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.