NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY PROTOCOL

Study Title:	Observational, Cross-Sectional Post-Authorisation Safety Study to Assess Healthcare Provider Awareness of Risks Related to Sofosbuvir and Ledipasvir/Sofosbuvir
Protocol ID:	GS-EU-337-2030
Protocol Version/Date:	Final: Version 1.2, 11 July 2016 Amendment 1, 04 March 2016 Original: 26 October 2015
EU PAS Register No:	To be registered prior to start of data collection
Active substance:	ATC Code: J05AX15 Active substance: Sofosbuvir (Sovaldi®) and ledipasvir/sofosbuvir (Harvoni®)
Medicinal Product:	Sovaldi® and Harvoni®
Indication:	Treatment of chronic hepatitis C (CHC) in adults.
Product reference / Procedure number:	EU/1/13/894/001 (Sovaldi®) EU/1/13/894/002 (Sovaldi®) EU/1/14/958/001 (Harvoni®) EU/1/14/958/002 (Harvoni®)
Joint PASS:	No
Research Question and Objectives:	Investigate healthcare provider awareness of the risk of clinically significant arrhythmias when sofosbuvir (in combination with daclatasvir or simeprevir) or ledipasvir/sofosbuvir is prescribed concurrently with amiodarone, and determine perceptions of co-medication frequency, reported changes in prescribing behaviour, and reported approaches to patient monitoring following dissemination of a direct healthcare professional communication
Countries of study:	European Union countries where Sovaldi® and Harvoni® are marketed.
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CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Gilead Sciences, Inc., and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you. You will not disclose any of the information to others without written authorisation from Gilead Sciences, Inc., except to the extent necessary to obtain informed consent from those persons who will participate in the study.

TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
CHC	chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
DCV	daclatasvir
DHPC	direct healthcare professional communication
DSPH	Drug Safety & Public Health
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GSI	Gilead Sciences, Inc.
GVP	Good Pharmacovigilance Practices (guidelines for)
HCV	hepatitis C virus
HMA	Heads of Medicines Agency
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
LDV/SOF	ledipasvir/sofosbuvir
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
SMV	simeprevir
SmPC	Summary of Product Characteristics
SOF	sofosbuvir

1. RESPONSIBLE PARTIES

Table of Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation	Contact Information
Principal Investigator, Study Co-Director	Anand Chokkalingam, PhD Associate Director, Epidemiology Gilead Sciences	Gilead Sciences 333 Lakeside Drive, Foster City CA 94404
Study Co-Director	Amanda Singer, PhD MPH Manager, Epidemiology Gilead Sciences	Gilead Sciences 333 Lakeside Drive, Foster City CA 94404
Clinical Operations	Melanie Cain Senior Clinical Program Manager Gilead Sciences	Gilead Sciences 2 Roundwood Avenue, Stockley Park, Uxbridge UB11 1AF, UK
Vendor Hall & Partners	Hannah Derbyshire Research Director	Hall & Partners Bankside 2, 100 Southwark St, London, SE1 0SW, UK

2. PROTOCOL SYNOPSIS/ABSTRACT

Gilead Sciences International Ltd.
Cambridge, CB21 6GT, United Kingdom

Title:	Observational, Cross-Sectional Post-Authorisation Safety Study to Assess Healthcare Provider Awareness of Risks Related to Sofosbuvir and Ledipasvir/Sofosbuvir
Rationale and Background:	Post-marketing cases of serious symptomatic cardiac arrhythmia (bradycardia) have been reported in patients taking the antiarrhythmic drug amiodarone with sofosbuvir (SOF, Sovaldi®) in combination with the direct-acting antivirals daclatasvir (DCV, DaklinzaTM) or simeprevir (SMV, Olysio ™), or with ledipasvir/sofosbuvir (LDV/SOF, Harvoni®). This post-authorisation safety study is intended to assess the awareness of European healthcare providers of this risk following the dissemination of a direct healthcare professional communication (DHPC) in May 2015. The study will examine if healthcare providers are aware of the risk associated with concomitant use of these drugs and patient monitoring recommendations following distribution of the DHPC.

Research Question and Objectives:

The primary objective of this study is as follows:

- Determine the proportion of healthcare providers aware of the risk of clinically significant arrhythmias when SOF (in combination with DCV or SMV) or LDV/SOF is prescribed concurrently with amiodarone.

The secondary objectives of this study are as follows:

- Assess healthcare provider perceptions regarding the current frequency of concomitant use of amiodarone with either SOF + DCV, SOF + SMV, or LDV/SOF among patients in their care.
- Characterize and assess the frequency of current reported healthcare provider approaches to assessing and reducing patient risk related to co-medication with amiodarone and either SOF + DCV, SOF + SMV, or LDV/SOF.
- Determine the proportion of respondents who report having changed their prescribing behaviour following awareness of the risk and assess the frequency of specific reported prescribing changes.
- Among the subset of respondents who have cared for patients co-prescribed amiodarone with either SOF + DCV, SOF + SMV, or LDV/SOF, determine the proportion of respondents who have implemented increased patient monitoring following awareness of the risk and characterize the approaches to patient monitoring being employed to reduce the occurrence of these events.

Study Design:

This study is a cross-sectional survey of European healthcare providers responsible for the treatment of chronic hepatitis C (CHC) patients.

Population:

The survey questionnaire will collect response data from healthcare providers responsible for the treatment of CHC patients. The study population will be drawn from several European countries and is intended to be as representative as possible of the various practice specialties that received the DHPC and care for CHC patients. These include gastroenterologists, hepatologists, infectious disease physicians, cardiologists, general practitioners/internists, and specialty and hospital pharmacists. All data collected will be in aggregate according to healthcare provider recall; no individual patient data will be collected.

Variables:	The questionnaire is designed to collect information on the following variables: country of practice, provider specialty and practice size, awareness and source of knowledge of the risk described in the DHPC, history of prescribing SOF or LDV/SOF, perceptions regarding the current frequency of co-medication with the drugs of interest, healthcare provider approaches to assessing and reducing patient risk associated with concomitant use of these drugs, and reported changes in prescribing behaviour following awareness of the risk. Among respondents who have cared for patients treated with amiodarone and either SOF + DCV, SOF + SMV, or LDV/SOF, the questionnaire will assess reported changes in patient monitoring following awareness of the risk.
Data Sources:	The data source will be the responses from the healthcare provider questionnaires.
Study Size:	A minimum of 200 completed surveys will be obtained for the final analysis.
Data Analysis:	Questionnaire data will be aggregated and summarized overall, as well as by country and provider specialty where sample size allows. Data from the survey of healthcare providers will be summarized descriptively (counts, proportions).
Milestones:	Date of survey: Estimated Q4 2016 /Q1 2017 Final report: Estimated Q2/Q3 2017

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

3. AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1 (version 1.1)	04 March 2016	Responsible Parties (3.0)	Study co-director added and vendor information updated	Study Management Team decision
		Protocol Synopsis/Abstract (4.0)	Revised the synopsis to be consistent with the changes detailed below	Study Management Team decision
		Milestones (6.0)	Revised estimated periods for data collection and report submission	Updated to be consistent with Pharmacovigilance Risk Assessment Committee (PRAC) assessment timeline
		Research Questions and Objectives (8.0)	Revised the objectives to clarify how they will be measured and assessed	Study Management Team decision
		Study Design (9.1)	Updated to reflect the revised objectives	Study Management Team decision
		Setting (9.2)	Provider specialties and sampling approach updated	Study Management Team decision
		Variables (9.3)	Revised the variable list to clarify how they will be measured and assessed	Study Management Team decision
		Data Sources (9.4)	Revised to indicate that the data will be summarized overall as well as by country and provider specialty	Minor edit for consistency throughout document
		Study Size (9.5)	Revised to indicate the minimum number of responses to be obtained for the final analysis	Revised for clarity
		Data Management (9.6)	Revised to indicate that surveys in Bulgaria and Hungary will be face-to-face interviews	Received further information from the vendor regarding study implementation
		Data Analysis (9.7)	Updated with awareness benchmark and clarified analysis approach for secondary objectives	Study Management Team decision

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
		Quality Control (9.8)	Revised to clarify strategy to ensure data completeness	Received further information from the vendor regarding study implementation
		Limitations of the Research Methods (9.9)	Revised to add lack of a written survey option for most countries as a limitation	Study Management Team decision
		Study Discontinuation (9.10.1)	Revised to indicate that the study will only be terminated in agreement with the PRAC	Study Management Team decision
		Adverse Events (11.1)	Revised to clarify that any adverse event reported through the survey will be collected	Study Management Team decision
		Study Report and Publications (12.1)	Revised estimated period for report submission	Updated to be consistent with Pharmacovigilance Risk Assessment Committee (PRAC) assessment timeline
Protocol version 1.2	11 July 2016	Throughout	Added SOF + SMV as regimen of interest	Study Management Team decision, in accordance with PRAC comments
		Data Management (9.6)	Added telephone-based structured interviews as an optional means of response	Study Management Team decision, in accordance with PRAC comments
		Milestones (6.0)	Revised estimated periods for data collection and report submission	Updated to be consistent with PRAC assessment timeline

Protocol Modifications

Protocol modifications may only be made by Gilead Sciences.

4. MILESTONES

Milestone	Planned date
Start of data collection	Q4 2016
End of data collection	Q1 2017/Q2 2016
Registration in the European Union (EU) Post-Authorisation Study (PAS) register	To be registered prior to start of data collection
Final report of study results	Q2 2017/Q3 2017

5. RATIONALE AND BACKGROUND

5.1. Rationale for the Current Study

Sovaldi® (SOF) received approval as the first nucleotide polymerase inhibitor for the treatment of hepatitis C from the European Union in January 2014 {European Association For The Study Of The Liver 2015}. Olysio ™ (SMV), an NS3/4A protease inhibitor, was approved in May 2014; Daklinza™ (DCV), a pangenotypic NS5A inhibitor, was approved in August 2014; and approval for Harvoni® (LDV/SOF) followed in November 2014. Since approval of these drugs, interferon-free treatment regimens for CHC have been used widely in Europe {European Association For The Study Of The Liver 2015}.

The European Association for the Study of the Liver (EASL) recommends the use of SOF in combination with other hepatitis C virus (HCV) therapies for the treatment of CHC. For CHC patients without cirrhosis, EASL treatment guidelines recommend the following interferon-free, SOF-based medication regimens: 1) SOF and ribavirin for HCV genotypes 2 and 3; 2) LDV/SOF without ribavirin for HCV genotypes 1a, 1b, 4, 5, and 6; 3) SOF and SMV without ribavirin for HCV genotypes 1a, 1b, and 4; and 4) SOF and DCV without ribavirin for treatment of all HCV genotypes {European Association For The Study Of The Liver 2015}.

Since the approval of these medications, cases of symptomatic bradycardia have been reported in patients treated with amiodarone concurrently with LDV/SOF or with SOF in combination with either of the direct-acting antivirals DCV or SMV. Following recognition of this risk in Q2 2015, Gilead notified prescribers in the EU and other countries worldwide of the risk of severe bradycardia or heart block associated with concomitant use of these medications through dissemination of a DHPC in May 2015. The EU Summaries of Product Characteristics (SmPCs) for Sovaldi® and Harvoni® were also updated with information about this risk in Q2 2015. The mechanism of the interaction and the role of other concomitant medications is unknown {European Association For The Study Of The Liver 2015}.

5.2. Purpose of the Study

This post-authorisation safety study (PASS) is intended to assess the awareness of European healthcare providers of this risk following the dissemination of a DHPC in May 2015. This cross-sectional survey will examine if healthcare providers are aware of the risk associated with concomitant use of these drugs following the DHPC dissemination, and will measure reported changes in prescribing behaviour or patient monitoring.

6. RESEARCH QUESTIONS AND OBJECTIVES

The primary objective of this study is as follows:

- Determine the proportion of healthcare providers aware of the risk of clinically significant arrhythmias when SOF (in combination with DCV or SMV) or LDV/SOF is prescribed concurrently with amiodarone.

The secondary objectives of this study are as follows:

- Assess healthcare provider perceptions regarding the current frequency of concomitant use of amiodarone with either SOF + DCV, SOF + SMV, or with LDV/SOF among patients in their care.

- Characterize and assess the frequency of current reported healthcare provider approaches to assessing and reducing patient risk related to co-medication with amiodarone and either SOF + DCV, SOF + SMV, or LDV/SOF.

- Determine the proportion of respondents who report having changed their prescribing behaviour following awareness of the risk and assess the frequency of specific reported prescribing changes.

- Among the subset of respondents who have cared for patients co-prescribed amiodarone with either SOF + DCV, SOF + SMV, or LDV/SOF, determine the proportion of respondents who have implemented increased patient monitoring following awareness of the risk and characterize the approaches to patient monitoring being employed to reduce the occurrence of these events.

7. RESEARCH METHODS

7.1. Study Design

For this observational cross-sectional PASS, healthcare providers responsible for the treatment of CHC patients will be surveyed to determine the proportion of providers aware of the potential risk of bradycardia in patients receiving amiodarone concurrently with either LDV/SOF, SOF + DCV, or SOF + SMV. This survey will also examine healthcare provider perceptions regarding the frequency of concomitant use of these drugs (i.e. the proportion of patients under the respondent's care who are co-prescribed these drugs), will characterize reported healthcare provider approaches to assessing and reducing the risk of patients under their care, and will assess reported changes in prescribing behaviour following awareness of the risk. Among the subset of respondents who have cared for patients co-prescribed amiodarone with either SOF + DCV, SOF + SMV, or LDV/SOF and express awareness of the risk, the survey will characterize and assess the frequency of reported changes in patient monitoring intended to minimize the risk of adverse events in patients receiving these medications.

7.2. Setting

The study questionnaire will collect data on healthcare providers responsible for the treatment of CHC patients. The study population will be drawn from several European countries. The source population is all healthcare providers responsible for the treatment of CHC patients in Europe. The sample will be selected from a panel of healthcare providers and will be as representative as possible of the various practice specialties that received the DHPC and care for CHC patients (including gastroenterologists, hepatologists, infectious disease physicians, cardiologists, general practitioners/internists, and specialty and hospital pharmacists). Collection of select variables on non-respondents (e.g. country, provider specialty) will also be attempted.

7.3. Variables

This is a cross-sectional study without follow-up. The study questionnaire is designed to collect information on the following variables: country of practice, provider specialty and practice size, awareness and source of knowledge of the risk described in the DHPC, history of prescribing SOF or LDV/SOF, perceptions regarding the frequency of co-medication with the drugs of interest (i.e. the proportion of patients under the respondent's care who are co-prescribed these drugs), reported healthcare provider approaches to assessing and reducing the risk of patients under their care, and the proportion of respondents who report having changed their prescribing behaviour following awareness of the risk and the frequency of specific prescribing changes. Among the subset of respondents who have cared for patients co-prescribed amiodarone with either SOF + DCV, SOF + SMV, or LDV/SOF, the survey will also determine the proportion of respondents who have implemented increased patient monitoring following awareness of the risk and will characterize the frequency of various reported approaches to patient monitoring. The questionnaire design will be optimised through pilot interviews with a small sample of healthcare providers.

7.4. Data Sources

The data source will be the aggregated individual healthcare provider survey responses. Responses will be aggregated and summarized overall, as well as by country and by provider specialty where sample size allows.

7.5. Study Size

Healthcare provider awareness of the specified risk associated with both LDV/SOF and with SOF will be assessed in the study sample. The expected proportion of physicians aware of the risk is unknown. A sample size of 200 participants is sufficient to detect a frequency of healthcare provider unawareness of 1.5% or greater with 95% confidence. A minimum of 200 responses will be obtained for the final analysis.

7.6. Data Management

For most respondents, the survey questionnaire will be self-administered online via an electronic data entry system. For respondents in Bulgaria and Hungary, face-to-face interviews will be conducted and data captured directly into the electronic data entry system, consistent with standard survey practices for those countries. Additionally, telephone-based structured interviews will be considered as an optional means of response. Participants will receive specific access codes to enable them to enter their data. The data entry system will be made available for a specified time period. After that time, the system will be closed for data entry and the data will be extracted and analysed.

7.7. Data Analysis

Data from the survey questionnaire will be summarized descriptively (counts, ranges, proportions) overall, as well as by country and provider specialty where sample size allows. For the primary objective, frequency point-estimates with two-sided 95% confidence intervals (CIs) using the binomial distribution (Wald or Clopper-Pearson method, as appropriate) will be constructed to describe the proportion of physicians aware of the specified risk. Gilead Sciences considers 80% the threshold for acceptable healthcare provider awareness of the risk, which is the threshold used in other risk minimization programs, such as US Risk Evaluation and Mitigation Strategies (REMS) and recent European surveys to assess HCP awareness of important administration conditions in the treatment of Human Immunodeficiency Virus (HIV).

The secondary objectives will produce categorical data which will be summarized by frequency distributions. Limited continuous data, e.g. healthcare provider assessments of the proportion of patients in their care co-prescribed amiodarone with either SOF + DCV, SOF + SMV, or LDV/SOF, will be categorized into quintiles or bins and summarized by frequency distributions. For some questions, respondents may be able to select more than one response. Analyses will be performed according to a pre-specified statistical analysis plan.

7.8. Quality Control

The electronic data entry system will require that respondents answer certain questions before proceeding in order to ensure that surveys are completed as fully as possible. The data will be stored on a secure network drive or a secure and validated cloud-based data storage system, with access to only authorized personnel from the study team and their delegates.

7.9. Limitations of the Research Methods

This survey may be limited by social desirability bias if physicians are hesitant to admit their lack of awareness of the specified risk. The survey instrument will be designed with the intention of minimizing this possible bias. In addition, random sampling will not be feasible for this survey and non-response is a common problem in observational studies. However, the study will attempt to obtain as representative a sample as possible, and the collection of select variables on providers who decline to participate will be attempted. The survey will also be administered online for respondents in most countries, which may exclude participants who are less comfortable with internet surveys. However, the number of respondents who are uncomfortable with internet surveys is expected to be low, and paper surveys would produce a larger respondent burden which would be expected to deter participation. Finally, as the DHPC has already been disseminated, this survey is unable to assess awareness both before and after the DHPC or changes in awareness as a result of the DHPC. Although this survey can only assess knowledge following the distribution of the DHPC, it will still provide an important assessment of the awareness of the prescribing population of the risk of interest.

7.10. Other Aspects

7.10.1. Study Discontinuation

Every effort will be made to ensure that this study is completed. Gilead Sciences will only terminate the study if there is sufficient cause following consultation with the PRAC. Should this be necessary, Gilead Sciences will arrange discontinuation procedures and notify the appropriate regulatory authorities in accordance with local legislation.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

This study will be conducted in accordance with the principles of the International Conference on Harmonisation (ICH) Pharmacovigilance Planning E2E guidelines, and with the laws and regulations of the country in which the research is conducted.

This study will be conducted in accordance with the guidelines of GPP, HMA GVP, and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), including archiving of essential documents.

8.2. Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Review

This study will not collect patient-level data. All national and EU regulations will be followed regarding the requirement for IRB or IEC review and approval of this study.

8.3. Informed Consent

No informed consent will be obtained.

8.4. Confidentiality

The collected data will contain no participant identifiable fields.

9. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

9.1. Adverse Events

The objective of this study is to determine healthcare provider awareness of certain risks associated with the use of SOF and LDV/SOF. This healthcare provider survey is observational in nature and does not evaluate safety in individual patients. Adverse events will not be solicited in this observational study. In the event that adverse events are incidentally reported through the survey, these events will be collected and reported to the regulatory agencies in accordance with standard safety reporting procedures. All study data will be in aggregate form only.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1. Study Report and Publications

A final report will be prepared and submitted to the regulatory authorities in Q2 2017/ Q3 2017. Gilead Sciences will ensure that the report meets the standards set out in the European Medicines Agency (EMA) Guideline on GVP Module VIII and the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) {von Elm et al 2008}.

Future publications in the form of abstracts and manuscripts have not been planned to date. Authorship of publications will follow the guidelines proposed by the International Committee of Medical Journal Editors (2006). All designated authors will meet the criteria for authorship and potential conflicts of interest will be disclosed.

11. REFERENCES

European Association For The Study Of The Liver. EASL Recommendations on Treatment of Hepatitis C J Hepatol 2015;63 (1):199-236.

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61 (4):344-9.

12. APPENDICES

12.1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
Appendix 1	NA	04 March 2016	ENCePP Checklist for Study Protocols
Appendix 2	NA	04 March 2016	Study Acknowledgement

Appendix 1. ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 2, amended)

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

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

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

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

Study title:
Observational, Cross-Sectional Post-Authorisation Safety Study to Assess Healthcare Provider Awareness of Risks Related to Sofosbuvir and Ledipasvir/Sofosbuvir

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	9, 13
1.1.2 End of data collection[2]	☒	☐	☐	9, 13
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	13
1.1.6 Final report of study results.	☒	☐	☐	9, 13

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.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	14
2.1.2 The objective(s) of the study?	☒	☐	☐	15
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	16
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

The objective of this cross-sectional survey is to determine healthcare provider awareness of certain risks associated with the use of SOF and LDV/SOF.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	16
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	16-17
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Data from the surveys of healthcare providers will be summarized descriptively (counts, proportions); no measure of association will be estimated.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	16
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?				
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	16
4.2.5 Co-morbidity?	☒	☐	☐	16
4.2.6 Seasonality?	☐	☒	☐	
	☐	☒	☐	
4.3 Does the protocol define how the study population				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	16

Comments:

The study population will be selected from a panel of healthcare providers responsible for the treatment of chronic hepatitis C patients.

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

Comments:

Healthcare providers responsible for the treatment of chronic hepatitis C patients will be surveyed to determine the proportion of providers aware of the potential risk of bradycardia in patients receiving amiodarone concurrently with either LDV/SOF, SOF + DCV or SOF + SMV

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	16-17
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Healthcare providers responsible for the treatment of chronic hepatitis C patients will be surveyed to determine the proportion of providers aware of the potential risk of bradycardia in patients receiving amiodarone concurrently with either LDV/SOF, SOF + DCV or SOF + SMV.

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

Comments:

Data from the surveys of healthcare providers will be summarized descriptively (counts, proportions); no measure of association will be estimated.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	16-17
8.1.3 Covariates?	☐	☐	☒	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	16-17
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

The data source is questionnaire responses from healthcare providers.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	17

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	17
10.3 Are descriptive analyses included?	☒	☐	☐	17
10.4 Are stratified analyses included?	☒	☐	☐	17
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Data from the surveys of healthcare providers will be summarized descriptively (counts, proportions); no measure of association will be estimated.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	18
11.3 Are methods of quality assurance described?	☐	☐	☒	
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☐	☒	
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	18
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	18
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.3 Does the protocol address other limitations?	☒	☐	☐	18

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	19
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	17-18

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	10 - 12

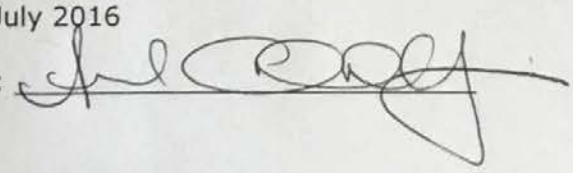
Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	21
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	21

Comments:

Name of the main author of the protocol: _Anand Chokkalingam, PhD_____

Date: 11 July 2016

Signature: 

Appendix 2. Study Acknowledgement

GILEAD SCIENCES, LTD.
CAMBRIDGE, CB21 6GT, UNITED KINGDOM

STUDY ACKNOWLEDGEMENT

Observational, Cross-Sectional Post-Authorisation Safety Study to Assess Healthcare Provider Awareness of Risks Related to Sofosbuvir and Ledipasvir/Sofosbuvir

Version 1.2 FINAL: 11 July 2016

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

Anand Chokkalingam

Anand Chokkalingam, PhD
Gilead Study Co-Director

Signature

13 July 2016

Date

Amanda Singer

Amanda Singer, PhD MPH
Gilead Study Co-Director

Signature

13 July 2016

Date

Anne-Ruth van Troostenburg de Bruyn,
tGP MD(Lond) FFPM
DipPharmMedRCP
Gilead EU QPPV

Signature

Date

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Anand Chokkalingam, PhD
Gilead Study Co-Director

Signature

Date

Amanda Singer, PhD MPH
Gilead Study Co-Director

Signature

Date

AR van Troostenburg

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Gilead EU QPPV

AR van Troostenburg

Signature

14 July 2016

Date