1.2. Study dossier and filing of dossiers

The investigator must maintain adequate and accurate records to enable the conduct of the study 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) patient clinical source documents.
The investigator's will be responsible for maintenance of a study folder, at least containing the protocol and any amendment, positive opinions from regulatory authorities and related correspondence, patient information form, and other appropriate documents. These study files shall be archived for at least 5 years after the final study report approval (or first publication of study results). The investigator will keep an up-to-date list (accessible exclusively to the investigator, the appropriate personnel of the study site, the study monitor or appropriately qualified personnel from Gilead Sciences or its representatives) documenting the correspondence between each patient's identification number and the medical file from which data were extracted and included in the database. The patient clinical source documents consist of the usual

patient files kept at the site of the investigator and falls within the local regulations for such files and documents.

9.10.1.3. Audits and Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from Gilead Sciences or its representatives.

9.10.1.4. Protocol Compliance

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

9.10.1.5. Protocol Modifications

Protocol modifications may be made only by Gilead Sciences.

9.10.1.6. Access to Information for Monitoring

In accordance with the study contract and the patient's consent on data protection (through patient information form signature), if required the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

9.10.1.7. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies and boards. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. PROTECTION OF HUMAN SUBJECTS AND REGULATORY CONSIDERATIONS

10.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The investigator will ensure that this study is conducted in accordance with the principles of the International Conference on Harmonization (ICH) Pharmacovigilance Planning E2E guidelines, and with the laws and regulations of the country in which the research is conducted.

The investigator will conduct this study in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs), Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

10.2. *Comité de Protection des Personnes (CPP) [IEC/IRB]*

This non-interventional, post-marketing study is pragmatic and does not modify the usual medical management of patients included in the study except for questionnaire completion by the patient. It does not affect their physical or mental integrity and does not require any particular follow-up visits for patients included in the study in addition to the routine care. Under these conditions, this study does not fall under the scope of Act 2004-806 dated 9 August 2004 and does not require declaration to a “Comité de Protection des Personnes (CPP)”.

10.3. Commission Nationale de l’Informatique et des Libertés (CNIL) [National Computers and Privacy Commission]

This study involves collection of indirectly named-patient data under the terms of the French “Informatique et Libertés” (Computers and Privacy) Act. Consequently, and in accordance with this Act, the patient must have been comprehensibly informed before being included in the study about the nature, objective and possible consequences of the study, recording of indirectly named patient data and automated processing of these data, the objectives of this data collection and the patient’s right of access and correction. A patient information form must be signed by each patient included.
This study is therefore subject to the French “Informatique et Libertés” Act, dated 6 January 1978, and the Act dated 6 August 2004 concerning medical research data processing. As a consequence, the protocol will be submitted to both CCTIRS and CNIL for approval.

10.4. Patient information form

Prior to study participation and before performing any study-related activities, the investigator is responsible for obtaining written patient information form from each individual participating in

this study after adequate explanation of the aims, methods and objectives, the possible consultation of the patient's medical file by representatives of Gilead Sciences and data collection and transmission of these data for analysis. The investigator must utilize the most current approved patient information form for documenting patient's agreement. Each information form (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and also by an impartial witness if required by local requirements.

10.5. ENCePP, PRAC and ANSM (French CA)

This study will be registered in the European PAS register, ENCePP register before the first patient in. The protocol will be provided to PRAC and or ANSM upon request.

10.6. Archives

All study documentation (including case report forms) must be stored for 5 years after the final study report approval (or first publication of study results).

10.7. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only a unique identifier (as allowed by local law) and a unique study identification code should be recorded on any study-related document. The investigator must keep a list indicating the correspondence between the patient's identification number he attributed for the purposes of identification (site number plus 2-digit number plus 1st letter of the firstname and 1st letter of the last name), and the patient's file.

The investigator agrees that all information received from Gilead, including but not limited to this protocol, CRFs and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study 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. 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.

11. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

This study will collect the following safety information:

- all Adverse Drug Reactions related to HCV treatment from its initiation to the end of the patient follow-up
- all fatal Adverse Events (i.e. causes of death) from HCV treatment initiation to the end of the patient follow-up
- all pregnancies occurring during the HCV treatment and within 30 days after HCV treatment discontinuation whether maternal or paternal exposure to the product
- all other Special Situations concerning HCV treatment occurring to patient while under HCV treatment

Patients initiating a new HCV treatment during the post treatment follow-up period should discontinue the study. In such case, any safety information related to the study treatment occurring within 30 days after study HCV treatment should still be reported.

In the context of this voluntary PASS, serious and non-serious adverse reactions to HCV treatment and fatal adverse events will be collected rather than all adverse events. The rationale for not collecting all adverse events is to mirror the real-life situation in which the prescribing physician distinguishes between events related to treatment from those events that are purely coincidental and those adverse events related to the underlying disease (hepatitis C). This distinction will reflect the reality of post-authorisation prescribing, while through the study collection process avoid the under-reporting connected with passive safety monitoring relying on spontaneous reporting only. The real-life study situation collection of ADRs as identified by the prescribing physician, who makes the causality assessment will aide efficient signal detection. The judgment call of the physicians regarding adverse reactions will generate a focused relevant dataset allowing a better understanding of the safety profile of the HCV treatment in the real life.

11.1. Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE.

- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)

- Any medical condition or clinically significant laboratory abnormality with an onset date before the patient information form is signed. These are considered to be preexisting conditions and should be documented on the medical history CRF (if applicable).

11.1.1. Adverse Drug Reactions

An **adverse drug reaction** (ADR) is defined as an untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or approved medicinal product at any dose administered. Adverse reactions may also arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure.

11.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death

- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect

- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself. Therefore, if death occurred, the event that led to death needs to be reported as a Fatal AE.

- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, is life-threatening, or meets any of the other definitions of an SAE, then it is an SAE.

- "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 investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis (and not the individual signs/symptoms) should be documented as the AE and/or SAE.

A distinction should be drawn between seriousness and severity of AEs. Severity is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed for severity. An AE is defined as "serious" when it meets one of the predefined outcomes described above.

11.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not considered as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to drug interruption, modification, or discontinuation must be considered as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be considered as an AE or SAE if they meet the definition of an AE or SAE as described in Section 11.1**.** If the laboratory abnormality is part of a syndrome, consider the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

All clinical laboratory abnormalities and other abnormal assessments will be collected if related to HCV treatment.

11.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and for final review and confirmation of accuracy of event information and assessments.

11.2.1. Assessment of Causality for Study Drugs

The investigator or qualified subinvestigator is responsible for assessing the relationship to drug therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is a reasonable possibility that the event may have been caused by the medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

11.3. Special Situations Reports

11.3.1. Definitions of Special Situations

Special situation reports include reports of pregnancy; medication error, abuse, misuse, or overdose; lack of effect; adverse reactions in infants following exposure from breastfeeding; and adverse reactions associated with product complaints.

A pregnancy report is used to report any pregnancy that occurs during the HCV treatment and within 30 days after HCV treatment discontinuation whether maternal or paternal exposure to the product occurred.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established

when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Lack of effect is defined as the failure of the expected or intended pharmacologic action or therapeutic effect as described in the pharmacology and/or indications section of the current product labeling.

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

11.3.2. Instructions for Reporting Special Situations

11.3.2.1. Instructions for Reporting Pregnancies

All pregnancies that occur in female subjects and female partners of male subjects while exposed to the drug and within 30 days after the drug discontinuation are to be reported to the CRO Safety Department using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours. The underlying medical reason for this procedure should be recorded as the event term on the SAE/SAR form.

A spontaneous abortion must be reported within 24 hours. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to the CRO Safety Department.

Pregnancy outcomes should be reported to CRO Safety Department using the pregnancy outcome report form.

11.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs).

Gilead is responsible for reporting and analyzing reports of all AEs and SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs) as

determined by country-specific legislation or regulations where the study is conducted. Gilead may be required to report to other regulatory agencies.

Assessment of expectedness for all events will be determined by Gilead using reference safety information specified in the relevant local label.

11.5. Investigator Requirements and Instructions for Reporting Fatal Adverse Events, Serious and Non Serious Adverse Drug Reactions and Special Situations reportsto Gilead

All related non-serious AEs and related SAEs, also known as adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs) occurring from time of HCV treatment initiated until study completion, loss to follow-up, withdrawal of consent, death or 30 days after discontinuation of Sofosbuvir-based regimen (whichever occurs first) will be reported to Gilead DSPH.

Timelines for reporting ADRs and SADRs to Gilead DSPH are as follows:

- Within 30 calendar days of knowledge of the event for ADRs
- Within 24 hours of knowledge of the event for SADRs.

All fatal AEs (i.e. leading to death during the patient follow-up occurring from time of HCV treatment initiated until study completion, loss to follow-up, withdrawal of consent, death or one month after discontinuation of Sofosbuvir-based regimen, whichever occurs first) will be reported to Gilead DSPH within 24 hours of knowledge of the event.

Special Situations will be reported to Gilead DSPH within 24 hours of knowledge of the event.

Details of the method for reporting ADRs, SADRs, fatal AEs and SSRs to DSPH will be described in the CRF Completion Guidelines.

Site personnel should record the ADR/SADR, fatal AEs or SSR on the appropriate paper reporting form (the *Non-Interventional Study AE/SAE Report Form* or the *Pregnancy Report Form* or the *Non-Interventional Study Special Situation Report Form*) and submit it by fax or email, within the timeframes given above, to:

ICTA PM - 11, rue du Bocage - 21121 Fontaine-les-Dijon – France - Tel. : +33 (0)3 80 53 40 00

Fax: +33 (0)3 80 57 10 22

E-mail: Helios@icta.fr

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the applicable regulatory agencies. Gilead will ensure that the report meets the standards set out in the Guideline on Good Pharmacovigilance Practices (GVP) Module VIII. Note that an abbreviated report may be prepared in certain cases. The final CSR will be written within 12 months of study completion.

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's 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.

Gilead shall communicate to the EMA and the competent authorities of the Member States in which the product is authorized the final manuscript within two weeks after first acceptance for publication.

Interim results of this cohort study (cohort1 and 2) will be presented at international conferences such as The International Liver Congress® (EASL) and the Liver Meeting® (AASLD) and at national conferences such as AFEF meeting and JFHOD meeting.

The complete results of the cohort study will also be published in a peer review journal.

13. REFERENCES

8074 Fattovich G, Ribero ML, Pantalena M, Diodati G, Almasio P, Nevens F, et al. Hepatitis C virus genotypes: distribution and clinical significance in patients with cirrhosis type C seen at tertiary referral centres in Europe. J Viral Hepat 2001;8 (3):206-16.

13693 Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49 (4):1335-74.

14093 Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999;341 (8):556-62.

16473 Muhlberger N, Schwarzer R, Lettmeier B, Sroczynski G, Zeuzem S, Siebert U. HCV-related burden of disease in Europe: a systematic assessment of incidence, prevalence, morbidity, and mortality. BMC public health 2009;9 (34):1-14.

19055 World Health Organisation/Europe: Hepatitis. October 2011. Available at http://www.euro.who.int/en/what-we-do/health-topics/communicablediseases/hepatitis. Accessed 28 October 2011.

19705 Esteban JI, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. J Hepatol 2008;48 (1):148-62.

22111 Nguyen MH, Keeffe EB. Prevalence and treatment of hepatitis C virus genotypes 4, 5, and 6. Clin Gastroenterol Hepatol 2005;3 (10 Suppl 2):S97-S101.

23275 Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med 2013;368 (1):34-44.

23299 Irish WD, Arcona S, Bowers D, Trotter JF. Cyclosporine versus tacrolimus treated liver transplant recipients with chronic hepatitis C: outcomes analysis of the UNOS/OPTN database. Am J Transplant 2011;11 (8):1676-85.

23321 CDC. Viral Hepatitis Surveillance United States, 2010. In: National Center for HIV/AIDS VH, STD & TB Prevention Division of Viral Hepatitis, ed. CDC, 2010

24713 Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013;368 (20):1867-77.

24715 Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368 (20):1878-87.

25891 Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011;9 (6):509-16 e1.

25892 Blatt LM, Mutchnick MG, Tong MJ, Klion FM, Lebovics E, Freilich B, et al. Assessment of hepatitis C virus RNA and genotype from 6807 patients with chronic hepatitis C in the United States. J Viral Hepat 2000;7 (3):196-202.

25896 Nainan OV, Alter MJ, Kruszon-Moran D, Gao FX, Xia G, McQuillan G, et al. Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. Gastroenterology 2006;131 (2):478-84.

27167 Centers for Disease Control and Prevention (CDC) National Vital Statistics System Division of Viral Hepatitis and National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Table 4.5. Number and rate* of deaths with hepatitis C listed as a cause of death†, by demographic characteristic and year — United States, 2006–2010. Last updated August 19, 2013. http://www.cdc.gov/hepatitis/Statistics/2011Surveillance/Table4.5.htm Accessed 14 January, 2014.

40001 Afdhal, N et al. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection. N Engl J Med 2014 DOI: 10.1056/NEJMoa1402454

40002 Afdhal, N et al. Ledipasvir and Sofosbuvir for Previously Treated HCV Genotype 1 Infection. N Engl J Med 2014 DOI: 10.1056/NEJMoa1316366

40003 Kowdley, KV et al. Ledipasvir and Sofosbuvir for 8 or 12 weeks for Chronic HCV without Cirrhosis. N Engl J Med 2014 DOI: 10.1056/NEJMoa1402355

40004 SOVALDI® (sofosbuvir) tablets, for oral use. EMA SmPC. Gilead Sciences, Inc. Foster City, CA.

40005 Ledipasvir/Sofosbuvir FDC EMA SmPC. Gilead Sciences, Inc. Foster City, CA.

40006 Dhumeaux, D. Prise en charge des personnes infectées par les virus de l'hépatite B ou de l'hépatite C - Rapport de recommandations 2014

40007 Pawlotsky JM et al. EASL recommendations on Treatment of Hepattiis C, April 2014

40008 Carreri P et al. J Acquir Immune Defic Synd 2001.

40009 Zeuzem S et al. Sofosbuvir and Ribavirin in HCV Genotypes 2 and 3. N Engl J Med 2014 DOI:10.1056/NEJMMoa1316145

14. APPENDICES

Appendix 1: List of Stand-Alone Documents

Appendix 2: ENCePP Checklist for Study Protocols

Appendix 3: Signature Page

Appendix 4: Study Assessment Tables

Appendix 5: GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Appendix 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	EQ-5D™ French version for France[2]	2010	Quality of Life (EQ-5D-5L) questionnaire
2	WPAI: Hepatitis C V2.2 French for France	28/MAY/2014	WPAI: Hepatitis C questionnaire
3	Adapted from: The role of adherence in virological suppression in patients receiving anti-HBV analogues. P. Sogni et al.;Antiviral Therapy 2012; 17:395-400		Adherence to treatment

[2] *France (French) © 2010 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group*

Appendix 2. ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
A Prospective cohort study on the use of Sofosbuvir in HCV-infected patients in clinical practice in France

Study reference number:
GS-FR-334-1530

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	12, 14
1.1.2 End of data collection[2]	☒	☐	☐	12, 14
1.1.3 Study progress report(s)	☐	☒	☐	/
1.1.4 Interim progress report(s)	☒	☐	☐	14
1.1.5 Registration in the EU PAS register	☒	☐	☐	14
1.1.6 Final report of study results.	☒	☐	☐	12, 14

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

ENCePP Checklist for Study Protocols (Revision 2)

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	16
2.1.2 The objective(s) of the study?	☒	☐	☐	17
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	20
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	/
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	18

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	18
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	18
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	/

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	19-21
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	14
4.2.2 Age and sex?	☐	☒	☐	/
4.2.3 Country of origin?	☐	☒	☐	/
4.2.4 Disease/indication?	☒	☐	☐	20
4.2.5 Co-morbidity?	☐	☒	☐	/
4.2.6 Seasonality?	☐	☐	☒	/
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	19

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	15, 16
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective				

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	15, 16
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	15, 16
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	15, 16
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	15, 16

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	18
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	/

Comments:

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	20-27
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	20-27

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	27
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	27
8.1.3 Covariates?	☒	☐	☐	27
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	27
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	27
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	27
8.3 Is a coding system described for:				

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	29
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	29
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	29
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	32

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	28

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	/
10.2 Is the choice of statistical techniques described?	☒	☐	☐	30
10.3 Are descriptive analyses included?	☒	☐	☐	30
10.4 Are stratified analyses included?	☒	☐	☐	30
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	30
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	/

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☐	☒	☐	/
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	/
11.3 Are methods of quality assurance described?	☒	☐	☐	29, 30
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	/
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	/

Comments:

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	31
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	/
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	28- 30
12.3 Does the protocol address other limitations?	☐	☒	☐	/

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	33
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	/
13.3 Have data protection requirements been described?	☒	☐	☐	33, 34

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	13

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	41
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	41

Comments:

Name of the main author of the protocol: O. LIBERT

Date: 04/ 11/ 2014

Signature:

Appendix 3. Study Acknowledgement

GILEAD SCIENCES
65 quai Georges Gorse
92100 Boulogne-Billancourt, France

A Prospective cohort study on the use of Sofosbuvir-based regimens in HCV-infected patients in clinical practice in France

Original, version 2.0, 5 December 2014

This protocol has been approved by Gilead Sciences. The following signatures document this approval.

OLIVIER LIBERT
Gilead Study Director (Printed)
Author

Signature

16/01/2015
Date

AR van Troostenburg
Gilead EU QPPV (Printed)

AR van Troostenburg
Signature

20 Jan 2015
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 study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study 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. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 4: Study Assessment Table

	V1 Baseline	**V2** End of treatment	**V3** 12 weeks post treatment	**V4** 1 year post treatment	**V5** 2 years post treatment
Patient Information	x				
Inclusion/exclusion criteria	x				
Demographic factors/Gender	x				
Body size measures	x	x	x	x	x
Medical history / Co infections	x				
Addictions	x	x	x	x	x
HCV genotype/sub-type	x				
Extra hepatic manifestations	x	x	x	x	x
Fibrosis/cirrhosis evaluation, Child-Pugh/MELD scores, Ascitis, HCC	x	x	x	x	x
History of HCV treatment	x				
HCV treatment	x	x			
Concomitant medication		x			
Laboratory tests	x	x	x	x	x
AR, SAR, Fatal AE, Special situation		x	x	x	x
Significant event or concomitant disease		x	x	x	x
Quality of Life (EQ-5D)	x	x	x	x	x
Individual productivity (WPAI)	x	x	x	x	x
Adherence to treatment *		x			
ALD status, and sick leave	x	x	x	x	x
Resources consumption		x	x	x	x

**: Questionnaire completed at week 4, week 12, and week 24 (if applicable)*

Appendix 5. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Version: 18 June 2012

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin HIV POSITIVE Adult and Pediatric ≥ 57 Days	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE Adult and Pediatric ≥ 57 Days	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Day 1 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Day 1 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Day 1 ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE) Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE) Infant, 1–21 Days (HIV positive or negative)	8.5 to 9.4 g/dL 85 to 94 g/L 9.5 to 10.5 g/dL 95 to 105 g/L 12.0 to 13.0 g/dL 120 to 130 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L 8.0 to < 9.5 g/dL 80 to < 95 g/L 10.0 to < 12.0 g/dL 100 to < 120 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L 7.0 to < 8.0 g/dL 70 to < 80 g/L 9.0 to < 10.0 g/dL 90 to < 100 g/L	< 6.0 g/dL < 60 g/L < 7.0 g/dL < 70 g/L < 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) Adult and Pediatric, > 7 Days Infant, 2 – ≤ 7 Days	1000 to 1300/mm3 1.00 to 1.30 GI/L 1250 to 1500/mm3 1.25 to 1.50 GI/L	750 to < 1000/mm3 0.75 to < 1.00 GI/L 1000 to < 1250/mm3 1.00 to < 1.25 GI/L	500 to < 750/mm3 0.50 to < 0.75 GI/L 750 to < 1000/mm3 0.75 to < 1.00 GI/L	< 500/mm3 < 0.50 GI/L < 750/mm3 < 0.75 GI/L

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Infant, 1 Day	4000 to 5000/mm3 4.00 to 5.00 GI/L	3000 to < 4000/mm3 3.00 to < 4.00 GI/L	1500 to < 3000/mm3 1.50 to < 3.00 GI/L	< 1500/mm3 < 1.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY Adult and Pediatric > 13 Years	300 to 400/mm3 300 to 400/µL	200 to < 300/mm3 200 to < 300/µL	100 to < 200/mm3 100 to < 200/µL	< 100/mm3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY Adult and Pediatric > 13 Years	600 to 650/mm3 0.60 to 0.65 GI/L	500 to < 600/mm3 0.50 to < 0.60 GI/L	350 to < 500/mm3 0.35 to < 0.50 GI/L	< 350/mm3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm3 100 to < 125 GI/L	50,000 to < 100,000/mm3 50 to < 100 GI/L	25,000 to < 50,000/mm3 25 to < 50 GI/L	< 25,000/mm3 < 25 GI/L
WBCs	2000/mm3 to 2500/mm3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm3 1.00 to < 1.50 GI/L	< 1000/mm3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

CHEMISTRY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	146 to 150 mEq/L 146 to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia Adult and Pediatric ≥ 1 Month Infant, < 1 Month	 55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	 40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	 30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	 < 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) Adult and Pediatric ≥ 7 Days Infant, < 7 Days	 7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L 6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	 7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L 6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	 6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L 5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	 < 6.1 mg/dL < 1.51 mmol/L < 5.5 mg/dL < 1.36 mmol/L

CHEMISTRY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (corrected for albumin if appropriate*) Adult and Pediatric ≥ 7 Days	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia Adult and Pediatric > 14 Years Pediatric 1 Year–14 Years Pediatric < 1 Year	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L 3.0 to 3.5 mg/dL 0.96 to 1.12 mmol/L 3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L 2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L 2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.0 mg/dL < 0.31 mmol/L < 1.5 mg/dL < 0.47 mmol/L < 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia Adult and Pediatric > 14 Days Infant, ≤ 14 Days (non-hemolytic) Infant, ≤ 14 Days (hemolytic)	> 1.0 to 1.5 × ULN NA NA	> 1.5 to 2.5 × ULN 20.0 to 25.0 mg/dL 342 to 428 µmol/L NA	> 2.5 to 5.0 × ULN > 25.0 to 30.0 mg/dL > 428 to 513 µmol/L 20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 5.0 × ULN > 30.0 mg/dL > 513 µmol/L > 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL	> 10.0 to 12.0 mg/dL	> 12.0 to 15.0 mg/dL	> 15.0 mg/dL

CHEMISTRY				
	Grade 1	Grade 2	Grade 3	Grade 4
	>ULN to 597 µmol/L	> 597 to 716 µmol/L	> 716 to 895 µmol/L	> 895 µmol/L
Hypouricemia	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting)	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting) Pediatric < 18 Years	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN

ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below Females	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection Adult and Pediatric ≥ 10 Years Pediatric > 3 Mo to < 10 Years	200 to 999 mg/24 h 201 to 499 mg/m2/24 h	>999 to 1999 mg/24 h >499 to 799 mg/m2/24 h	>1999 to 3500 mg/24 h >799 to 1000 mg/m2/24 h	> 3500 mg/24 h > 1000 mg/ m2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:
Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.
With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated
Prolonged PR Interval Pediatric ≤ 16 Years	PR interval 0.21 to 0.25 sec 1st degree AV block (PR > normal for age and rate)	PR interval > 0.25 sec Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec Type II 2nd degree AV block	Complete AV block Complete AV block
Prolonged QTc Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above Day 1 Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above Day 1 Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above Day 1 Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA

CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress Pediatric < 14 Years	Dyspnea on exertion with no or minimal interference with usual social & functional activities Wheezing OR minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from Day 1)	Visual changes causing no or minimal interference with usual social & functional	Visual changes causing greater than minimal interference with usual social & functional	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

	activities	activities		

SKIN				
	Grade 1	Grade 2	Grade 3	Grade 4
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4

GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea Adult and Pediatric ≥ 1 Year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over Day 1/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over Day 1 per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock

GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Developmental delay – Pediatric ≤ 16 Years	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weak-ness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from Day 1 either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Seizure – Pediatric < 18 Years	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences

MUSCULOSKELETAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	Grade 2	Grade 3	Grade 4
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	Grade 2	Grade 3	Grade 4
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from Day 1	10% to 19% loss in body weight from Day 1	≥ 20% loss in body weight from Day 1 OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	Grade 2	Grade 3	Grade 4
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR	Erythema OR Induration	Erythema OR	Necrosis (involving dermis

	Induration OR Edema present but ≤ 2.5 cm diameter	OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	and deeper tissue)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	Grade 2	Grade 3	Grade 4
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)

ENDOCRINE/METABOLIC				
	Grade 1	Grade 2	Grade 3	Grade 4
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	Grade 2	Grade 3	Grade 4
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated

GENITOURINARY				
	Grade 1	Grade 2	Grade 3	Grade 4
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	Grade 2	Grade 3	Grade 4
Infection (any other than HIV infection)	Localized, no systemic antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.