NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	An Observational Drug Utilization Study of Ledipasvir/Sofosbuvir and Tenofovir Disoproxil Fumarate + Pharmacokinetic Enhancer Co-Administration in Adults Co-Infected with Chronic Hepatitis C and HIV-1 Infections
Protocol ID	GS-EU-337-1820
Protocol Version/Date:	Original : 16 March 2016
EU PAS Register No	To be registered prior to start of data collection
Clinical Trials.gov Identifier	N/A
Active Substance	Ledipasvir 90 mg/Sofosbuvir 400 mg
Medicinal Product	Harvoni®
Procedure Number	EMEA/H/C/3850
Joint PASS	No
Research Question and Objectives	Primary objective: • To characterize the frequency of co-administration of Harvoni with TDF+PK enhancers in the post-marketing setting. Secondary objective: • To characterize renal adverse events (serious and non-serious) and renal function testing in concomitant users of Harvoni and TDF+PK enhancers. Exploratory objective: • To assess HIV-treatment regimen changes with Harvoni utilization.

Countries of study	Anticipated European states: Austria, France, Germany, Italy, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland and the United Kingdom.	
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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
BMI	Body Mass Index
CRF, eCRF	Case Report Form, electronic Case Report Form
DSPH	Drug Safety & Public Health
DUS	Drug Utilization Study
EMA	European Medicines Agency
ESRD	End-Stage Renal Disease
eGFR	estimated Glomerular Filtration Rate
EU	European Union
FAS	Full Analysis Set
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GS	Gilead Sciences International Limited
GSEL	Gilead Sciences Europe Limited
GVP	Good Pharmacovigilance Practices (guidelines for)
HIV, HIV-1	Human Immunodeficiency Virus, Human Immunodeficiency Virus Type 1
HCV	Hepatitis C Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
LDV	Ledipasvir
MedDRA	Medical Dictionary for Regulatory Activities
PASS	Post-Authorization Safety Study
PK	Pharmacokinetic
RMP	Risk Management Plan
SAE	Serious Adverse Event
SADR	Serious Adverse Drug Reaction
SmPC	Summary of Product Characteristics
SOF	Sofosbuvir
SSR	Special Situation Report

1. RESPONSIBLE PARTIES

Title, Responsibility	Name, Qualifications	Contact Information
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2. PROTOCOL ABSTRACT

Gilead Sciences Europe Ltd
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Title:	An Observational Drug Utilization Study of Ledipasvir/Sofosbuvir and Tenofovir Disoproxil Fumarate + Pharmacokinetic Enhancer Co-Administration in Adults Co-Infected with Chronic Hepatitis C and HIV-1 Infections
Rationale and Background:	Ledipasvir/sofosbuvir (LDV/SOF, Harvoni®), a 90 mg/400 mg fixed-dose combination tablet, has been approved in the European Union (EU) for the treatment of chronic Hepatitis C virus (HCV) infection in adults. An important potential risk included in the Harvoni European Union (EU) Risk Management Plan (RMP) is the following: Drug-drug interaction between Harvoni with certain antiretroviral (ARV) regimens containing tenofovir disoproxil fumarate (TDF) + a pharmacokinetic (PK) enhancer Harvoni has been shown to increase tenofovir exposure (Study GS-US-337-1306), when used together with an ARV regimen containing TDF + PK enhancer (e.g., ritonavir or cobicistat). The frequency of co-administration of Harvoni with TDF+PK enhancer is currently not known and warrants further investigation. This observational drug utilization study has been planned to assess the frequency of co-administration of an ARV regimen containing TDF + PK enhancer amongst HCV-HIV co-infected patients who are prescribed Harvoni. Understanding the size of this exposed population will provide an insight into the extent of any potential public health concern associated with TDF-related adverse events in the post-marketing setting in Europe. If the use of TDF+PK enhancers amongst HCV-HIV co-infected patients treated with remain low, the public health impact of such limited duration combination therapy during the treatment of HCV infection may be minimal. Renal events will be collected in those subjects who receive Harvoni with TDF+PK enhancers and will provide insight into the renal safety of co-administration.
Research Objectives:	This non-interventional drug utilization study will assess the utilization of Harvoni and TDF+PK enhancers among chronic HCV and HIV-1 co-infected patients ≥ 18 years of age that are prescribed Harvoni whilst receiving any HIV treatment regimen in Europe. The objectives of this study are as follows: Primary: To characterize the frequency of co-administration of Harvoni with TDF + PK enhancers in the post-marketing setting. Secondary: To characterize renal adverse events (serious and non-serious) and renal function testing in concomitant users of Harvoni and TDF+PK enhancers. Exploratory: To assess HIV-treatment regimen changes with Harvoni utilization.
Study Design:	Prospective, observational cohort study of HCV and HIV-1 co-infected subjects receiving ARV therapy who initiate treatment with Harvoni. Subjects who receive Harvoni concomitantly with TDF + PK enhancer containing HIV treatment will have data collected during and post treatment.

Population:	The study population will be comprised of chronic HCV and HIV-1 co-infected adults aged ≥ 18 years receiving any HIV treatment regimen who initiate treatment with Harvoni and attend clinics across several European countries. Subjects who specifically receive concomitant Harvoni and an ARV regimen containing TDF+PK enhancer will have data variables collected at baseline (Harvoni initiation) and during the follow-up period.
Variables:	In addition to Harvoni and TDF + PK enhancer utilization and all renal events data, the following baseline (Harvoni initiation) and follow-up variables will be captured: demographics, comorbid clinical conditions (including prior renal, cardiac, and hepatic diseases), laboratory measurements (including CD4 count, HIV viral load, serum creatinine, serum and urine phosphate, and urine protein) and medications (i.e., prior HCV and HIV therapy and concomitant medications).
Data Sources:	Available clinical data from medical records will be collected using case report forms.
Study Size:	It is anticipated 2000 co-infected patients receiving any ARV regimen, who initiate Harvoni treatment, will be enrolled.
Data Analysis:	Descriptive analysis will be conducted on enrolled subjects. The proportion of subjects with concomitant Harvoni and TDF+PK enhancer use will be estimated with 95% confidence intervals (CIs) among all HCV-HIV co-infected, Harvoni-treated subjects included in the study. The incidence rate of renal events with 95% CIs will be assessed, taking into account the person-time of subjects with concomitant Harvoni and TDF+PK enhancer utilization. Also, subject demographics and selected clinical conditions at baseline will be descriptively summarized. In addition, the clinical characteristics and changes in renal-associated laboratory measurements of subjects and HIV-treatment regimen changes (i.e., discontinuation of TDF+PK enhancer use) will be summarized upon further evaluation.
Milestones:	Start of data collection: October 2016 End of data collection: October 2019 Final report: May 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.

3. AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
N/A				
1	16 March 2016	Sections 4, 6, 7, 8, and 9	Update	Protocol updated to address CHMP comments in the PRAC assessment report dated 28 January 2016 (EMEA/H/C/003850/MEA/013.1).

4. MILESTONES

Milestone	Planned Date
Start of subject enrollment/data collection	October 2016
Interim study progress report 1	October 2017
Interim study progress report 2	October 2018
End of subject enrollment	May 2019
End of data collection	October 2019
Final report of study results	May 2020

5. RATIONALE AND BACKGROUND

5.1. Rationale for the Current Study

There are an estimated 4 to 5 million people worldwide who are co-infected with Human Immunodeficiency Virus (HIV) and Hepatitis C virus (HCV) {Alter 2007}. In Europe, the prevalence of HIV patients co-infected with HCV is approximately 25% {Rockstroh et al 2013}. Wide regional variation within Europe has been recorded in data from the EuroSIDA study showing the prevalence of anti-HCV antibody in HIV patients is higher in the Eastern (57.7%), Eastern Central (34.0%) and Southern (44.9%) EuroSIDA regions compared to the Northern (17.3%) or Western (20.1%) regions {Peters et al 2014}. In addition, a greater prevalence is associated with urban areas with between 50 – 90% of HIV patients also having HCV {World Health Organization (WHO) 2012}.

Harvoni (ledipasvir (LDV)/sofosbuvir (SOF)) combines 2 HCV specific direct-acting antiviral (DAA) agents into a single tablet for the treatment of chronic hepatitis C. LDV is a HCV NS5A inhibitor that has demonstrated potent anti-HCV activity. SOF is a nucleotide nonstructural protein 5B (NS5B) polymerase inhibitor that potently inhibits genotypes 1 to 6 HCV ribonucleic acid (RNA) replicons in vitro.

The results from a phase 1 clinical study, GS-US-337-1306, revealed increases in tenofovir disoproxil fumarate (TDF) exposure following administration of LDV/SOF with ritonavir boosted atazanavir (ATV/r) or darunavir (DRV/r) plus Truvada (emtricitabine [FTC]/TDF) when compared to the HIV regimens alone. Inhibition of intestinal efflux transport by P-glycoprotein (Pgp) and Breast Cancer Resistance Protein (BCRP) likely explains the increase in tenofovir exposure, with LDV in particular having been shown to inhibit transportation by Pgp and BCRP at concentrations achievable in the gastrointestinal tract after Harvoni oral administration. As an inhibitor of Pgp and BCRP, cobisistat when co-administered with TDF also is expected to increase tenofovir plasma concentration.

TDF is principally eliminated by the kidney. Renal failure, renal insufficiency, elevated creatinine, and Fanconi syndrome have been reported with the use of TDF in clinical practice. However, the risk of renal toxicity may be mitigated by the short duration of Harvoni treatment while co-administered with a TDF-containing regimen + PK enhancer, thereby providing a self-limiting opportunity for TDF-associated renal toxicity. The current SmPC advises Harvoni can be used with all ARTs without dose reduction, however further guidance recommends careful risk/benefit assessment before co-administration with an ARV regimen containing TDF and a PK enhancer (ritonavir or cobicistat), particularly in patients at increased risk of renal dysfunction, and additional renal monitoring applied where necessary.

Due to this association, renal adverse events will be collected in the study to allow for a greater insight into the renal safety for those receiving co-administration of Harvoni and TDF+PK enhancer. Adverse events not associated with renal outcomes are not within the scope and objective of this study and will therefore not be solicited. Reported adverse drug reactions attributable to Harvoni or any TDF-containing product also will be collected.

The Harvoni Risk Management Plan (RMP) highlights the risk of this drug-drug interaction increasing tenofovir exposure as an important potential risk. Therefore to provide further information on this population and to identify the potential size of the public health risk, this observational drug utilization study (DUS) will assess the frequency of co-administration of Harvoni and an ARV regimen containing TDF+PK enhancer and if co-administered, to obtain information on the occurrence of renal AEs in a representative HCV-HIV co-infected population.

6. RESEARCH QUESTIONS AND OBJECTIVES

This prospective, non-interventional, multi-centre cohort study will collect and evaluate information on the utilization of Harvoni in conjunction with an ARV regimen containing TDF + PK enhancer, in routine clinical practice in Europe.

The primary objective of this study is:

- To characterize the frequency of co-administration of Harvoni with TDF + PK enhancers in the post-marketing setting.

The secondary objective of this study is:

- To characterize renal adverse events (serious and non-serious) and renal function testing in concomitant users of Harvoni and TDF+PK enhancers.

The exploratory objective of this study is:

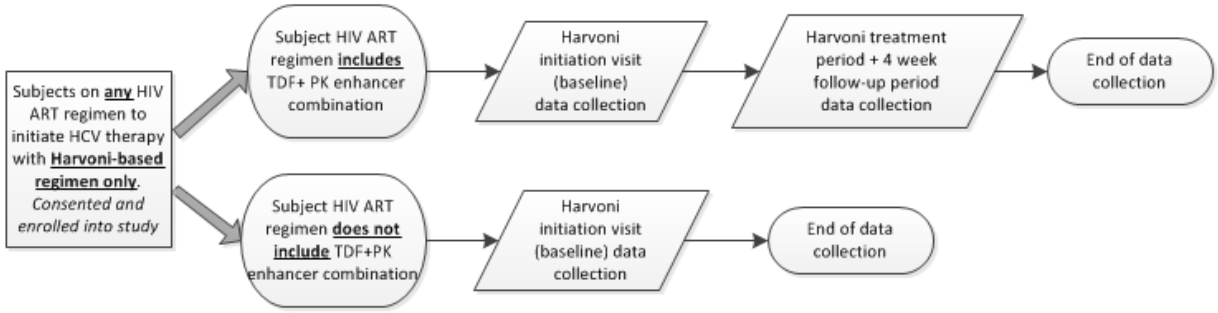
- To assess HIV-treatment regimen changes with Harvoni utilization.

7. RESEARCH METHODS

7.1. Study Design

The study is a prospective, non-interventional, multi-centre cohort study comprised of adults aged ≥ 18 years old co-infected with HCV and HIV-1 who are on HIV treatment and initiate Harvoni-based HCV therapy in Europe. The study subjects who initiate treatment with Harvoni while receiving an ARV regimen containing TDF + PK enhancer will be followed during active treatment with Harvoni and for 4 weeks after Harvoni treatment completion (or discontinuation) to collect data on renal events and renal-related laboratory measurements. The study subjects who initiate Harvoni while receiving a HIV regimen not containing TDF+PK enhancer will not be followed past the Harvoni initiation (baseline) visit.

Each site will be expected to identify chronic HCV and HIV-1 patients receiving any locally approved HIV ARV regimen who are likely to start Harvoni. Prior to the start of Harvoni treatment, patients who meet the inclusion/exclusion criteria, will provide consent for data to be collected into case report forms. Where the patient's current HIV regimen includes TDF and a PK enhancer, the data collection will be more extensive, as described below.



7.1.1. Inclusion Criteria

- Aged ≥ 18 years
- Co-infected with chronic HCV and HIV-1
- Receiving any locally approved HIV antiretroviral regimen
- Initiation of a HCV treatment with a Harvoni-based regimen, per the approved prescribing information, as determined by the subject's treating physician.
- Subject, or legal representatives of the subject, must be willing and able to provide written informed consent.

7.1.2. Exclusion Criteria

- Subject not eligible for treatment with Harvoni as per the approved prescribing information.

7.2. Variables

Subjects will be followed according to the local prescribing information and routine clinical practice in terms of visit frequency and type of assessments performed. Data generated from these activities such as demographics, diagnoses, procedures, medications, and laboratory tests will be collected from medical records as part of this study and are listed below.

Exposure:

Harvoni and TDF+PK enhancer use will be defined in two ways: (1) the count of participating subjects and (2) the person-time exposure. Person-time of exposure will be defined as (treatment end date – treatment initiation date + 1), regardless of temporary interruptions in exposure (<30 days), and will be expressed in days (recorded in whole days, e.g., 40 days). Exposure starts the first day the medication is known to have been taken. Person-time exposed is defined as the number of days that the subject is known to have been exposed. Aggregated person-time may also be expressed in person-years ((number of person days)/365.25). Dates of treatment completion, discontinuation, reasons for treatment discontinuation and study completion will also be captured.

Outcomes:

All renal adverse events (serious and non-serious) will be collected from the time of subject consent until 4 weeks after completion/discontinuation of Harvoni treatment.

Where available from medical records using an electronic case report form (eCRF), the following key variables will be collected after consent at baseline for all subjects. In addition, for those subjects receiving HIV regimens containing TDF+PK enhancer, data also will be collected throughout Harvoni treatment through the post 4-week follow-up period.

Demographics:

- Age/Year of birth
- Sex at birth
- Race
- Country
- Body mass index (BMI)
- Height
- Weight

Clinical Comorbid Conditions (six months prior to baseline and concurrent diagnoses):

- HCV (including HCV genotype)
- HIV-1/AIDS
- Compensated or decompensated cirrhosis
  - Child-Pugh score (including related clinical and laboratory parameters)
  - Hepatic encephalopathy
  - Ascites
  - Esophageal variceal bleeding
- Fibrosis stage and test method (e.g., biopsy, FibroScan, FibroTest, or FibroMeter).
- Liver transplantation
- MELD score
- Hepatitis B virus (HBV)
- Hepatocellular carcinoma (HCC)
- Chronic liver disease of a non-HCV etiology (except HBV and HCC)
- Diabetes
- Cancer (except non-melanoma skin cancer and HCC)
- Renal disease or impairment (including end-stage renal disease (ESRD), dialysis, and renal transplantation)
- Cardiovascular disease (including bradycardia or other cardiac arrhythmia, coronary artery disease, congestive heart failure, stroke, and myocardial infarction)
- Hypertension

Laboratory Measurements:

- Laboratory values and date(s) of test(s) listed below will be collected, where available from routinely collected data. For study baseline, most recent results from a maximum of 6 months prior to study initiation can be used.
- CD4+ cell count (including nadir)
- HIV viral load
- Creatinine (serum, urine)
- Creatinine clearance = estimated glomerular filtration rate (eGFR; mL/min/1.73m^2) based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculation {Levey et al 2009}. The older Cockcroft-Gault method used in the STB SmPC recommendations will also be calculated as a comparison.

  [$eGFR_{CKD} = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.]
- Phosphate (serum, urine)
- Glucose (serum, urine)
- Total protein (serum, urine)
- Albumin (serum, urine)
- Potassium (serum)
- Sodium (serum)
- Chloride (serum)
- Bicarbonate (serum)
- Blood urea nitrogen (BUN)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphate (ALP)
- Bilirubin (total and direct)

- Hemoglobin
- Platelet count
- Reticulocytes
- White blood cell (WBC) count and differential
- International normalized ratio (INR)/Prothrombin time (PT)

Medications (any, date(s) of initiation and/or exposure duration):

- Harvoni and all concurrent and prior prescribed HCV therapies
- Most recent prior treatment and currently prescribed medications to treat HIV (e.g., ARV regimen containing TDF+PK enhancer)
- Other currently prescribed medications, including prescription quantity or duration

Other variables:

Fatal events and any adverse drug reactions attributable to Harvoni or any TDF-containing product, occurring from subject consent and up to 4 weeks after completion/discontinuation of Harvoni treatment. As this is a non-interventional study to monitor post-marketing drug utilization, participating physicians will continue to proceed with their normal clinical practice and will apply their individual assessments for causality. All other adverse events not associated with renal outcomes are not within the scope of the study and will not be solicited.

Additional follow-up data will not be collected on subjects who are receiving Harvoni with other HIV treatment regimens (i.e., not containing TDF+PK enhancers).

7.3. Data Sources

Data will be collected from sites in multiple European countries that have access to Harvoni to treat patients. Each participating site will offer the study to all HIV/HCV co-infected patients on an existing HIV treatment regimen, who are expected to initiate a Harvoni-based regimen. All potential participants will be asked to sign a consent form in advance of the collection of prospective data from their medical records. The data collected will be from local routine visits and procedures only – no additional visits or procedures will be required as part of this study.

7.4. Study Size

The anticipated sample size for this study is 2000 subjects. This sample size has been projected based on estimates of the uptake of Harvoni in Europe during the enrollment period of the study and the accessible HCV/HIV co-infected patient population known to be managed by clinics and receiving any HIV treatment regimen.

The following table displays the potential number of subjects that could be expected for a range of proportions for the utilization of Harvoni with an ARV regimen containing TDF+PK enhancer, as the frequency of co-administration will not be fixed within the study.

Proportion of TDF+PK Enhancer Use with Harvoni (%)	Expected # of Subjects with TDF+PK Enhancer with Harvoni (n)
5%	100
10%	200
20%	400
30%	600

Although expected rates of renal AEs under real world use of Harvoni in Europe are unknown, the results from several clinical trials in Europe and the US demonstrated favorable safety profiles of TDF-containing regimens. With a range of 5 – 30% of the 2000 study subjects exposed to Harvoni and an ARV regimen containing TDF+PK enhancer and conservatively assuming 12 weeks of observation followed by 4 weeks of safety follow up after the end of the treatment, this post-marketing surveillance study will be able to observe a single renal AE if it occurs at rates of 0.02 – 0.10 per year with 95% confidence.

7.5. Data Management

All individual data will be collected using a commercial web-based electronic data capture tool deployed at each participating site. For each subject enrolled, investigators will record the data (from the variables listed in Section 9.2) into an eCRF specifically designed for this study. Each investigator will be assigned with a unique log-in and password for accessing the eCRF.

The data coordinating center will retrieve, manage, and prepare the datasets for analysis from eCRFs. Data will be stored on a secure network drive with access for authorized personnel. Values for missing eCRF data will not be inputted.

Investigators should keep source documentation for each subject included in the study, consisting of case and consultation notes (e.g., from clinic medical records) containing demographic and medical information, results of any tests or assessments performed as part of routine clinical practice.

7.6. Data Analysis

The proportion of subjects with concomitant Harvoni and TDF+PK enhancer use will be estimated with 95% confidence intervals (CIs) among all HCV-HIV co-infected, Harvoni-treated subjects included in the study. Also, baseline information on subject demographics (i.e., age, sex at birth, and BMI) and other clinical characteristics will be summarized using descriptive statistics (i.e., sample size, mean, standard deviation, median, and interquartile range) for continuous data and by the numbers and percentages of subjects for categorical data.
The proportions of several subgroups will be included in the analysis (i.e., those at baseline with

a history of renal disease or eGFR < 60 mL/min/1.73m^2, older age [≥65 years], and other relevant clinical renal-related risk factors). Summaries will be provided for subjects overall, and for those with renal AEs. The incidence rate of renal AEs with 95% CIs will be assessed, taking into account the person-time of subjects with concomitant Harvoni and TDF+PK enhancer utilization. In addition, the incidence rates of specific renal AEs that have been previously studied in TDF-treated patients will be estimated and include the following: Fanconi syndrome, acute/chronic renal failure, renal tubular disorder, renal tubular acidosis, renal tubular necrosis, and hypophosphatemia. Also, the clinical characteristics and changes in renal-associated laboratory measurements of subjects (i.e., decreases in eGFR measurements) will be evaluated.

In addition, as an exploratory analysis, HIV-treatment regimen changes (i.e., the frequency of discontinuation of TDF+PK enhancer use) during follow-up will be summarized and characterized upon further evaluation.

All statistical summaries and analyses will be conducted using SAS® software (SAS Institute, Cary, North Carolina, USA) or other standard software tools, including STATA® (StataCorp LP, College Station, Texas, USA).

7.7. Quality Control

Data and queries will be monitored, remotely and at the site, for consistency and completeness. The electronic data entry system will contain automatic checks for data to identify inconsistent data and generate related queries, when necessary. Manual queries will be issued to the investigative site staff as data inconsistencies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. Site selection and training of site staff will ensure suitably qualified personnel are involved at every stage of the data gathering process.

7.8. Limitations of the Research Methods

Limitations of this study are those common to non-randomized observational studies. There may be residual confounding in the computation of the incidence rates that is not completely addressed by adjusting for demographics or other covariates. Selection bias may also be present, as the sites may elect to enroll patients in the study that may either have a better or worse health status compared with the general HCV-HIV co-infected treated population. Specifically, channeling bias may also be present as health care providers may enroll subjects without prior, or with less severe, prognoses in the cohort. Another limitation is that the study design does not include a comparison group. Upon a feasibility assessment of the applicable patient population and treatment accessibility, the study would not be able to enroll sufficient numbers in a comparison group for a quantitative comparative analysis to detect a low risk of specific renal AEs in the treated HCV/HIV co-infected study patient population.

7.9. Other Aspects

7.9.1. Joint Investigator/Sponsor Responsibilities

7.9.1.1. 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 IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

8. PROTECTION OF HUMAN SUBJECTS

8.1. 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), and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), including archiving of essential documents.

8.2. Independent Ethics Committee (IEC) Review

Where required by local regulation for non-interventional studies, the investigator or sponsor will submit this protocol and any accompanying material to an IEC. The investigator will not begin any study-related activities until the appropriate approval, acknowledgment or waiver from the IEC has been documented and provided as a letter to the sponsor and investigator.
Any subsequent modifications made to the protocol or any accompanying material to be provided to the subject after initial IEC approval will also be submitted for IEC approval prior to use, with the exception of those necessary to reduce immediate risk to study subjects.

8.3. Informed Consent

The investigator and appropriately delegated staff are responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards prior to study participation and before data is collected. The investigator must utilize the most current IEC approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IEC or local requirements. Subjects who participate may discontinue from the study by withdrawing informed consent at any time.

8.4. 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 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.

9. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

The safety events that will be collected in this study are fatal events (regardless of causality), renal adverse events (serious and non-serious), special situation reports, and any adverse drug reactions attributable to Harvoni or any TDF-containing products. Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

9.1. Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a study subject administered a medicinal 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, or drug abuse/misuse reports. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the 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 and should be reported.

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

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

9.1.1. 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 arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, or overdose.

9.1.2. 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 an SAE.
- 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.

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

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

9.2. Assessment of Adverse Events and Serious Adverse Events

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

9.2.1. Assessment of Causality for Study Drugs

The investigator or qualified sub-investigator 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 (e.g., preexisting condition, underlying disease, inter-current 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.

9.3. Special Situations Reports

9.3.1. 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 study, whether or not 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.

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

Drug 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 labelling.

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

Off-label use is defined as the intentional use of licensed medicinal product by a Health Care Professional for a medical purpose not in accordance with the authorized product information with respect to indication, dose, route of administration, or patient population (e.g., the elderly).

9.3.2. Instructions for Reporting Special Situations

9.3.2.1. Instructions for Reporting Pregnancies

All pregnancies that occur in female subjects and in female partners of male subjects while exposed to the drug and the outcome of the pregnancy are to be reported to the Gilead Drug Safety & Public Health (DSPH) using the pregnancy report form within 3 calendar days of becoming aware of the pregnancy and even if the end of pregnancy occurs after the study has completed.

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 (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 3 calendar days as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 9.4. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The outcome should be reported to Gilead DSPH using the pregnancy outcome report form.

9.4. Investigator Requirements and Instructions for Reporting Safety Events to Gilead

All renal and fatal events (regardless of causality) and all Harvoni and/or TDF product related SAEs and non-serious AEs, also known as adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs), occurring from the time of informed consent until loss of follow-up, withdrawal of consent, death, or 4 weeks after discontinuation of Harvoni and/or TDF, (e.g., Stribild) whichever comes first, will be reported to Gilead DSPH. Renal AE/SAEs, ADR/SADRs, fatal events, pregnancies, and SSRs will be reporting electronically via the eCRF, if the system is functioning, otherwise paper reporting will be utlilized.

Timelines for reporting safety events to Gilead are as follows:

- Within 3 calendar days of knowledge of all renal SAEs, fatal events and SADRs
- Within 30 calendar days of knowledge of all renal non-serious AEs, ADRs and SSRs

Details of the methods for reporting renal and fatal events, ADRs, SADRs, and SSRs to Gilead DSPH will be described in the CRF Completion Guidelines. If reporting of events is by electronic submission via eCRF, this method must always be used unless the eCRF system is not functioning at which time site personnel should record details of the renal or fatal event, ADR, SADR, or SSR on the appropriate paper reporting form (the *Non-Interventional Study AE/SAE Report Form* or the *Non-Interventional Study Special Situation Report Form*) and submitted by fax or e-mail, within the timelines given above, to:

Gilead DSPH: Fax: 1-650-522-5477

E-mail:Safety_fc@gilead.com

9.5. Investigator and Sponsor Reporting Requirements

Gilead is responsible for reporting and analyzing reports of all AEs, SAEs, ADRs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs), and special situation reports (SSRs) as determined by country-specific legislation or regulations where the study is conducted and other applicable countries. Gilead may be required to report to other regulatory agencies.

Assessment of expectedness for AEs, SAEs and SSRs will be determined by Gilead using reference safety information specified in the relevant local label.

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).

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1. Study Report and Publications

Progress reports and a final study report will be prepared and provided to the EMA based on the timelines provided in Section 4. Gilead will ensure that the report meets the standards set out in the Guideline on Good Pharmacovigilance Practices (GVP) Module VIII. The final study report will be submitted within 12 months of study completion.

No future publications in the form of abstracts and manuscripts have been planned to date. Authorship of these 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

Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol 2007;13 (17):2436-41.

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Rockstroh JK, Bhagani S. Managing HIV/hepatitis C co-infection in the era of direct acting antivirals. BMC medicine 2013;11:234.

World Health Organization (WHO). Management of Hepatitis C and HIV Coinfection (6). Clinical Protocol for the WHO European Region. 2012:

12. APPENDICES

Number	Document Reference Number	Date	Title
Appendix 1	N/A	16 March 2016	ENCePP Checklist for Study Protocols
Appendix 2	N/A	16 March 2016	Study Acknowledgement

Appendix 1. ENCePP Checklist for Study Protocols

Study title: An Observational Drug Utilization Study of Ledipasvir/Sofosbuvir and Tenofovir Disoproxil Fumarate + Pharmacokinetic Enhancer Co-Administration in Adults Co-Infected with Chronic Hepatitis C and HIV-1 Infection

Study reference number: GS-EU-337-1820

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]	☒	☐	☐	10
1.1.2 End of data collection[2]	☒	☐	☐	10
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☐	10
1.1.5 Registration in the EU PAS register	☒	☐	☐	1
1.1.6 Final report of study results.	☒	☐	☐	10

Comments:

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)	☒	☐	☐	11
2.1.2 The objective(s) of the study?				
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒ ☒	☐ ☐	☐ ☐	14 15
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 study is not testing any hypotheses.

[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 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g., cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	15
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☒	
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)	☒	☐	☐	20

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	19
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	15
4.2.2 Age and sex?	☒	☐	☐	15
4.2.3 Country of origin?	☒	☐	☐	15
4.2.4 Disease/indication?	☒	☐	☐	15
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.2 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	15

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how the exposure is defined and measured? (e.g., operational details for defining and categorizing exposure)	☒	☐	☐	15
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)	☒	☐	☐	16, 21
5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use)	☒	☐	☐	15
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:

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?	☐	☐	☒	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

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

Comments: Study does not include a comparative analysis.

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.)	☒	☐	☐	19
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.)	☐	☐	☒	
8.1.3 Covariates?	☒	☐	☐	19
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)	☒	☐	☐	16 – 19
8.2.2 Endpoints? (e.g., date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
8.2.3 Covariates? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	16 – 19
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g., International Classification of Diseases [ICD]-10)	☒	☐	☐	25
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:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	19

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?	☒	☐	☐	20
10.3 Are descriptive analyses included?	☒	☐	☐	20
10.4 Are stratified analyses included?	☒	☐	☐	20
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	20
11.2 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	19
11.3 Are methods of quality assurance described?	☒	☐	☐	21
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?	☒	☐	☐	20
12.1.2 Information biases? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g., sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	15, 19
12.3 Does the protocol address other limitations?	☒	☐	☐	20

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?	☒	☐	☐	22
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	22

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?	☒	☐	☐	9

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)?	☒	☐	☐	29
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	29

Comments:

Name of the main author of the protocol: Leslie Ng

Date: 17 March 2016

Signature:

Appendix 2. Study Acknowledgement

GILEAD SCIENCES EUROPE LIMITED
2 Roundwood Avenue, Stockley Park, Uxbridge UB11 1AZ
United Kingdom

An Observational Drug Utilization Study of Ledipasvir/Sofosbuvir and Tenofovir Disoproxil Fumarate + Pharmacokinetic Enhancer Co-Administration in Adults Co-Infected with Chronic Hepatitis C and HIV-1 Infections

Original Protocol, 16 March 2016

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

Leslie Ng
Gilead Study Director (Printed)

Signature

17 March 2016
Date

Anne-Ruth van Troostenburg de Bruyn
Gilead EU QPPV (Printed)

Signature

17 March 2016
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this 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 Europe Limited. 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