Title Page

Title	A study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C (De Novo DAA PASS)
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Procedure Number	Not yet assigned.
Marketing Authorisation Holder(s)	AbbVie; Bristol-Myers Squibb; Gilead Sciences; Merck Sharp & Dohme
Joint PASS	Yes
Research Question and Objectives	Evaluate the potential risk of de novo hepatocellular carcinoma following direct-acting antiviral treatment in hepatitis C virus infected patients with compensated cirrhosis without a history of hepatocellular carcinoma.
Country(-ies) of Study	United States
Author	[redacted] Baylor College of Medicine Medical Center, McNair Campus 7200 Cambridge St [redacted] Houston, TX 77030 [redacted]

This study will be conducted in compliance with this protocol.
Confidential Information

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	AbbVie; Bristol-Myers Squibb; Gilead Sciences; Merck Sharp & Dohme
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1.0 Table of Contents

2.0 Abbreviations

AASLD	American Association for the Study of Liver Diseases
AFP	alpha fetoprotein
ANCOVA	analysis of covariance
APRI	aspartate aminotransferase to platelet ratio
AST	aspartate aminotransferase
BMI	body mass index
CAPRI	Compensation and Pension Records Interchange
CCR	Central Cancer Registry
CDW	Corporate Data Warehouse
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CP-A	Child-Pugh class A
CT	computed tomography
DAA	direct-acting antiviral agents
DCCI	Deyo-Charlson Comorbidity Index
EMA	European Medicines Agency
EMR	Electronic Medical Record
EOT	end of treatment
EU	European Union
FIB-4	fibrosis-4
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IFN	interferon
INR	international normalized ratio liver function test
IPTW	inverse probability of treatment weighting
IRB	institutional review board
LLOQ	Lower limit of quantification
MAH	Marketing Authorization Holder
MRI	magnetic resonance imaging
PASS	post-authorization safety study

pegIFN	pegylated IFN
PRAC	Pharmacovigilance Risk Assessment Committee
RNA	ribonucleic acid
SVR	sustained virologic response
TNM	Tumor Node Metastasis staging
US	United States
VA	Veterans Health Administration

3.0 Responsible Parties

Responsible Party	Name and Affiliation
MAHs	AbbVie; Bristol-Myers Squibb; Gilead Sciences; Merck Sharp & Dohme (refer to Annex 3 for full details)
Principal/coordinating investigators	[redacted]

4.0 Abstract

Title: A study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C (De Novo DAA PASS)

Rationale and Background:

In December 2016, 4 Marketing Authorization Holders (MAHs) (AbbVie, Bristol-Myers Squibb [BMS], Gilead Sciences [Gilead], Janssen-Cilag International NV [Janssen]), subject to the Pharmacovigilance Risk Assessment Committee (PRAC) requirement resulting from a procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1438), began to assess hepatitis C virus (HCV) registries and databases worldwide in order to determine the feasibility of using existing data sources to evaluate the potential risk of de novo hepatocellular carcinoma (HCC) following direct-acting antiviral agent (DAA) treatment in hepatitis C virus (HCV)-infected patients with compensated cirrhosis (Child Pugh class A; CP-A) without a history of HCC. Merck Sharp & Dohme [MSD] received formal regulatory notification March 2017 to adhere to the outcome of the Article 20 referral procedure, and at that time joined the MAH's consortium. Janssen is no longer part of the procedure following the withdrawal of the Olysio European Union (EU) license, but data from the use of simeprevir will still be part of the analysis of DAA-treated patients.

A feasibility assessment was submitted to the PRAC on 14 June 2017. This report summarized the state of the evidence on the risk of incident HCC following treatment with DAA therapy and described a large number of studies indicating no increased risk of HCC following treatment with DAA therapy, including a systematic review and meta-analysis of 26 studies by Waziry et al 2017 that found no evidence of increased risk of de novo HCC associated with DAA treatment. In addition, the MAHs assessed multiple existing data sources to determine the feasibility of assessing de novo HCC rates among HCV infected patients who were untreated or received DAA- or interferon (IFN)-based therapies. The MAHs concluded that the growing body of evidence and existing datasets were well positioned to provide a timely and definitive answer to this question.

The September 2017 PRAC Assessment Report requested further review of existing data sources with consideration of particular study attributes. In an updated feasibility assessment submitted in October 2017, the MAHs provided an updated summary of the growing number of existing data sources and evidence base supporting that there is no increased risk of de novo HCC following treatment with DAAs, including discussion of findings from large, well-defined cohort studies, other publications in the literature, and over 20 abstracts presented at the American Association for the Study of Liver Diseases Liver Meeting in October 2017. The updated feasibility assessment concluded that the current evidence continues to demonstrate the absence of an increased risk of de novo HCC associated with DAA exposure and that it is feasible to address the safety questions raised by the PRAC using existing data sources.

Based on the updated feasibility assessment that the MAHs conducted, the MAHs proposed using the US Veterans Health Administration (VA) data source to continue to investigate the risk of de novo HCC in patients with compensated cirrhosis treated with DAA therapy. The US VA is a national multicenter integrated health system, containing a large number of patients in the target national population, with compensated cirrhosis and HCV infection, who have been followed longitudinally using multiple sources that include the VA Central Cancer Registry (CCR), VA Corporate Data Warehouse (CDW), and VA Electronic Medical Record (EMR) chart abstraction. These features allow for an in-depth assessment of cirrhotic HCV patients treated in real-world clinical care settings

including tests and diagnoses, anywhere in the VA system and excellent ascertainment of cancer and
Rationale and Background (Continued): death occurrence. In addition to investigating the risk of de novo HCC in compensated cirrhotic patients treated with DAA therapy, the MAHs will also evaluate tumor characteristics (e.g., tumor size, tumor number, tumor stage and tumor type) for cases with this information available in the VA CCR. To address the safety concern expressed by the PRAC, the MAHs agreed to generate a report on de novo HCC risk following DAA exposure relative to patients treated with IFN-containing regimens or untreated chronic hepatitis C patients within the US VA cohort. In their Assessment Report dated 11 January 2018, adopted by CHMP on 25 January 2018, the PRAC agreed that "A post-authorisation safety study to investigate the impact of DAA therapies on the incidence and type of de novo HCC is feasible using the VETERANS HEALTH ADMINISTRATION COHORT as a secondary data source."
Research Question and Objectives: This protocol defines a retrospective cohort study as a longitudinal analysis of data from the VA data source. This analysis examines the following research question: among compensated cirrhotic patients, does DAA therapy for chronic HCV infection increase the risk of incident HCC compared to no treatment or treatment with IFN-based regimens? The primary objectives of this study are as follows: 1. Estimate the risk of de novo HCC associated with DAA therapy exposure in cirrhotic HCV patients compared to no anti-HCV therapy exposure in cirrhotic HCV patients. 2. Estimate the risk of de novo HCC in cirrhotic HCV patients treated with DAA therapy compared to those treated with IFN-based therapy. The secondary objective is to compare, in a subset of patients with available data recorded in the VA CCR, tumor characteristics (i.e., tumor size, tumor number, tumor stage, tumor type) of the de novo HCC cases observed following initiation of DAA therapy to those of de novo HCC cases observed (a) following initiation of IFN-containing regimens and (b) in untreated patients.
Study Design: A retrospective cohort study of HCV infected patients seeking care in the VA system will be conducted. The primary analyses for this study will 1) evaluate the impact of DAA therapies on the risk of de novo HCC in HCV infected patients with compensated liver cirrhosis without a history of HCC compared to no anti-HCV therapy exposure, and 2) evaluate the risk of de novo HCC among patients who received IFN-free DAA therapy relative to historical controls in the same dataset who received IFN-based therapy.
Population: The analysis will be conducted among US veterans, aged 18 years or older, with chronic HCV who sought care at any of the medical centers and ambulatory care and community-based outpatient clinics that comprise the national VA healthcare system. This analysis will be restricted to HCV mono-infected (i.e., no hepatitis B virus or human immunodeficiency virus coinfection) patients with compensated liver cirrhosis. Within the VA, the decision to treat patients with antiviral therapy for HCV, regimen choice, and subsequent clinical care was at the discretion of the provider and was determined and registered prior to the diagnosis of de novo HCC. Within the VA healthcare system, all HCV-infected patients were eligible for HCV treatment during the study period. VA pharmacies had several DAAs (sofosbuvir-containing medications, simeprevir, ombitasvir/paritaprevir/ritonavir with or without dasabuvir, daclatasvir, elbasvir and grazoprevir and glecaprevir and pibrentasvir) on formulary and there were no limitations to DAA availability based on income, fibrosis stage or psychosocial disorders.

Population (Continued):

Our sampling frame will comprise HCV infected patients with compensated cirrhosis who have data included in the VA sources. For analysis of the first primary objective, HCV infected patients will be included if they have a clinical encounter (i.e., office visit, procedure, lab result, prescription, etc.) recorded in the VA sources in the 6 months preceding and including January 01, 2013 or between January 01, 2013 and December 31, 2017. A patient will contribute to DAA exposure starting at the date of DAA initiation if the patient-initiated treatment with an IFN-free DAA regimen between January 01, 2013 and December 31, 2017. For analysis of the second primary objective, 2 groups of HCV patients will be included in the analysis: (a) those who initiated treatment with an IFN-free DAA regimen between January 01, 2014 and December 31, 2017, and (b) those who initiated treatment with IFN-based regimen between January 01, 2005 and December 31, 2013 (historical control).

Interferon-free DAA (DAA only) treatment initiation will be defined as one or more filled prescriptions (at least 28 days of prescription filled) of sofosbuvir-containing medications, simeprevir, ombitasvir/paritaprevir/ritonavir with or without dasabuvir, daclatasvir, elbasvir and grazoprevir and glecaprevir and pibrentasvir between January 01, 2013 and December 31, 2017. Interferon-based (IFN based) treatment initiation will be defined as one or more filled prescriptions of pegylated IFN (pegIFN) or regular IFN (at least 28 days of prescription filled) with or without ribavirin without any DAAs between January 01, 2005 and December 31, 2013. The date of the first filled prescription will be used as the treatment initiation date. The use of filled prescriptions as an indicator of receipt of treatment has been validated using the VA pharmacy data, with high agreement between these definitions and those based on EMR. The treatment completion date will be defined as last date covered by final filled prescription. For patients with multiple HCV treatment courses, the first course of DAA treatment between January 01, 2014 and December 31, 2017 and follow-up thereafter will be used for the first primary objective. For the second primary objective, the first course of HCV treatment in each of the specified time intervals will be used to establish the index date for each patient in either the IFN or DAA treatment cohort.

Inclusion criteria:

1. Patients with chronic HCV defined as a positive test for HCV ribonucleic acid (RNA) in plasma by qualitative or quantitative assays or genotype test between January 01, 2005 and December 31, 2017.
2. For the first primary objective (DAA only treated and untreated patients): a clinical encounter (i.e., office visit, procedure, lab result, prescription, etc.) recorded in the 6 months preceding and including January 01, 2013 or between January 01, 2013 and December 31, 2017.
3. For the second primary objective: for IFN treated patients, the IFN based treatment was initiated after the above HCV diagnosis, but between January 01, 2005 and December 31, 2013. If DAA-only exposed, the DAA treatment was initiated after the above HCV diagnosis, but between January 01, 2014 and December 31, 2017.
4. Patients with data in VA sources to establish a diagnosis of compensated cirrhosis as follows:
   - At least 1 fibrosis-4 (FIB-4) > 3.25 within 24 months before or 6 months after the index date but before any HCV treatment (and with all measurements for FIB-4 calculation within 6 months of each other) or at least 1 ICD-9 (571.2, 571.5) or ICD-10 (K70.30, K70.31, K74.60, K74.69, K74.3, K74.4 and K74.5) code indicating cirrhosis, and
   - No diagnosis codes for hepatic decompensation defined as ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome based on inpatient

or outpatient ICD-9 codes of 789.5, 456.0–2, 572.4, 572.2, 348.3×, 070.0, 070.2×, 070.4×, 070.6, 070.71, or corresponding ICD-10 codes during the 2 years prior to the index date.

5. Patients with at least 1 health care encounter recorded in a VA source (outpatient or inpatient) at least 1 year prior to the index date. This is to ensure that the analytic cohorts have a minimum uniform period during which the covariates are defined and captured.

Exclusion criteria:

1. Patients with a diagnosis of HCC, defined as at least 1 ICD-9 code 155.0 or ICD-10 code C22.0, C22.8, C22.9, or D01.5 (the VA switched to ICD-10 codes on 10/01/2015) ever recorded prior to the index date.
2. History of liver transplantation.

Variables:

The **index date** defines the start of de novo HCC risk.

For the **first primary objective**, **the index date** for untreated time will be the date of the first clinical encounter (i.e., office visit, procedure, lab result, prescription, etc.) recorded in the 6 months preceding and including January 01, 2013 or anytime during the January 01, 2013 to December 31, 2017 time interval. This will serve as the start of untreated time in both patients who were never treated and patients who were as yet untreated as of the first clinical encounter. The index date for DAA exposed time will be at the start of DAA therapy.

For the **second primary objective**, **the index date** will be the date of initiation of first IFN treatment between January 01, 2005 and December 31, 2013 for IFN-treated patients and the date of initiation of first DAA treatment between January 01, 2014 and December 31, 2017 for DAA treated patients.

De novo HCC diagnosis is defined based on a hierarchical approach. First, patients are classified as having HCC based on VA CCR. For the remaining patients, patients identified with > 1 instance of ICD-9 (155.0) or ICD-10 codes (C22.0, C22.8, C22.9, D01.5) for HCC but not recorded in VA CCR will have a manual structured review of the EMR performed via Compensation and Pension Records Interchange (CAPRI) to confirm HCC diagnosis and determine the date of diagnosis. Patients with de novo HCC will be counted as having an event at the date of first diagnosis of HCC in the study interval.

Compensated cirrhosis and sustained virologic response (SVR) will also be defined for patients.

Multiple covariates including demographic variables, alcohol use and drug abuse, other medical comorbidities (including cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, diabetes, mental illness, esophageal/gastric varices, portal hypertension and hypertension), laboratory values, SVR, health care utilization, last prior HCV treatment, Deyo-Charlson Comorbidity Index (DCCI), and HCC surveillance rate during follow-up will be determined and used for analysis.

Data Sources: The VA data sources will include the following 3 registries: VA Corporate Data Warehouse (CDW), VA Central Cancer Registry (CCR), and VA Electronic Medical Record (EMR); chart abstraction will be completed using the CAPRI.

Study Size: For the first primary objective, sample sizes of approximately 8000 patients treated with DAA only regimens meeting the inclusion criteria and approximately 8000 untreated patients meeting the inclusion criteria are expected. Based on Li et al, we assume an incidence rate of 3.5% de novo HCC per patient year of exposure among both the DAA treated and untreated patients (assuming an average of 1 year of follow up in both groups). These assumptions, along with assuming an exponential distribution of de novo HCC-free survival, give an unadjusted hazard ratio (HR) of 1 with a 2-sided 95% confidence interval of (0.85, 1.18) for risk of de novo HCC among DAA treated vs untreated. The precision of the estimate depends on the HR; however, with a half-width of ≤ 0.18, the planned sample size is considered sufficient to clearly distinguish from a HR of 1.5 or more if there is no additional de novo HCC risk related to DAA treatment versus no treatment.

The VA database includes a minimum 3750 patients with compensated cirrhosis treated with IFN based therapy between January 1, 2005 and December 31, 2013. Thus, for the second primary objective, sample sizes of approximately 8000 cirrhotic patients treated with DAA only regimens and at least 3750 cirrhotic patients treated with IFN-based regimens are expected. We assume an annual incidence rate of 2.0% de novo HCC among both DAA-treated and IFN-treated patients and assume an average of 1 year of follow-up for DAA-treated and an average of 2.5 years of follow-up for IFN treated. These assumptions, along with assuming an exponential distribution of de novo HCC-free survival, give an unadjusted hazard ratio of 1.0 with a 2-sided 95% confidence interval of (0.81, 1.24) for the risk of de novo HCC among DAA treated vs IFN treated. The precision of the estimate depends on the HR; however, with a half-width of ≤ 0.24, the planned sample size is considered sufficient to clearly distinguish from a HR of 1.5 if there is no additional de novo HCC risk related to DAA treatment versus IFN treatment.

Data Analysis: For the first primary objective, a multivariable Cox proportional hazards regression model will be used to examine the risk of HCC associated with DAA exposed time compared to untreated time using DAA exposure as a time-varying covariate and adjusting for values of potential confounders ascertained at index date or most recently prior to index date and updated at 12-month time intervals until DAA exposure start or through untreated person time if no DAA start: age, gender, race/ethnicity, body mass index, HCV genotype, HCV viral load, alcohol use, substance abuse, medical comorbidities (i.e., cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, diabetes, mental illness, esophageal/gastric varices, portal hypertension and hypertension), FIB-4, laboratory values (platelet count, serum albumin, AFP), healthcare utilization, last prior HCV treatment, and DCCI, as well as HCC surveillance rate during follow-up. Patients can contribute person-time to both DAA exposed time and untreated exposed time. Untreated patients will contribute person-time at risk to the untreated group until first of HCC diagnosis or receipt of DAA treatment or censored at death or end of data availability (i.e., date of last VA encounter). Untreated patients that subsequently initiate DAA treatment will contribute time at risk to the DAA treated group from the date of DAA treatment initiation until HCC diagnosis, or censored at death, initiation of IFN-containing HCV treatment or end of data availability (i.e., date of last VA encounter). Separately, multivariable Cox proportional hazards regression will also be used to examine the risk of HCC with DAA exposure in DAA-treated patients achieving SVR compared to untreated time, and with DAA exposure in DAA-treated patients not achieving SVR compared to untreated time. Patients will be censored at time of death or end of data availability.

Data Analysis (Continued):

For the second primary objective, another multivariable proportional hazards model will be used to examine the risk of HCC in the DAA treated patients compared to the IFN-based therapy treated patients. This analysis will include evaluation of the potential explanatory effect of SVR status using multiple methods, including using SVR status as a factor in the model. We recognize that the feasibility of these analyses accounting for SVR status will be dependent on the number of HCC cases observed among the relatively small number of DAA-exposed patients who do not achieve SVR. The following potential confounders ascertained at the index date or most recently prior to the index date will be considered for adjustment in the multivariable model: demographic variables, alcohol use, substance abuse, other medical comorbidities (including cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, diabetes, mental illness, esophageal/gastric varices, portal hypertension and hypertension), FIB-4, laboratory values (platelet count, serum albumin, and alpha fetoprotein [AFP]), last prior HCV treatment, health care utilization, DCCI, and HCC surveillance rate during follow-up. Follow-up will continue until the first HCC event, initiation of DAA treatment (in the IFN based treated group), or initiation of IFN-containing treatment (in the DAA-treated group), and patients will be censored at death or end of data availability. For the second primary objective, the index date will be the date of initiation of IFN treatment for IFN-treated patients and the date of initiation of DAA treatment for DAA treated patients.

To mitigate potential confounding by indication inherent in observational studies, propensity scores that model the probability of treatment status (DAA treatment vs IFN treatment) on the basis of values of variables ascertained at the index date or the most recent value prior to the index date will be incorporated into the model for the second primary objective. Propensity score matching of IFN-treated patients to DAA-treated patients will be the preferred analysis; however, in the event that matching proves to be infeasible, inverse probability of treatment weighting (IPTW) with stabilized weights will be applied to multivariate models instead.

For the secondary objective, in all patients with HCC recorded in the VA CCR, the first occurrence of de novo HCC during the observation period will be identified by any instance of primary site code C220 and histology codes 817XX through 818XX. Demographic characteristics (age at HCC diagnosis, sex, race/ethnicity, geographic region and type of VA facility where the HCC diagnosis was made) and pattern of presentation of cases will be descriptively analyzed for this subset of patients by HCV treatment group (DAA, IFN or untreated). Specific tumor characteristics of interest include number, size, type, stage based on the TNM staging system, and HCC treatment. Tumor characteristics will be compared between the HCV DAA treatment group to 1) the HCV IFN treated group and 2) the untreated group using CMH tests for categorical variables and ANCOVA or stratified Mann-Whitney tests for quantitative variables, as appropriate.

Milestones:

The study is planned to commence following approval of the study protocol by the PRAC. It is estimated that following approval of the protocol, retrospective data procurement will complete 18 months after approval by the Institutional Review Board and PRAC. The final report will be provided 12 months after the end of data procurement.

5.0 Amendments and Updates

None.

6.0 Milestones

Major study milestones and their planned dates are as follows:

Sampling Timeframe:	01 January 2005 through 30 April 2018 (retrospective)
End of Data Procurement:	18 months after protocol approval by Institutional Review Board and PRAC
Study Progress Report	N/A
Interim Report:	N/A
Registration in the EU PAS register	Post protocol finalization
Final Report of Study Results:	12 months after end of data procurement

7.0 Rationale and Background

Chronic infection with hepatitis C virus (HCV) is a primary etiological risk factor of hepatocellular carcinoma (HCC).[1] Patients infected with HCV who have cirrhosis are at particularly high risk for the development of HCC. The annual incidence of HCC in patients with HCV-related cirrhosis has been estimated to range from approximately 0.5% to 10%.[2,3] The incidence of HCC in the United States (US) has almost tripled since the 1980s, due in large part to the high prevalence of chronic HCV infections among persons born from 1945 to 1965 and the aging of this birth cohort.[3-5] Patient characteristics, other than cirrhosis, shown to increase the risk of HCC in HCV-infected populations include older age, male sex, race/ethnicity, diabetes, obesity, smoking, HCV genotype 3 infection, heavy alcohol use, human immunodeficiency virus (HIV) co-infection, and hepatitis B virus (HBV) co-infection.[3,6-11]

Sustained virologic response (SVR) following treatment with interferon (IFN) and ribavirin (RBV) significantly reduces, but does not eliminate, the risk of developing HCC.[8,12-16] A meta-analysis using 12 studies published through February 2012 found an approximate 75% reduction in HCC risk following SVR among HCV patients at all stages

of fibrosis compared to patients who did not achieve SVR following treatment with any antiviral regimen (available prior to 2013) capable of viral eradication.[12] This meta-analysis found a similar reduction in risk of HCC in patients with advanced liver disease who achieved SVR, though this estimate was based on a small number of studies. Even following attainment of SVR, some HCV patients remain at increased risk of HCC for many years.[17,18] A recent review paper found that HCC incidence in HCV patients (with and without cirrhosis) who achieve SVR following IFN-based antiviral therapy was estimated to be 0.5 – 2.0% at 3 years, 2.3 – 8.8% at 5 years, and 3.1% – 11.1% at 10 years.[8] Risk factors for the development of HCC after attaining SVR in recent studies include older age, male sex, cirrhosis, diabetes, obesity, glucose metabolism disorders, alcohol intake, high aspartate aminotransferase (AST) to platelet ratio (APRI) and high fibrosis-4 (FIB-4) index.[8,19-22] Unadjusted incidence rates of HCC following SVR attained with direct-acting antiviral agent (DAA) therapy may be higher than those observed with IFN-based SVR given the higher prevalence of HCC risk factors in patients treated with DAA therapy compared to patients treated with IFN in the pre-DAA era.[23]

The approval of all oral DAA therapies to treat HCV in 2014 greatly expanded the possibility of treatment and attainment of SVR to millions of patients. Globally, over 1.5 million patients with chronic HCV infection have been treated with DAA therapy, including patients with advanced liver disease. The European Association for the Study of the Liver recommends that all treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease related to HCV infection must be considered for therapy.[24] It is recommended that treatment for HCV infection be considered without delay in patients with significant fibrosis or cirrhosis, including decompensated cirrhosis.

Based on the evidence of a reduced risk of HCC following SVR with IFN-based therapy, the high SVR rates associated with DAAs, and the ability to treat populations at the highest risk of HCC, it has been postulated that increasing treatment with DAAs will lead to further reductions in HCC incidence among HCV-infected populations.[25,26] However, despite several well-controlled studies indicating no or even reduced risk of de novo HCC

associated with DAA exposure,[23,27,28] a few studies reported a possibly unexpected high incidence of de novo HCC,[29,30] raising the question as to whether HCC incidence among DAA-treated patients may be higher than what would be expected. Reig et al 2017[31] proposed a potential biological mechanism for a possible increase in risk of incident HCC (primary or metastatic) associated with DAA therapy, related to immune distortion due to the rapid decrease in HCV RNA viral load. This immune distortion would subsequently change the inflammatory profile of the infected liver and entire body, such that it favors growth of existing preclinical cancer clones until they become clinically detectable. While this premise may be considered biologically plausible, there has been no published clinical research to support the proposed mechanism of action. Furthermore, the preponderance of published reports have demonstrated that there is no evidence to suggest DAA exposure is associated with a higher risk of HCC among patients with chronic HCV infection compared to untreated HCV patients.[27,32,33]

Despite several well-controlled studies indicating no or even a reduced risk of de novo HCC associated with DAA exposure,[23,27,28] other earlier case reports and retrospective analyses suggested that all-oral DAA use was associated with a more aggressive pattern and presentation of incident HCC cases. Specifically, it has been suggested that more aggressive tumor histological patterns (i.e., microvascular invasion, tumor marker-doubling time, etc.) were observed post-start of DAA treatment in a small number of patients within 1.5 years of follow-up.[34,35,36,37] Potential mechanisms to support this hypothesis included the absence of IFN activation, reconstitution of innate immunity, abrupt reduction of natural killer cells and their toxicity, which may contribute to a more rapid progression of HCC post-initiation of DAA therapy.[34,36] These conclusions were based on tumor histology and/or historical comparison of incident HCC cases, but of note, these reports lacked a contemporaneous comparator cohort. The absence of appropriate controls makes it difficult to rule out baseline factors, such as more advanced underlying liver disease, as potential confounders.

Recently, additional publications have become available that include a contemporaneous comparator cohort and reported on the tumor characteristics (macroscopic pattern, number

of tumors at diagnosis, total nodule size, largest nodule size, etc.) of incident HCC among HCV patients diagnosed after starting all-oral DAA therapy. In a well-characterized cohort of over 800 cirrhotic (i.e., Child-Turcotte-Pugh scores A-C) patients, risk of incident HCC was not significantly different among patients who achieved SVR with all-oral DAA treatment regimens compared to those who achieved SVR with IFN-containing regimens (aHR = 1.15, 95% confidence interval [CI]: 0.49 – 2.71), and there was no significant difference in tumor characteristics (number and size of HCC nodules) between HCC cases occurring after exposure to all-oral DAA regimens vs those occurring after exposure to IFN-containing regimens.[38] The second study, based on the ANRS HEPATHER prospective cohort of over 10,000 patients, reported a decrease in the incidence of HCC associated with DAA therapy (adjusted HR = 0.66, 95% CI: 0.46 – 0.93), and among HCC cases, no difference in tumor characteristics (macroscopic pattern, number and size of HCC nodules) was observed between the DAA treated versus the DAA untreated group with a median follow-up time of up to 3 years.[39]

These recent reports on de novo HCC tumors among patients treated with all-oral DAAs compared to untreated patients or those treated with IFN-containing regimens have been consistent with those previously reported in the protocol showing no significant difference (or improvement) in the aggressiveness of tumor characteristics.

In December 2016, 4 Marketing Authorization Holders (MAHs) (AbbVie, Bristol-Myers Squibb [BMS], Gilead Sciences [Gilead], Janssen-Cilag International NV [Janssen]), subject to the Pharmacovigilance Risk Assessment Committee (PRAC) requirement resulting from a procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1438), began to assess HCV registries and databases worldwide in order to determine the feasibility of using existing data sources to evaluate the potential risk of de novo HCC following DAA treatment in HCV-infected patients with compensated cirrhosis (Child-Pugh class A; CP-A) without a history of HCC. Merck Sharp & Dohme [MSD] received formal regulatory notification March 2017 to adhere to the outcome of the Article 20 referral procedure, and at that time joined the MAH's consortium. Janssen

is no longer part of the procedure following the withdrawal of the Olysio EU license, but data from use of simeprevir will still be part of the analysis of DAA treated patients.

A feasibility assessment was submitted to the PRAC on 14 June 2017. This report summarized the state of the evidence on the risk of incident HCC following treatment with DAA therapy and described a large number of studies indicating no increased risk of HCC following treatment with DAA therapy, including a systematic review and meta-analysis of 26 studies by Waziry et al 2017[40] that found no evidence of increased risk of de novo HCC associated with DAA treatment. In addition, the MAHs assessed multiple existing data sources to determine the feasibility of de novo HCC rates among HCV-infected patients who were untreated or received DAA- or IFN-based therapies. The MAHs concluded that the growing body of evidence and existing datasets were well positioned to provide a timely and definitive answer to this question.

The September 2017 PRAC Assessment Report requested further review of existing data sources with consideration of particular study attributes. In an updated feasibility assessment submitted in October 2017, the MAHs provided an updated summary of the growing number of existing data sources and evidence base supporting that there is no increased risk of de novo HCC following treatment with DAAs, including discussion of findings from large, well-defined cohort studies, other publications in the literature, and over 20 abstracts presented at the American Association for the Study of Liver Diseases (AASLD) Liver Meeting in October 2017. The updated feasibility assessment concluded that the current evidence continues to demonstrate the absence of an increased risk of de novo HCC associated with DAA exposure and that it is feasible to address the safety questions raised by the PRAC using existing data sources.

Based on the updated feasibility assessment that the MAHs conducted, the MAHs proposed using the US Veterans Health Administration (VA) data source to continue to investigate the risk of de novo HCC in patients with compensated cirrhosis treated with DAA therapy. The US VA is a national multicenter integrated health system, containing a large number of patients in the target national population, with compensated cirrhosis and HCV infection, who have been followed longitudinally using multiple sources that

include the VA Central Cancer Registry (CCR), VA Corporate Data Warehouse (CDW), and VA Electronic Medical Record (EMR) chart abstraction. These features allow for an in-depth assessment of cirrhotic HCV patients treated in real-world clinical care settings including tests and diagnoses, anywhere in the VA system and excellent ascertainment of cancer and death occurrence. In addition to investigating the risk of de novo HCC in compensated cirrhotic patients treated with DAA therapy, the MAHs will also evaluate tumor characteristics (e.g., tumor size, tumor number, tumor stage, tumor type) for a subset of cases with this information available in the VA CCR.

To address the safety concern expressed by the PRAC, the MAHs agreed to generate a report on de novo HCC risk following DAA exposure relative to patients treated with interferon-containing regimens or untreated chronic hepatitis C patients within the US VA cohort. In their Assessment Report dated 11 January 2018, adopted by the Committee for Medicinal Products for Human Use (CHMP) on 25 January 2018, the PRAC agreed that "A post-authorisation safety study to investigate the impact of DAA therapies on the incidence and type of de novo HCC is feasible using the VETERANS HEALTH ADMINISTRATION COHORT as a secondary data source."

8.0 Research Question and Objectives

This protocol defines a retrospective cohort study as a longitudinal analysis of data from the VA data source. This analysis examines the following research question: among compensated cirrhotic patients, does DAA therapy for chronic HCV infection increase the risk of incident HCC compared to no treatment or treatment with IFN-based regimens?

The primary objectives of this study are as follows:

1. Estimate the risk of de novo HCC associated with DAA therapy exposure in cirrhotic HCV patients compared to no anti-HCV therapy exposure in cirrhotic HCV patients.
2. Estimate the risk of de novo HCC in cirrhotic HCV patients treated with DAA therapy compared to those treated with IFN-based therapy.

The secondary objective is to compare, in a subset of patients with available data recorded in the VA CCR, tumor characteristics (i.e., tumor size, tumor number, tumor stage, tumor type) of the de novo HCC cases observed following initiation of DAA therapy to those of de novo HCC cases observed (a) following initiation of IFN-containing regimens and (b) in untreated patients.

9.0 Research Methods

9.1 Study Design

A retrospective cohort study of HCV infected patients seeking care in the VA system will be conducted. The primary analysis will 1) evaluate the impact of DAA therapies on the risk of de novo HCC in HCV infected patients with compensated liver cirrhosis without a history of HCC compared to no anti-HCV therapy exposure, and 2) evaluate the risk of de novo HCC among patients who received IFN-free DAA therapy relative to historical controls in the same dataset who received IFN-based therapy.

The secondary objective is to compare, in a subset of patients with available data in the VA CCR, tumor characteristics of the de novo HCC cases observed following initiation of DAA therapy to those of de novo HCC cases observed (a) following initiation of IFN-containing regimens and (b) in untreated patients.

9.2 Setting

The analysis will be conducted among US veterans, aged 18 years or older, with chronic HCV who sought care at any of the medical centers and ambulatory care and community-based outpatient clinics that comprise the national VA healthcare system. This analysis will be restricted to HCV mono-infected (i.e., no HBV- or HIV-coinfection) patients with compensated liver cirrhosis. Within the VA, the decision to treat patients with antiviral therapy for HCV, regimen choice, and subsequent clinical care was at the discretion of the provider and was determined and registered prior to the diagnosis of de novo HCC. Within the VA healthcare system, all HCV-infected patients were eligible for HCV treatment during the study period. VA pharmacies had several DAAs

(sofosbuvir-containing medications, simeprevir, ombitasvir/paritaprevir/ritonavir with or without dasabuvir, daclatasvir, elbasvir and grazoprevir, and glecaprevir and pibrentasvir) on formulary and there were no limitations to DAA availability based on income, fibrosis stage or psychosocial disorders.

Our sampling frame will comprise HCV infected patients with compensated cirrhosis who have data included in the VA CDW sources. For analysis of the first primary objective, HCV infected patients will be included if they have a clinical encounter (i.e., office visit, procedure, lab result, prescription, etc.) recorded in the VA CDW sources in the 6 months preceding January 01, 2013 or between January 01, 2013 and December 31, 2017, inclusive. A patient will contribute to DAA exposure starting at the date of DAA initiation if the patient-initiated treatment with an IFN-free DAA regimen between January 01, 2013 and December 31, 2017. Untreated time is defined as any time between January 01, 2013 and April 30, 2018 that precedes initiation of IFN-free DAA treatment or occurs in a patient who does not initiate IFN-free DAA treatment. For analysis of the second primary objective, 2 groups of HCV patients will be included in the analysis: (a) those who initiated treatment with an IFN-free DAA regimen between January 01, 2014 and December 31, 2017, and (b) those who initiated treatment with IFN-based regimen between January 01, 2005 and December 31, 2013 (historical control). Regardless of the objective, follow-up for IFN treated patients will end at December 31, 2013 and follow-up for untreated and DAA treated patients will end at April 30, 2018.

Exposure

Interferon-free DAA treatment initiation will be defined as one or more filled prescriptions (at least 28 days of prescription filled) of sofosbuvir-containing medications, simeprevir, ombitasvir/paritaprevir/ritonavir with or without dasabuvir, daclatasvir, elbasvir and grazoprevir, and glecaprevir and pibrentasvir between January 01, 2013 and December 31, 2017. Such IFN-free DAA treatments will be referred to as "**DAA only**" hereafter. Interferon (IFN)-based treatment initiation will be defined as one or more filled prescriptions of pegylated IFN (pegIFN) or regular IFN (at least 28 days of prescription

filled) with or without RBV without any DAAs between January 01, 2005 and December 31, 2013. Such IFN-based DAA-free treatments will be referred to as "**IFN-based**" hereafter. The date of the first filled prescription will be used as the treatment initiation date. The use of filled prescriptions as an indicator of receipt of treatment has been validated using the VA pharmacy data, with high agreement between these definitions and those based on EMR. The treatment completion date will be defined as last date covered by final filled prescription. Regimens that include both IFN and DAAs such as telaprevir plus pegylated interferon and RBV, boceprevir plus pegylated interferon and RBV, or sofosbuvir plus pegylated interferon with or without RBV will not be investigated as an exposure of interest. Instead, these will be considered as a type of prior HCV treatment for adjustment as a covariate and are hereafter referred to as "**DAA + IFN**."

For the first primary objective, any patient treated with DAA only therapy will be considered as DAA treated thereafter. Thus, the first DAA treatment between January 01, 2013 and December 31, 2017 will be used to define the start of DAA treatment. Additional DAA treatment courses will not be used in the analysis. However, patients will be censored if they subsequently receive any IFN-containing regimen. The last prior HCV treatment, whether DAA-only treatment before the index date, any prior IFN-based regimen, or DAA+IFN regimen will be used to define a covariate for prior HCV treatment (none, DAA only, IFN-based, DAA+IFN).

For the second primary objective, only the first course of HCV treatment in the time interval will be used to establish the index date for each patient in either the IFN or DAA treatment cohort. Direct-acting antiviral agents treated patients will be censored if any IFN-containing regimen is begun, and IFN-treated patients will be censored if any DAA only regimen is begun. Technically, the same patient could appear in both the DAA and IFN groups; to address this, robust standard error estimates that account for potential non-independence of observations will be incorporated into the regression. Similar to the first primary objective, the most recent HCV treatment prior to the time interval, if any, will be used to define a covariate (none, DAA only, IFN-based, DAA+IFN).

Inclusion/Exclusion Criteria

Patients will be assessed for inclusion in the study cohort based on the criteria below. For patients receiving IFN-free DAA therapy, entry criteria referencing the index date will be assessed separately for each study objective as the index dates are different. For the first primary objective, the first index date (most often expected to be defined relative to the untreated exposure time) will be used for assessing entry criteria (see Section 9.3 for definition of index dates).

Inclusion criteria:

1. Patients with chronic HCV defined as a positive test for HCV ribonucleic acid (RNA) in plasma by qualitative or quantitative assays or genotype test between January 01, 2005 and December 31, 2017.
2. For the first primary objective (IFN-free DAA treated and untreated patients): a clinical encounter (i.e., office visit, procedure, lab result, prescription, etc.) recorded within 6 months before January 01, 2013 or between January 01, 2013 and December 31, 2017.
3. For the second primary objective: for IFN treated patients, the IFN treatment was initiated after the above HCV diagnosis, but between January 01, 2005 and December 31, 2013. If DAA exposed, the DAA treatment was initiated after the above HCV diagnosis, but between January 01, 2014 and December 31, 2017.
4. Patients with data in VA sources to establish a diagnosis of compensated cirrhosis as follows:
    - At least 1 FIB-4 > 3.25 within 24 months before to 6 months after the index date but before any HCV treatment (and with all measurements for FIB-4 calculation within 6 months of each other) with at least 1 ICD-9 (571.2, 571.5) or ICD-10 (K70.30, K70.31, K74.60, K74.69, K74.3, K74.4 and K74.5) code indicating cirrhosis, and
    - No diagnosis codes for hepatic decompensation defined as ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome based on inpatient or outpatient ICD-9 codes of 789.5,

456.0–2, 572.4, 572.2, 348.3×, 070.0, 070.2×, 070.4×, 070.6, 070.71, or corresponding ICD-10 codes during the 2 years prior to and including the index date (see Section 9.3).

5. Patients with at least 1 health care encounter recorded in a VA source (outpatient or inpatient) at least 1 year prior to the index date. This is to ensure that the analytic cohorts have a minimum uniform period during which the covariates are defined and captured.

Exclusion criteria:

1. Patients with a diagnosis of HCC, defined as at least 1 ICD-9 code 155.0 or ICD-10 code C22.0, C22.8, C22.9, D01.5 (the VA switched to ICD-10 codes on 10/01/2015) ever recorded prior to and including the index date (see Section 9.3).
2. History of liver transplantation.

Finally, if feasible, the patient population for both primary objectives will be limited to patients who have an image of the liver (defined as an ultrasound, computerized tomography [CT] or magnetic resonance image [MRI] of the liver) in the 6 month period immediately prior to and including the index date (more restrictive), or the 12 month period immediately prior to and including the index date (less restrictive). This (along with Exclusion Criterion 1) will be done to exclude potential prevalent HCC cases. However, should the imposition of both these restrictions limit the sample size such that the analyses for the primary objectives become infeasible, then the affected primary analyses will proceed without these restrictions, and instead these restrictions will be included in sensitivity analyses to permit assessment of the impact of potential inclusion of prevalent HCC cases in the primary analyses.

9.3 Variables

Index Date:

The **index date** defines the start of de novo HCC risk.

For the **first primary objective**, **the index date** for untreated time will be the date of the first VA clinical encounter (i.e., office visit, procedure, lab result, etc.) recorded in the 6 months preceding and including January 01, 2013 or anytime during the January 01, 2013 to December 31, 2017 time interval. This will serve as the start of untreated time in both patients who were never treated and patients who were as yet untreated as of the first clinical encounter. For untreated patients who subsequently initiate DAA, the index date for DAA exposed time will be defined as the start of DAA therapy.

For the **second primary objective**, **the index date** will be the date of initiation of first IFN treatment between January 01, 2005 and December 31, 2013 for IFN-treated patients and the date of initiation of the first DAA treatment between January 01, 2014 and December 31, 2017 for DAA treated patients.

The index dates will be defined as above for all sensitivity analyses of the first and second primary objectives.

Demographic Variables and Other Covariates:

Demographic variables and other covariates will be determined by the last available value prior to or on the index date for both the treated and untreated patients. For DAA-treated patients, covariate values will be defined separately for each objective using the respective index date. Diagnosed comorbidities will be defined on the basis of ICD-9/10 codes. Covariates include age, gender, race/ethnicity, body mass index (BMI), diabetes, HCV genotype, and prior HCV treatment regimen with corresponding treatment duration, and alanine aminotransferase, albumin, AST, creatinine, platelets, alpha fetoprotein (AFP), INR liver function test, hemoglobin, bilirubin, FIB-4 score, and HCV RNA. FIB-4 must be within 24 months before to 6 months after the index date, all other lab values must be within 12 months before the index date.

Outcome:

De novo HCC diagnosis is defined based on a hierarchical approach. First, patients are classified as having HCC based on VA CCR. For the remaining patients, patients identified with > 1 instance following their index date of ICD-9 (155.0) or ICD-10 codes (C22.0, C22.8, C22.9, D01.5) for HCC that is not recorded in VA CCR will have a manual structured review of the EMR performed via Compensation and Pension Records Interchange (CAPRI) to confirm HCC diagnosis and determine the date of diagnosis. Personnel conducting medical records review will be masked to patients' exposure status. Patients with de novo HCC will be counted as having an event at the time of first diagnosis of HCC in the study interval.

Compensated Cirrhosis:

A patient will be considered to have compensated cirrhosis at start of follow-up if:

1. At least 1 FIB-4 > 3.25 within 24 months before to 6 months after the index date but before any HCV treatment (and all measurements for FIB-4 calculation within 6 months of each other) or with at least 1 ICD-9 (571.2, 571.5) or corresponding ICD-10 (K70.30, K70.31, K74.60, K74.69, K74.3, K74.4 and K74.5) code indicating cirrhosis, and
2. No diagnosis codes for hepatic decompensation defined as ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome based on an inpatient or outpatient ICD-9 codes of 789.5, 456.0–2, 572.4, 572.2, 348.3X, 070.0, 070.2X, 070.4X, 070.6, 070.71 (or similar ICD-10 codes) within 2 years prior to and including the index date.

Sustained Virologic Response:

- SVR: all HCV RNA tests were negative [serum HCV RNA viral load test below the lower limit of quantification (LLOQ) or detection after end of HCV treatment

(IFN-based or all-oral DAA)] with at least 1 HCV RNA result recorded at least 10 weeks after end of treatment (EOT).

- No SVR: an HCV RNA above LLOQ 10 or more weeks after EOT, or any time during treatment or after EOT with no subsequent negative HCV RNA.

Covariates:

- Demographic variables: age, gender, race/ethnicity, BMI
- Disease-related characteristics: HCV genotype, HCV viral load, FIB-4
- Alcohol use: alcohol use will be indicated by at least 1 ICD-9/10 code or by an Alcohol Use Disorders Identification Test score ≥ 4 (≥ 3 for women) documented on or before the index date.
- Substance abuse disorders (including drugs of abuse, except alcohol and marijuana) will be indicated by at least 1 ICD-9/10 code documented on or before the index date.
- Other medical comorbidities of interest will be defined as at least 1 ICD-9/10 codes on or before the index date: cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, diabetes mellitus, mental illness, esophageal/gastric varices, portal hypertension and hypertension.
- Laboratory values within 1 year before the index date: platelet count, serum albumin, and AFP.
- Health care utilization: the number of outpatient visits in the year prior to the index date as a surrogate.
- Deyo-Charlson Comorbidity Index (DCCI) by presence of ICD-9/10 codes prior to the index date.
- SVR(Yes/No/missing) will be included as a factor in the model for evaluation of the second primary objective.
- Last prior HCV treatment (DAA only, IFN-based, DAA+IFN, or none).
- Surveillance: the HCC surveillance rate, defined as the number of HCC surveillance assessments (liver ultrasound, liver CT, liver MRI, or AFP

measurements) during the follow-up period, divided by the amount of follow-up time.

VA CCR: Data elements available include:

- Demographic variables: age at diagnosis, sex, race/ethnicity, geographic region and type of VA facility where the HCC diagnosis was made.
- Cancer tumor characteristics: year of diagnosis, tumor size, tumor number, tumor stage [Tumor Node Metastasis (TNM)], tumor type.

9.4 Data Sources

The Veteran's Affairs data sources that we propose to use include the 3 registries listed below. All are linked using a unique identifier (based on Social Security Number) for each patient.

VA CDW combines information from Medicare, VA, Social Security, and VA compensation and pension benefits to determine date of death (sensitivity 98.3%; specificity 99.8% relative to National Death Index).[41] CDW is updated in real time.

VA CCR is a centralized VA registry that was initiated in 1995 and serves as a national data repository for over 750,000 VA patients with cancer. Cancer registrars manually abstract data, conforming to standards set by the North American Association of Central Cancer Registries. Data are then aggregated into the national cancer registry. Once the data are centralized, cases are merged and quality assurance checks are conducted. Hepatocellular carcinoma is identified with primary site code C220 with histology codes 817XX through 818XX.

VA EMR chart abstraction will be completed using the CAPRI, a VA application that provides access to the EMR at any VA nationwide. Compensation and Pension Records Interchange has been used for several studies.[42,43] EMR abstraction methods that use a combination of radiological and histological criteria to confirm HCC diagnosis have

developed and tested.[43,44] Data from EMR will be used to verify HCC diagnosis (and diagnosis date) for cases not contained in VA CCR.

9.5 Study Sample Size

For the first primary objective, sample sizes of approximately 8000 patients treated with DAA only regimens meeting the inclusion criteria and approximately 8000 untreated patients meeting the inclusion criteria are expected. Based on Li et al,[45] we assume an incidence rate of 3.5% de novo HCC per patient year of exposure among both the DAA treated and untreated patients (assuming an average of 1 year of follow up in both groups). These assumptions, along with assuming an exponential distribution of de novo HCC-free survival, give an unadjusted hazard ratio (HR) of 1 with a 2-sided 95% CI of (0.85, 1.18) for risk of de novo HCC among DAA treated vs untreated. The precision of the estimate depends on the HR; however, with a 95% CI half-width of ≤ 0.18, the planned sample size is considered sufficient to clearly distinguish from a HR of 1.18 or more if there is no additional de novo HCC risk related to DAA treatment versus no treatment.

The VA database includes a minimum 3750 patients with compensated cirrhosis treated with IFN based therapy between January 01, 2005 and December 31, 2013. Thus, for the second primary objective, sample sizes of approximately 8000 cirrhotic patients treated with DAA-only regimens and at least 3750[27] cirrhotic patients treated with IFN-based regimens are expected. We assume an annual incidence rate of 2.0% de novo HCC among both DAA treated and IFN treated patients, and assume an average of 1 year of follow up for DAA treated and an average of 2.5 years of follow for IFN treated.[33] These assumptions, along with assuming an exponential distribution of de novo HCC-free survival, give an unadjusted hazard ratio of 1.0 with a 2-sided 95% CI of (0.81, 1.24) for the risk of de novo HCC among DAA treated vs IFN treated. The precision of the estimate depends on the HR; however, with a half-width of ≤ 0.24, the planned sample size is considered sufficient to clearly distinguish from a HR of 1.24 if there is no additional de novo HCC risk related to DAA treatment versus IFN treatment.

If the requirement of an image of the liver ≤ 6 or ≤ 12 months prior to the index date (Section 9.2) decreases the sample sizes described above for either primary objective by > 20%, then the population for the primary analysis for that objective will exclude this inclusion criterion. In this case, the analysis for that objective will be performed on the subpopulation meeting this inclusion criterion as a sensitivity analysis (Section 9.7.4).

For the secondary objective, approximately 50% of all cancer cases diagnosed in VA patients are captured in the VA CCR. The tumor characteristics of all subjects in the study with HCC cases captured in the VA CCR will be examined. In consultation with the VA Principal Investigator and based on previous research conducted in this study population, it is estimated that approximately N = 500 incident HCC cases among DAA exposed patients will be included in the analysis, with comparable numbers of cases in the untreated and IFN-treated patients. Therefore, approximately N = 250 incident HCC cases after DAA treatment will have data available in the VA-CCR to evaluate tumor characteristics (i.e., tumor size, tumor number, tumor stage, tumor type). Similar numbers are expected for HCC cases after IFN treatment and after no treatment.

9.6 Data Management

Data from the sources described in Section 9.4 are aggregated to the VA CDW. Project-specific data will be extracted from source databases and placed in SQL tables and will be maintained at the Houston HSR&D COIN under the direct supervision of [redacted]. This data will be protected with appropriate ID, password and data-access restrictions in place, housed within the Houston HSR&D COIN Computation Center and protected by the VA's internal firewall.

All statistical analysis will be performed in SAS (SAS Institute Inc., Cary, NC).

9.7 Data Analysis

9.7.1 Demographic Variables and Other Characteristics

For the analysis population for the first primary objective, descriptive summaries of demographic variables and clinical factors ascertained at each index date or most recently

prior to each index date will be provided for the untreated time and the DAA exposed time. For the analysis population for the second primary objective, demographic and clinical factors will be summarized and compared between the DAA only therapy group and the IFN based treatment group using chi-square tests for categorical variables and Wilcoxon rank-sum or t tests, as appropriate, for continuous variables. The unadjusted incidence rate of HCC per 1000 person-years will be calculated with 95% CI as the number of HCC events divided by total person-years of follow-up for DAA exposed time and untreated time, and for the DAA only therapy group and IFN based treatment group.

9.7.2 Analyses of Primary Objectives

For the first primary objective, a multivariable Cox proportional hazards regression model will be used to examine the risk of HCC associated with DAA exposed time compared to untreated exposed time using DAA exposure as a time-varying covariate and adjusting for potential confounders ascertained at each index date or the most recent value prior to each index date and updated at 12-month time intervals until DAA exposure start or through untreated person time if no DAA start: age, gender, race/ethnicity, BMI, HCV genotype, HCV viral load, medical comorbidities (e.g., diabetes mellitus, alcohol use, substance abuse disorders, mental illness, cardiovascular/cerebrovascular disease, esophageal/gastric varices, portal hypertension), FIB-4, laboratory values (platelet count, serum albumin, AFP), healthcare utilization, DCCI, and last prior HCV treatment, as well as HCC surveillance rate during follow-up. Patients can contribute person-time to both DAA exposed time and untreated exposed time. Untreated patients will contribute person-time at risk to the untreated group until first of HCC diagnosis or receipt of DAA treatment, or censored at death or end of data availability (i.e., date of last VA encounter). Untreated patients that later initiate DAA treatment will contribute time at risk to the DAA treated group from the date of treatment initiation until HCC diagnosis, or censored at death, initiation of IFN-containing HCV treatment or end of data availability (i.e., date of last VA encounter). Separately, multivariable Cox proportional hazards regression will also be used to examine the risk of HCC with DAA exposure in DAA-treated patients achieving SVR compared to untreated time, and the risk associated with DAA exposure in

DAA-treated patients not achieving SVR compared to untreated time. For the first primary objective, the index date for untreated time will be the date of the first clinical encounter recorded within 6 months before January 01, 2013 or anytime during the January 01, 2013 to December 31, 2017 time interval, inclusive. The index date for DAA-treated time will be the date of DAA initiation.

For the second primary objective, another multivariable proportional hazards model will be used to examine the risk of HCC in the DAA treated patients compared to the IFN-based therapy treated patients. This analysis will evaluate the potential explanatory effect of SVR status on the association between HCV treatment exposure and HCC using multiple methods, including using SVR status as a factor in the model. We recognize that the feasibility of these analyses accounting for SVR status will be dependent on the number of HCC cases observed among the relatively small number of DAA-exposed patients who do not achieve SVR. The following potential confounders ascertained at the index date or the most recent value prior to the index date will be considered for adjustment in the multivariable model: demographic variables, alcohol use and substance abuse disorders, other medical comorbidities (including cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, diabetes mellitus, mental illness, esophageal/gastric varices, portal hypertension and hypertension), FIB-4, laboratory values (platelet count, serum albumin, and AFP), last prior HCV treatment, health care utilization, DCCI, and HCC surveillance rate during follow-up. Follow-up will continue until the first HCC event, and patients will be censored at initiation of DAA treatment (in the IFN based treated group) or initiation of IFN-containing treatment (in the DAA-treated group), death or end of data availability. For the second primary objective, the index date will be the date of initiation of IFN treatment for IFN-treated patients and the date of initiation of DAA treatment for DAA treated patients.

For the second primary objective, propensity score methods[46] will be used to adjust for potential confounding by indication (HCV treatment), based on values for variables ascertained at the index date or the most recent value prior to the index date: age, gender,

race/ethnicity, BMI, HCV genotype, HCV viral load, alcohol use, substance abuse disorders, other medical comorbidities (e.g., cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, diabetes, mental illness, esophageal/gastric varices, portal hypertension and hypertension), FIB-4, laboratory values (platelet count, serum albumin, and AFP), healthcare utilization DCCI, last prior HCV treatment. Propensity score matching of IFN-treated patients to DAA-treated patients will be the preferred analysis; however, in the event that matching proves to be infeasible, inverse probability of treatment weighting (IPTW) with stabilized weights will be applied to multivariate models instead.

9.7.3 Secondary Objective Analysis

The first occurrence of de novo HCC during the observation period will be identified in the VA CCR for any instance of primary site code C220 and histology codes 817XX through 818XX[33] for the subset of patients with tumor characteristic evaluation defined in Section 9.5. Demographic characteristics (age at HCC diagnosis, sex, race/ethnicity, geographic region and type of VA facility where the HCC diagnosis was made) and pattern of presentation of cases will be descriptively analyzed for this subset of patients by HCV treatment group (DAA, IFN or untreated) strata. Specific tumor characteristics of interest include number, size, type, stage based on the TNM staging system, and HCC treatment. Data reported will include frequency counts and percentages for categorical variables and mean/median and standard deviation/standard errors, respectively, calculated for continuous variables. Tumor characteristics will be compared between the HCV DAA treatment group and both 1) the HCV IFN treated group and 2) the untreated group, using Cochran-Mantel-Haenszel (CMH) tests for categorical variables and analysis of covariance (ANCOVA) or stratified Mann-Whitney tests for quantitative variables, as appropriate.

9.7.4 Supporting Summaries

The following activities are planned to evaluate the robustness of the analysis results to perturbations of the methods and assumptions used, and to fully explore and describe the

data. All sensitivity analyses of the analysis fulfilling the first primary objective (ie comparing DAA treated time to untreated time) will use the date of the first clinical encounter as the index date for untreated time, and the date of DAA treatment as the index date for treated time. All sensitivity analyses of the analysis fulfilling the second primary objective will use the date of HCV treatment initiation as the index date (see Sections 9.2 and 9.3 for details).

- Verification of proportional hazards assumption to confirm the appropriateness of the models for both primary objectives.[47] The proportional hazards assumption will be assessed by introducing a treatment and time interaction term into the main Cox proportional hazards models and testing its significance. If statistically significant, follow-up time will be split into intervals over which the proportional hazards assumption is met, and separate proportional hazards models will be fit for each of these intervals.
- Sensitivity analyses for both primary objectives for patients with more than one HCV treatment course during the study period by including covariates with the number of DAA only courses and the number of IFN-based treatment courses (for second primary objective only) for each patient after the index date.
- Sensitivity analyses of both primary objectives that exclude patients with diagnosis of de novo HCC within 8 weeks, 12 weeks, and 20 weeks after index date. The purpose of these sensitivity analyses is to exclude potential HCC events that occur before the estimated time to viral suppression across all DAAs (8 weeks from treatment start)[48,49] and/or the minimum time to HCC induction or ability to be detected on liver imaging (a further 12 weeks).[50,51,52,53,54,55]
- Sensitivity analysis of the second primary objective that includes time to first documented continuous HCV viral suppression as a time-dependent covariate, and is limited to patients with at least 1 HCV RNA result recorded at least 10 weeks after EOT (see Section 9.3). Continuous viral suppression is defined as achieving and maintaining HCV RNA below LLOQ during follow-up.
- In addition, among those with at least 1 HCV RNA result recorded at least 10 weeks after EOT, we will conduct a sensitivity analysis of the second primary objective after stratifying by SVR status (yes/no) and re-calculating propensity scores and re-applying them within each stratum.

- As noted earlier (Section 9.2), if restriction of the primary analyses to patients with an HCC free image up to 6 or 12 months prior to index date proves infeasible due to its impact on sample size and statistical power, then analyses incorporating this restriction will be included as sensitivity analyses.
- The patients who die in the first 6 months of follow-up in each HCV treatment group (DAA, IFN or untreated) will be summarized according to their HCC status at the time of death as HCC Yes, HCC No, or HCC Unknown. Efforts will be made to access case-finding sources such as electronic notes for outpatient and inpatient encounters, pathology reports, death certificates and other sources of clinical data within the VA Health System.
- Finally, the analysis for both primary objectives will be repeated using the population where cirrhosis at follow-up start is defined only by having at least 1 FIB-4 > 3.25 within 24 months before to 6 months after the index date but before any HCV treatment (and all measurements for FIB-4 calculation within 6 months of each other).

9.7.5 Additional Summaries of Study Data

Descriptive summaries will be provided by cohort to assist in the study reporting as described below. The cohorts for the first primary objective will include during DAA treated time versus untreated time (as appropriate) and the cohorts for the second primary objective are DAA only treated patients and IFN-based therapy treated patients.

- Information on patient participation, participant study completion status, total duration of follow-up, and for treated patients/person-time, the duration of follow-up after HCV treatment initiation (DAA or IFN)
- Timing of HCV treatment by calendar year
- Information relating to the overall survival and timing of any deaths
- Time between HCV treatment initiation and first HCC diagnosis, among patients developing de novo HCC;
- Time between HCV treatment initiation and achieving SVR;
- SVR outcomes for patients initiating HCV treatment: number of patients achieving SVR, not achieving SVR, missing SVR values, dead before achieving

SVR, developing HCC before achieving SVR, or last clinical encounter before achieving SVR.

- A descriptive summary of HCC-free survival for each primary objective will be presented using adjusted Kaplan-Meier curves.
- Available demographic features and characteristics, including diagnosed co-morbidities, as recorded in the VA-CDW will be compared between patients with HCC included in the VA-CCR and patients with HCC not included in the VA-CCR.

The study may also summarize laboratory values before and after the index date.

9.8 Quality Control

Missing values will not be imputed; therefore, covariates missing for **> 10% of patients** will be excluded from the PH models.

For any data analyses completed, the data used in the analysis will be archived.

For all data sources used, quality control procedures (SOPs, guidelines, etc.) will be in place to ensure that data quality and integrity allow for the accurate data reporting, interpretation, and verification.

9.9 Limitations of the Research Methods

- This study includes only US veterans, potentially limiting generalizability of results.
- Inclusion of patients with IFN-based treatment as a comparator group introduces variability of follow-up durations, as well as considerable differences in characteristics of patients treated in the interferon era vs. all-oral DAA era. For all oral DAA therapies, shorter average follow-up time compared to IFN-based therapies is a limitation. However, we expect an average follow-up time of > 1 year for DAA only treated.
- Furthermore, there may be some variability in the methods of HCC surveillance/diagnosis in the IFN era (2005-2013) vs the DAA era (2014 onward). For example, AASLD clinical practice guidelines recommend a greater frequency

of liver ultrasounds from 2010 onwards than in 2005.[56,57,58] If anything, this might tend to decrease the time to HCC events in the DAA era relative to the IFN era, biasing the results against DAAs.

- Some factors, such as noncompliance and lack of interest in treatment, are unmeasurable in the database.
- Treatment with early all oral DAA regimens may represent a novel confounding factor contributing to selection bias that has not been previously reported nor rigorously adjusted for in prior studies. This bias will influence the results toward higher HCC risk with DAA treatment; therefore, any risk reduction estimate related to DAA treatment is likely to be conservative.
- Diagnostic code (ICD-9/10) misclassification may be a potential limitation inherent in the study design. Use of multiple diagnostic codes commonly reported in observational studies to identify co-morbidities of interest may mitigate this risk and improve the ability to accurately identify physician diagnosed patients. Importantly some of the key variables are not dependent on ICD-9 codes (e.g., HCV status, SVR status, medications). The primary outcome definition will be cross validated against VA CCR data. In addition, codes for cirrhosis have been manually validated by the research group.
- Individual patient characteristics may have influenced whether and when to treat with DAA therapy in the analysis for the first primary objective, and may also affect the risk of HCC occurrence independent of DAA treatment. Thus, individual patient characteristics shown or thought to influence treatment with DAAs and/or HCC risk are included as covariates in the HR model. If unknown confounders exist and are not adequately measured controlled for by related confounders in the analysis, the overall effect estimate may be biased. However, many similar analyses of the risk of DAA treatment have been published, so the covariates predictive of HCC risk and DAA treatment are fairly well known. Most of these are available in the VA databases and have been included in the model.

9.10 Other Aspects

Not applicable.

10.0 Protection of Human Subjects

This study will be conducted in accordance with the Good Pharmacovigilance Practices issued by the European Medicines Agency (EMA) (EMA 2013), the Declaration of Helsinki and its amendments (Declaration of Helsinki 2008), Guide on Methodological Standards in Pharmacoepidemiology (EMA 2010)[59] and any applicable guidelines of participating nations. This study will follow current governance for the use of patient data included in the US Veterans Administration database which include approval by the VA Research and Development office and institutional review board (IRB) approval by the VA's academic affiliate, Baylor College of Medicine.

11.0 Management and Reporting of Adverse Events/Adverse Reactions

This is a retrospective non-interventional database study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol. No reporting of individual adverse events to regulatory agencies is planned for this database study because there is no access to individual patient/subject records or specific anti-HCV regimen taken and it is not possible to assess the causality of individual cases. Pre-specified health outcomes of interest, including any that qualify as adverse events, will be summarized as part of any interim analysis (including safety analysis, if required) and in the final study report, which will be provided to regulatory agencies by the sponsor as required.

Any relevant safety information will be summarized in the appropriate Periodic Safety Update Report, Periodic Benefit Risk Evaluation Report, and/or Development Safety Update Reports if required.

12.0 Plans for Disseminating and Communicating Study Results

The final report will be submitted to the EMA and other regulatory agencies, as required, as well as the MAH Product Safety Teams and Safety Review Boards. Subsequent to the

approval of the final report, study findings will be disseminated in professional journals and at professional society meetings.

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Annex 1. List of Stand-Alone Documents

None.

Annex 2. ENCePP Checklist for Protocols

Annex 3. MAH Details and Direct-Acting Antiviral Information

MAH Details

Marketing Authorisation Holder	Address and Regulatory Contact
AbbVie, Ltd	[redacted] AbbVie House Vanwall Road Maidenhead Berkshire SL6 4UB Phone: E-mail:
Bristol-Myers Squibb Pharma EEIG	[redacted] Research and Development Parc de l'Alliance Avenue de Finlande 4 - 1420 Braine-l'Alleud, Belgium Phone: Fax: E-mail:
Gilead Sciences Ireland UC	[redacted] Gilead Science International Granta Park, Abington, Cambridge CB21 6GT Phone: Fax: E-mail:
Merck Sharp & Dohme Limited	[redacted] Merck Sharp & Dohme (Europe), Inc. 5, Clos du Lynx 1200 Bruxelles Phone: Fax: E-mail:

Direct-Acting Antiviral Information

Active Substance(s)	ATC Code	Product Numbers	Medicinal Product(s)	Product Reference	MAH(s)
daclatasvir	J05AP07	EU/1/14/939/001-004	Daklinza	EMEA/H/C/003768	Bristol-Myers Squibb Pharma EEIG
dasabuvir	J05AP09	EU/1/14/983/001	Exviera	EMEA/H/C/003837	AbbVie, Ltd
elbasvir/grazoprevir	J05AP54	EU/1/16/1119/001	Zepatier	EMEA/H/C/004126	Merck Sharp & Dohme Limited
glecaprevir/pibrentasvir	J05AP57	EU/1/17/1213/001	Maviret	EMEA/H/C/004430	AbbVie, Ltd
ombitasvir/paritaprevir/ritonavir	J05AP53	EU/1/14/982/001	Viekirax	EMEA/H/C/003839	AbbVie, Ltd
simeprevir*	J05AP05	EU/1/14/924/001 – 002	Olysio	EMEA/H/C/002777	Janssen-Cilag International NV
sofosbuvir	J05AP08	EU/1/13/894/001-002	Sovaldi	EMEA/H/C/002798	Gilead Sciences International Ltd
sofosbuvir/ledipasvir	J05AP51	EU/1/14/958/001-002	Harvoni	EMEA/H/C/003850	Gilead Sciences International Ltd
sofosbuvir/velpatasvir	J05AP55	EU/1/16/1116/001	Epclusa	EMEA/H/C/004210	Gilead Sciences International Ltd
sofosbuvir/velpatasvir/voxilaprevir	J05AP56	EU/1/17/1223/001	Vosevi	EMEA/H/C/004350	Gilead Sciences International Ltd

ATC = Anatomical Therapeutic Chemical classification system; EEIG = European Economic Interest Grouping; EMEA = European Medicines Evaluation Agency; EU = European Union; MAH = Marketing Authorization Holder; MAH = Marketing Authorisation Holder

* Olysio (simeprevir) European Union Marketing Authorisation was withdrawn on 01 May 2018 and is no longer effective within Europe.