



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 : HEpatitis C real-LIfe study for patients On Sofosbuvir
Protocol ID	GS-FR-334-1530
Protocol Version/Date:	Original, version 2.0, 5 December 2014 Amendment 1 : 19 Dec 2016 Amendment 2: 09 August 2017
EU PAS Register No	EUPAS11074
Clinical Trials.gov Identifier	Study not registered
Active substance	Sofosbuvir (ATC code J05AX15), Ledipasvir/Sofosbuvir (ATC code J05AX65), Sofosbuvir/Velpatasvir and other anti HCV treatment authorized in France associated with Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir.
Medicinal Product	Sofosbuvir and Ledipasvir/Sofosbuvir Fixed Dose Combination (FDC) and Sofosbuvir/Velpatasvir (FDC) and other anti HCV treatments authorized in France associated with Sofosbuvir, Ledipasvir/Sofosbuvir (FDC) or Sofosbuvir/Velpatasvir (FDC)
Product reference	Sofosbuvir CIP Code: 34009 277 070 7 0 Ledipasvir/Sofosbuvir CIP Code: 34009 300 008 8 5 Sofosbuvir/Velpatasvir CIP Code 34009 300 673 1 4
Procedure number	NA
Joint PASS	No
Research Question and	This cohort study will collect and evaluate information on safety and efficacy of sofosbuvir-based regimens in routine clinical practice in France.

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 objectives of this study are to assess:

- The safety and tolerability of Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir,± Ribavirin, in adult patients with chronic HCV infection treated in routine clinical practice.
- The efficacy of Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir,± Ribavirin, in adult patients with chronic HCV infection treated in routine clinical practice.
- The characteristics of patients treated with Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir in clinical practice: severity of the liver disease, history of treatment, HCV genotypes and sub-types.
- The impact of treatment with Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir on Quality of Life (QoL).
- 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

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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	<i>Affection Longue Durée</i> (a long-term condition for which the treatment qualifies for full reimbursement in the French healthcare system)
ALT	Alanine Aminotransferase
ANSM	<i>Agence Nationale de Sécurité du Médicament et des produits de santé</i> (French competent authority)
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CA	Competent Authority
CCTIRS	<i>Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé</i> (Advisory Committee on Information Processing in health research)
CRF	Case report form
CDC	Centers for Disease Control
CNIL	<i>Commission Nationale de l'Informatique et des Libertés</i> (National Computers and Privacy Commission)
CPP	<i>Comité de Protection des Personnes</i> (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	<i>Journées Francophones d'Hépatologie et d'Oncologie Digestives</i> (Hepatology and Digestive Oncology Francophones days)
HCC	Hepatocellular Carcinoma
LDV	Ledipasvir
MELD	Model For End-Stage Liver Disease
NAFLD	Non Alcoholic Fatty Liver Disease
QoL	Quality of Life
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
Sofosbuvir based regimen	Sofosbuvir-based regimen is defined as a treatment including Sofosbuvir (Sovaldi®), Ledipasvir/Sofosbuvir fixed-dose combination (Harvoni®) or Sofosbuvir/Velpatasvir fixed-dose combination (Epclusa®)
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
VEL	Velpatasvir
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
Sofobuvir based regimen	Sofosbuvir-based regimen is defined as a treatment including Sofosbuvir (Sovaldi®), Ledipasvir/Sofosbuvir fixed-dose combination (Harvoni®) or Sofosbuvir/Velpatasvir fixed-dose combination (Epclusa®).

3. RESPONSIBLE PARTIES

Table 1. Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
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3.1. Scientific Committee

A Scientific Committee has been composed for this study.

Table 2. Scientific Committee

Name	Affiliation, Address
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BAILLY, François	Hôpital de la Croix Rousse, Lyon
GUYADER, Dominique	Hôpital Pontchaillou, Rennes
OUZAN, Denis (Coordinator)	Institut Arnault Tzanck, Saint-Laurent du Var
POL, Stanislas	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
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France

Title:	A Prospective cohort study on the use of Sofosbuvir-based regimens in HCV-infected patients in clinical practice in France HELIOS : HEpatitis C real-Life study for patients On Sofosbuvir
Rationale and Background:	<p>Hepatitis C Virus (HCV) infection is a global health challenge with an estimated 180 million individuals infected worldwide {Ghany 2009}. It is a leading cause of chronic hepatitis, cirrhosis and liver cancer and a primary indication for liver transplantation in the Western world.</p> <p>The efficacy and safety profiles of Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir have been established in phase III clinical trials {Jacobson 2013}, {Lawitz 2013}, {Khatri 2014}, {U. S. Department of Health and Human Services 2014}, {Vandooren 2013}, {Aglund 2004}, {Di Nezza 2002}, {Vairaktaris 2008}, {Ross 2001}. 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, LDV/SOF or SOF/VEL.</p>
Research Question and Objectives:	<p>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.</p> <p>The secondary objective(s) of this study are to assess:</p> <ul style="list-style-type: none">• The safety and tolerability of Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir,±Ribavirin, in adult patients with chronic HCV infection treated in routine clinical practice.

- The efficacy of Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir,±Ribavirin, in adult patients with chronic HCV infection treated in routine clinical practice.
- The characteristics of patients treated with Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir in clinical practice: severity of the liver disease, history of treatment, HCV genotypes and sub-types.
- The impact of treatment with Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir 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 in adult patients with HCV infection in clinical practice.

Population:

Adult patients with HCV infection initiating a treatment with Sofosbuvir, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir.

Inclusion Criteria:

- Age 18 years
- HCV-infected patients (HCV RNA positive)
- Patient initiating treatment with Sofosbuvir*, Ledipasvir/Sofosbuvir* or Sofosbuvir/Velpatasvir*
- Signed Patient Information Form

* prescribed according to the respective SmPC

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)

- 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 will be collected from subject's medical records at the following time points: Baseline (start of Sofosbuvir, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir). Follow-up: approximately end of treatment, 12 weeks, 1 year and 2 years after end of treatment according to clinical practice. Paper 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:**
- Around 1000 subjects will be recruited. The following sub-groups will be analyzed
- Group 1: Subjects initiating a treatment with Sofosbuvir ± Ribavirin
 - Group 2: Subjects initiating a treatment with Ledipasvir/Sofosbuvir ± Ribavirin
 - Group 3: Subjects initiating a treatment with Sofosbuvir/Velpatasvir ± Ribavirin

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 SADR.

Milestones:

Start of data collection (first patient in): Q2 2015

End of data collection (last patient out): Q3 2020

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
1	19 December 2016	Cover page, Sections 2.0, 4.0, 6.0, 8.0, 9.1.1, 9.1.2, 9.1.3, 9.2.1, 9.2.2, 9.2.3, 9.3, 9.4, 9.5	Update	Clarifications/corrections to reflect the current treatment regimen and to fit with the statistical analysis planned.
2	09 August 2017	Cover page, Sections 2.0, 3.0, 3.1,4.0, 6.0, 8.0, 9.1.1 ,9.1.2, 9.1.3, 9.2.2, 9.2.3, 9.3, 9.4, 9.5, 10.2, 10.5	Update	Addition of a group of patients treated with Sofosbuvir/Velpatasvir Wording clarification

- **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
Registration in the EU PAS register	Q2 2015
Start of data collection (first patient in)	Q4 2015
Last patient in	Q4 2017
<Interim report 1> SVR12 (groups 1 and 2)	Q2 2017
<Interim report 2> SVR 12 (group 3)	Q2 2018
End of data collection (last patient out)	Q3 2020
<Final report	Q4 2020

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 {[Ghany 2009](#)}. 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 {[Centers for Disease Control and Prevention \(CDC\) National Vital Statistics System Division of Viral Hepatitis and National Center for HIV/AIDS 2013](#)}. In Europe, an estimated 7.3 to 8.8 million people have chronic HCV infection leading to approximately 86,000 deaths each year {[World Health Organization \(WHO\) 2011](#)}, {[Muhlberger 2009](#)}. 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 {[Decock 2011](#)}.

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 {[Backus 2011](#)}; genotypes 2 and 3 HCV infection represent the majority of the remaining cases of chronic HCV infection in the US and Europe {[Fattovich 2001](#)}, {[Alter 1999](#)}, {[Esteban 2008](#)}, {[Nainan 2006](#)}, {[Blatt 2000](#)}, {[Backus 2011](#)}. Genotype 4, 5, and 6 HCV infections are most prevalent in the Middle East, South Africa, and Southeast Asia, respectively {[Nguyen 2005](#)}.

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 {[Gilead Sciences Inc 2013](#)}, {[Gane 2013](#)}, {[Jacobson 2013](#)}, {[Lawitz 2013](#)}. 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. {[Asuthkar 2011](#)}

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. {[Khatri 2014](#)}, {[U. S. Department of Health and Human Services 2014](#)}, {[Vandooren 2013](#)}. 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 {[Colotta 2009](#)}, for further information on LDV/SOF.

7.2.3. Sofosbuvir/Velpatasvir (SOF/VEL) Fixed Dose Combination (FDC)

Sofosbuvir/Velpatasvir fixed-dose combination (Epclusa® or SOF/VEL) combines two HCV specific direct acting antiviral (DAA) agents into a single tablet for the treatment of chronic HCV infection. Velpatasvir is a novel pangenotypic HCV NS5A inhibitor that has demonstrated potent anti HCV activity against genotypes 1, 2, 3, 4, 5 and 6 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 SOF 90 mg / VEL 100 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. {[Di Nezza 2002](#)}, {[Vairaktaris 2008](#)}, {[Ross 2001](#)}. These doses represent the proposed marketed doses of SOF and VEL. SOF/VEL has been administered to more than 3,000 subjects with HCV infection in clinical trials. No safety issues related to SOF/VEL administration have been identified to date.

Overall, SOF/VEL has been well tolerated. The most frequently reported adverse events (AEs) for SOF/VEL were fatigue and headache.

Please refer to Epclusa® EMA SmPC {[Darby 1997](#)}, for further information on SOF/VEL.

7.3. Rationale for the Current Study

The efficacy and safety profiles of Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir have been established in phase III clinical trials {[Jacobson 2013](#)},

{Lawitz 2013}, {Khatri 2014}, {U. S. Department of Health and Human Services 2014}, {Vandooren 2013}, {Aglund 2004}, {Di Nezza 2002}, {Vairaktaris 2008}, {Ross 2001}. 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 missing¹.

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®, Harvoni® and Epclusa®.

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, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir 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, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir,±Ribavirin, in adult patients with chronic HCV infection treated in routine clinical practice.
- The efficacy of Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir,±Ribavirin, in adult patients with chronic HCV infection treated in routine clinical practice.
- The characteristics of patients treated with Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir in clinical practice: severity of the liver disease, history of treatment, HCV genotypes and sub-types.
- The impact of treatment with Sofosbuvir, Ledipasvir/Sofosbuvir and Sofosbuvir/Velpatasvir 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, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir will be based on the prescribing doctor's own judgement, and will not be influenced in any manner by the present study.

Around 1000 subjects will be recruited. The following sub-groups will be analysis

Group 1: Subjects initiating a treatment with Sofosbuvir ± Ribavirin.

Group 2: Subjects initiating a treatment with Ledipasvir/Sofosbuvir ± Ribavirin

Group 3: Subjects initiating a treatment with Sofosbuvir/Velpatasvir ± Ribavirin

9.1.2. Observation period

Data will be collected when treatment with Sofosbuvir, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir 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 will be evaluated by determining rates of Adverse Drug Reaction (ADR) leading to permanent discontinuation of treatment with Sofosbuvir, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir.
 - Secondary efficacy endpoints include the rates 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 (QoL) 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).
 - Rate 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.

- Up to 60 sites will be selected all around France, primarily in departments of Hepato-Gastro-Enterology, Infectious Diseases and Internal Medicine.

9.2.2. Eligibility criteria

Inclusion Criteria

- Age 18 years

- HCV-infected patients(HCV RNA positive)
- Patient initiating treatment with Sofosbuvir*, Ledipasvir/Sofosbuvir* or Sofosbuvir/Velpatasvir therapy*
- Patient Information Form signed

* prescribed according to the respective SmPC

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, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir (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, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir (V2)

The following variables will be collected at the end of treatment with Sofosbuvir, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir, 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
- HCV Treatment regimen
- Sofosbuvir, Ledipasvir/Sofosbuvir, Sofosbuvir/Velpatasvir 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
- QoL: 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, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir (V3)

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

- Patients characteristics
 - Body size measures : weight, Body Mass Index
- Addictions : alcohol consumption, tobacco, 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
- QoL: 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, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir (V4)

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

- Patients characteristics
 - Body size measures : weight, Body Mass Index
- Addictions : alcohol consumption, tobacco, 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
- QoL: 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, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir (V5)

The following variables will be collected 96 weeks after the end of treatment with Sofosbuvir, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir, 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, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir therapy and the corresponding descriptive and clinical outcome by the treating physician.

Clinical data will be collected from subject's medical records at the following time points:

Baseline (start of Sofosbuvir, Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir)

Follow-up: approximately end of treatment, 12 weeks, 1 year and 2 years after end of treatment according to clinical practice.

Paper 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. 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.

9.5. Study Size

The objectives of this study are purely descriptive in nature and preclude any statistical comparison between the three different treatment arms.

The primary endpoint, on which this study will be powered, is concerned with the comparison of a proportion to a reference value. Given a desired precision of 3% and a desired significance level of 0.05 the following formula is used:

$$n = 1,96^2 \times \frac{P(1 - P)}{\text{precision}^2}$$

Assuming a percentage of 85% of SVR12 with a desired precision of 3%, the number of patients to be included is calculated as:

$$n = 1.96^2 \times \frac{0.85(1 - 0.85)}{0.03^2} = 545$$

A participant feasibility count estimated the potential number of patients that will be recruited into each treatment arm. These estimates are presented in table 5:

Table 5. Estimated number of patients available for each treatment arm

Group	Regimen	Number of patients
1	SOF ± DAA* ± R	Up to 300
2	LDV/SOF ± R	At least 300
3	SOF/VEL ± R	At least 400

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

As the actual final sample size is subject to external factors such as the availability of patients, [Table 2](#) presents the expected confidence intervals for estimates based on different scenarios of sample size and SVR12 values. As can be seen the width of the confidence interval is a function of the sample size.

Table 6. Confidence intervals based on differing sample sizes and SVR12 Proportions.

Sample Size	85%	90%	95%
100	(78.0, 92.0)	(84.1, 95.9)	(90.7, 99.3)
200	(80.1, 90.0)	(85.8, 94.1)	(92.0, 98.0)
300	(81.0, 89.0)	(86.6, 93.4)	(92.5, 97.5)
400	(81.5, 88.5)	(87.1, 92.9)	(92.9, 97.1)
500	(81.9, 88.1)	(87.4, 92.6)	(93.1, 96.9)
600	(82.1, 87.9)	(87.6, 92.4)	(93.3, 96.7)

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 SADR 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.

This study amendment falls under the scope of the ordinance 2016-800 dated 16 June 2016 and of the decree 2016-1537 dated 16 November 2016 and will require submission to a “Comité de Protection des Personnes” (CPP).

The investigator will not initiate any study-related subject activities until approval from the CPP has been documented and provided as a letter to the investigator.

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 protocol amendment complies with the reference methodology MR003 from the CNIL (*Commission Nationale de l’Informatique et des Libertés* [French Data Protection Commission]) requirements in matters of personal data protection in accordance with deliberation 2016-263 dated 21 July 2016.

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, and as required by relevant regulatory guidance. CPP approval and protocol synopsis will be sent to ANSM for information.

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. Signed informed consent forms and patient identification list must be kept strictly confidential and enable patient identification at the site. Patients will be informed that representatives of Gilead or regulatory authorities, if applicable, may need to review directly their medical records to complete the eCRF and or verify the authenticity and consistency of information collected. If required, data can be corrected and/or completed while respecting confidentiality rules. Patients will be also informed that all consulted information is subject to confidentiality and professional secrecy (Article 226-13 and 226-14 of the Penal Code). These quality controls will be performed under the supervision of the investigator.

Investigators will have the rights to access, rectification and opposition to the processing of their data. These rights shall be exercised as to "the Legal Department" of Gilead, 65 Quai Georges Gorse, 92100 Boulogne Billancourt."

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 or CRO

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 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.

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14. APPENDICES

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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 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 section number 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). 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-based regimens in HCV-infected patients in clinical practice in France

Study reference number:

GS-FR-334-1530

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.2 End of data collection ²	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.3 Study progress report(s)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
1.1.4 Interim progress report(s)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	14
1.1.5 Registration in the EU PAS register	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.6 Final report of study results.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6

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 3)

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Section 2: Research question	Yes	No	N/A	Section Number
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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4
2.1.4 Which hypothesis(-es) is (are) to be tested?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	/
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	/

Comments:

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Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11.5

Comments:

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Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
4.2.2 Age and sex?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	/
4.2.3 Country of origin?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	/
4.2.4 Disease/indication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.2
4.2.5 Duration of follow-up?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1.2,9.2.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1.1

Section 4: Source and study populations	Yes	No	N/A	Section Number
event or inclusion/exclusion criteria)				

Comments:

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Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.2.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.3
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.3
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.2.2

Comments:

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Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1.3
6.2 Does the protocol describe how the outcomes are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	/
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYs, health care services utilisation, burden of disease, disease management)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1.3

Comments:

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Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol describe how confounding will be addressed in the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4
7.1.1. Does the protocol address confounding by indication if applicable?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	/
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9

ENCePP Checklist for Study Protocols (Revision 3)

Section 7: Bias	Yes	No	N/A	Section Number
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9
7.3 Does the protocol address the validity of the study covariates?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3

Comments:

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Section 8: Effect modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Comments:

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Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
9.1.3 Covariates?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
9.2 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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6
9.3.3 Covariates?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6

Comments:

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Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Is the choice of statistical techniques described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.2 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.3 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.4 Does the plan describe methods for adjusting for confounding?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.5 Does the plan describe methods for handling missing data?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	/
10.6 Is sample size and/or statistical power estimated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5

Comments:

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Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	/
11.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.8
11.3 Is there a system in place for independent review of study results?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	/

Comments:

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Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9
12.1.2 Information bias?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	/
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	/
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6, 9.1.2 & 9.2.2

Comments:

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Section 13: Ethical issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	/
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	10.3

ENCePP Checklist for Study Protocols (Revision 3)

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12

Comments:

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

Date: 30/03/2017

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

Amendment 2 version of 09 August 2017

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

Olivier LIBERT

Gilead Study Director (Printed)
Author

14 AUG 2017

Date

A R van Troostenburg de Bruyn

Gilead EU QPPV (Printed)

14 AUG 2017

Date



Signature



Signature

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)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV positive or negative)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) Adult and Pediatric, > 7 Days	1000 to 1300/mm ³	750 to < 1000/mm ³	500 to < 750/mm ³	< 500/mm ³
	1.00 to 1.30 GI/L	0.75 to < 1.00 GI/L	0.50 to < 0.75 GI/L	< 0.50 GI/L
Infant, 2 – ≤ 7 Days	1250 to 1500/mm ³ 1.25 to 1.50 GI/L	1000 to < 1250/mm ³ 1.00 to < 1.25 GI/L	750 to < 1000/mm ³ 0.75 to < 1.00 GI/L	< 750/mm ³ < 0.75 GI/L

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Infant, 1 Day	4000 to 5000/mm ³ 4.00 to 5.00 GI/L	3000 to < 4000/mm ³ 3.00 to < 4.00 GI/L	1500 to < 3000/mm ³ 1.50 to < 3.00 GI/L	< 1500/mm ³ < 1.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY Adult and Pediatric > 13 Years	300 to 400/mm ³ 300 to 400/μL	200 to < 300/mm ³ 200 to < 300/μL	100 to < 200/mm ³ 100 to < 200/μL	< 100/mm ³ < 100/μL
Absolute Lymphocyte Count HIV NEGATIVE ONLY Adult and Pediatric > 13 Years	600 to 650/mm ³ 0.60 to 0.65 GI/L	500 to < 600/mm ³ 0.50 to < 0.60 GI/L	350 to < 500/mm ³ 0.35 to < 0.50 GI/L	< 350/mm ³ < 0.35 GI/L
Platelets	100,000 to < 125,000/mm ³ 100 to < 125 GI/L	50,000 to < 100,000/mm ³ 50 to < 100 GI/L	25,000 to < 50,000/mm ³ 25 to < 50 GI/L	< 25,000/mm ³ < 25 GI/L
WBCs	2000/mm ³ to 2500/mm ³	1,500 to < 2,000/mm ³	1000 to < 1,500/mm ³	< 1000/mm ³
	2.00 GI/L to 2.50 GI/L	1.50 to < 2.00 GI/L	1.00 to < 1.50 GI/L	< 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL	75 to < 100 mg/dL	50 to < 75 mg/dL	< 50 mg/dL
	1.00 to 2.00 g/L	0.75 to < 1.00 g/L	0.50 to < 0.75 g/L	< 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL	> 600 mg/dL	—	—
	> ULN to 6.0 g/L	> 6.0 g/L	—	—
Fibrin Split Product	20 to 40 μg/mL	> 40 to 50 μg/mL	> 50 to 60 μg/mL	> 60 μg/mL
	20 to 40 mg/L	> 40 to 50 mg/L	> 50 to 60 mg/L	> 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

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
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
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	125 to < 130 mEq/L	121 to < 125 mEq/L	< 121 mEq/L
	130 to <LLN mmol/L	125 to < 130 mmol/L	121 to < 125 mmol/L	< 121 mmol/L
Hypernatremia	146 to 150 mEq/L	> 150 to 154 mEq/L	> 154 to 159 mEq/L	> 159 mEq/L
	146 to 150 mmol/L	> 150 to 154 mmol/L	> 154 to 159 mmol/L	> 159 mmol/L
Hypokalemia	3.0 to 3.4 mEq/L	2.5 to < 3.0 mEq/L	2.0 to < 2.5 mEq/L	< 2.0 mEq/L
	3.0 to 3.4 mmol/L	2.5 to < 3.0 mmol/L	2.0 to < 2.5 mmol/L	< 2.0 mmol/L
Hyperkalemia	5.6 to 6.0 mEq/L	> 6.0 to 6.5 mEq/L	> 6.5 to 7.0 mEq/L	> 7.0 mEq/L
	5.6 to 6.0 mmol/L	> 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mmol/L	> 7.0 mmol/L
Hypoglycemia Adult and Pediatric ≥ 1 Month	55 to 64 mg/dL	40 to < 55 mg/dL	30 to < 40 mg/dL	< 30 mg/dL
	3.03 to 3.58 mmol/L	2.20 to < 3.03 mmol/L	1.64 to < 2.20 mmol/L	< 1.64 mmol/L
Infant, < 1 Month	50 to 54 mg/dL	40 to < 50 mg/dL	30 to < 40 mg/dL	< 30 mg/dL
	2.8 to 3.0 mmol/L	2.2 to < 2.8 mmol/L	1.7 to < 2.2 mmol/L	< 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL	> 160 to 250 mg/dL	> 250 to 500 mg/dL	> 500 mg/dL
	6.42 to 8.91 mmol/L	> 8.91 to 13.90 mmol/L	> 13.90 to 27.79 mmol/L	> 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL	>125 to 250 mg/dL	>250 to 500 mg/dL	>500 mg/dL
	6.08 to 6.96 mmol/L	>6.96 to 13.90 mmol/L	>13.90 to 27.79 mmol/L	>27.79 mmol/L

CHEMISTRY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hypocalcemia (corrected for albumin if appropriate*) Adult and Pediatric ≥ 7 Days	7.8 to 8.4 mg/dL	7.0 to < 7.8 mg/dL	6.1 to < 7.0 mg/dL	< 6.1 mg/dL
	1.94 to 2.10 mmol/L	1.74 to < 1.94 mmol/L	1.51 to < 1.74 mmol/L	< 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) Adult and Pediatric ≥ 7 Days	>ULN to 11.5 mg/dL	> 11.5 to 12.5 mg/dL	> 12.5 to 13.5 mg/dL	> 13.5 mg/dL
	>ULN to 2.88 mmol/L	> 2.88 to 3.13 mmol/L	> 3.13 to 3.38 mmol/L	> 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	2.5 to < 3.0 mg/dL	2.0 to < 2.5 mg/dL	< 2.0 mg/dL
	0.74 mmol/L to < LLN	0.62 to < 0.74 mmol/L	0.49 to < 0.62 mmol/L	< 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL	> 6.0 to 6.5 mg/dL	> 6.5 to 7.0 mg/dL	> 7.0 mg/dL
	> ULN to 1.50 mmol/L	> 1.50 to 1.63 mmol/L	> 1.63 to 1.75 mmol/L	> 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL	1.04 to < 1.40 mg/dL	0.67 to < 1.04 mg/dL	< 0.67 mg/dL
	1.2 to <LLN mEq/L	0.9 to < 1.2 mEq/L	0.6 to < 0.9 mEq/L	< 0.6 mEq/L
	0.58 to <LLN mmol/L	0.43 to < 0.58 mmol/L	0.28 to < 0.43 mmol/L	< 0.28 mmol/L
Hypophosphatemia Adult and Pediatric > 14 Years	2.0 to < LLN mg/dL	1.5 to < 2.0 mg/dL	1.0 to < 1.5 mg/dL	< 1.0 mg/dL
	0.63 to < LLN mmol/L	0.47 to < 0.63 mmol/L	0.31 to < 0.47 mmol/L	< 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to 3.5 mg/dL	2.5 to < 3.0 mg/dL	1.5 to < 2.5 mg/dL	< 1.5 mg/dL
	0.96 to 1.12 mmol/L	0.80 to < 0.96 mmol/L	0.47 to < 0.80 mmol/L	< 0.47 mmol/L
Pediatric < 1 Year	3.5 to 4.5 mg/dL	2.5 to < 3.5 mg/dL	1.5 to < 2.5 mg/dL	< 1.5 mg/dL
	1.12 to 1.46 mmol/L	0.80 to < 1.12 mmol/L	0.47 to < 0.80 mmol/L	< 0.47 mmol/L

CHEMISTRY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyperbilirubinemia Adult and Pediatric > 14 Days	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 μmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 μmol/L	> 30.0 mg/dL > 513 μmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 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
	>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	1.0 to < 1.5 mg/dL	0.5 to < 1.0 mg/dL	< 0.5 mg/dL
	87 μmol/L to < LLN	57 to < 87 μmol/L	27 to < 57 μmol/L	< 27 μmol/L
Creatinine	> 1.50 to 2.00 mg/dL	> 2.00 to 3.00 mg/dL	> 3.00 to 6.00 mg/dL	> 6.00 mg/dL
	> 133 to 177 μmol/L	> 177 to 265 μmol/L	> 265 to 530 μmol/L	> 530 μmol/L
Bicarbonate	16.0 mEq/L to < LLN	11.0 to < 16.0 mEq/L	8.0 to < 11.0 mEq/L	< 8.0 mEq/L
	16.0 mmol/L to < LLN	11.0 to < 16.0 mmol/L	8.0 to < 11.0 mmol/L	< 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL	> 750 to 1200 mg/dL	> 1200 mg/dL
		5.64–8.47 mmol/L	> 8.47–13.55 mmol/L	> 13.55 mmol/L
LDL (Fasting)	130 to 160 mg/dL	>160 to 190 mg/dL	> 190 mg/dL	NA
	3.35 to 4.15 mmol/L	>4.15 to 4.92 mmol/L	>4.92 mmol/L	
Pediatric >2 to <18 years	110 to 130 mg/dL	>130 to 190 mg/dL	> 190 mg/dL	NA
	2.84 to 3.37 mmol/L	>3.37 to 4.92 mmol/L	>4.92 mmol/L	
Hypercholesterolemia (Fasting)	200 to 239 mg/dL	> 239 to 300 mg/dL	> 300 mg/dL	NA
	5.16 to 6.19 mmol/L	> 6.19 to 7.77 mmol/L	> 7.77 mmol/L	
Pediatric < 18 Years	170 to 199 mg/dL	> 199 to 300 mg/dL	> 300 mg/dL	NA
	4.39 to 5.15 mmol/L	> 5.15 to 7.77 mmol/L	> 7.77 mmol/L	
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
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	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Females				
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	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m ² /24 h	>499 to 799 mg/m ² /24 h	>799 to 1000 mg/m ² /24 h	> 1000 mg/ m ² /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	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above Day 1	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 ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above Day 1	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	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)

CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
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 activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

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
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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)

GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
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
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)

GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
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

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
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
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

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
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
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness 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)

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
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)
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 Pediatric < 21 Years	BMD t-score or z-score -2.5 to -1.0 BMD z-score -2.5 to -1.0	BMD t-score or z-score < -2.5 BMD z-score < -2.5	Pathological fracture (including loss of vertebral height) Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences 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
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 Pediatric ≤ 15 Years	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm ²) Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm ²) Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage Erythema OR 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	Necrosis (involving dermis and deeper tissue) Necrosis (involving dermis 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)
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)

ENDOCRINE/METABOLIC				
	Grade 1	Grade 2	Grade 3	Grade 4
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
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.