Title Page

Title	A prospective, observational cohort study utilizing the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of Grade 3+ ALT elevations in patients being treated for Hep C with paritaprevir with ritonavir (paritaprevir/r), ombitasvir and dasabuvir (3-DAA regimen) or paritaprevir/r and ombitasvir (2-DAA regimen) with or without ribavirin for Hepatitis C Infection (HCV) (SHORT – Evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA Regimens in a real world setting)
Protocol Version Identifier	Version 2.0
Date of Last Version of Protocol	22 December 2015
EU PAS Register Number	To be registered after PRAC approval.
Active Substance	Paritaprevir/ritonavir/Ombitasvir and Dasabuvir
Medicinal Product	Viekirax and Exviera film coated tablets
Product Reference	EMEA/H/C/003839 EMEA/H/C/003837
Procedure Number	EMEA/H/C/003839/PRO 001.2 EMEA/H/C/003837/PRO 001.2
Marketing Authorisation Holder(s)	AbbVie, Ltd
Joint PASS	No
Research Question and Objectives	Evaluate the potential for and clinical impact of increased ALT during treatment with the AbbVie 2- or 3-DAA regimen for hepatitis C infection.
Country(-ies) of Study	Americas and Europe
Author	

This study will be conducted in compliance with this protocol.

[redacted]

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	AbbVie, Ltd
MAH Contact Person	[redacted]

1.0 Table of Contents

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2.0 Abbreviations

AbbVie 3-DAA Regimen	paritaprevir/ritonavir, ombitasvir, dasabuvir with or without ribavirin
AbbVie's 2-DAA Regimen	paritaprevir/ritonavir, ombitasvir with or without ribavirin
ALT	alanine aminotransferase
CCC	Clinical Coordinating Center, University of Florida
CDAS	Centralized Data Abstraction Service
DCC	Data Coordinating Center, University of North Carolina at Chapel Hill
Gr 3+ ALT	Grade 3 (5 × ULN) or higher ALT elevations (Gr 3+ ALT)
ULN	Upper limit of normal

3.0 Responsible Parties

HCV-TARGET – Hepatitis C Therapeutic Registry and Research Network
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4.0 Abstract

Title: A prospective observational cohort study utilizing the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of Grade 3+ ALT elevations in patients being treated for Hep C with paritaprevir with ritonavir (paritaprevir/r), ombitasvir and dasabuvir (3-DAA regimen) or paritaprevir/r and ombitasvir (2-DAA regimen) with or without ribavirin for Hepatitis C Infection (HCV) (SHORT – Evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA regimens in a real world setting)

Rationale and Background: Hepatitis C virus (HCV) infection affects persons worldwide and is a leading cause of chronic liver disease and liver-related mortality. Treatment with direct acting antiviral agents without interferon represents a significant advance associated with high cure rates for HCV and without the side-effects associated with interferon. AbbVie's interferon-free 3-DAA regimen (paritaprevir/r, ombitasvir, dasabuvir with or without ribavirin) has been developed for treatment of genotype 1 HCV and is used with or without RBV. The regimen includes paritaprevir/r, a NS3/NS4A HCV protease inhibitor, ombitasvir, a nonstructural NS5A HCV inhibitor, and dasabuvir, a nonstructural protein 5B (NS5B) polymerase inhibitor. Ritonavir (denoted "r") is used as a pharmacokinetic enhancer for paritaprevir and has no anti-HCV activity. AbbVie's interferon-free 2-DAA regimen (paritaprevir/r, ombitasvir) has been developed for the treatment of genotype 4 HCV.

Over 2,600 subjects were treated in Phase 2 – 3 clinical trials during development of the 3-DAA regimen. Transient alanine aminotransferase (ALT) Grade 3 (5 × ULN) or higher elevations (Gr 3+ ALT) were observed in approximately 1% of subjects in randomized Phase 2 and 3 clinical trials of AbbVie's 3-DAA HCV treatment regimen. The ALT elevations in these subjects were asymptomatic and generally occurred within the first 4 weeks of DAA treatment. Improvement typically occurred with ongoing DAA treatment with resolution by Post-Treatment Week 4. Paritaprevir is a known inhibitor of bilirubin transporters and can cause elevations in total and indirect bilirubin. In addition, RBV can cause elevation in total and indirect bilirubin due to RBV-associated hemolytic anemia. Despite this, the ALT elevations were not synchronous with bilirubin elevations. When they occurred, the ALT elevations occurred after or during resolution of elevations in total (predominantly indirect) bilirubin. There were no clinically significant hepatic-related outcomes related to DAA treatment. Evaluation of ALT elevations revealed two risk factors: 1) ethinyl estradiol (EE) use and 2) administration of higher doses of paritaprevir which had been previously evaluated in the Phase 2 program (i.e., 200 mg or higher). In the absence of these two identified risk factors (i.e., by excluding paritaprevir doses of 200 mg or higher and excluding subjects receiving EE-containing medications) an incidence of Grade 3+ ALT elevations of 0.8% was observed. There was no evidence of an increased risk of ALT elevation among patients with compensated cirrhosis. Based on these observations from the clinical trials, EE-containing medications have been contraindicated with the AbbVie 2-DAA or 3-DAA regimens. Use of non-EE-estrogens is permitted during therapy. The Warnings and Precautions section of product labeling provides information patients should be aware of on important signs and symptoms.

Rationale and Background (Continued): The incidence rate and risk factors for Gr 3+ ALT elevation as well as the clinical outcomes in real-world settings remains unknown. This prospective observational cohort study utilizing a disease registry (HCV-TARGET) has been designed to provide additional characterization of the identified risk of serum ALT elevation and possible risk factors associated with it in a real world setting. In addition, although no serious hepatic outcomes have been linked to these Grade 3+ ALT elevations during clinical trials, this study will also evaluate clinical impact of these ALT elevations in a real world setting that may be observed within the 6 months following completion of treatment. In summary, HCV direct acting antivirals of the protease inhibitor class may be associated with ALT elevations. The clinical impact of these elevations is not known. The EU risk management plan (RMP) details the identified and potential risks, and areas of missing information for the AbbVie DAA regimen. Off-label use and use in populations with limited data, including; the elderly (age ≥ 65 years), pediatric patients, patients with renal impairment, patients co-infected with HIV or hepatitis B (HBV), and patients post liver transplant, are also examined. Lastly, product labeling for the AbbVie 3-DAA regimen specifies medications that are contraindicated for use during treatment. To evaluate compliance with the contraindicated medication section of product labeling, this study will also collect and summarize the proportion of patients receiving the AbbVie 2-DAA or 3-DAA regimens who use contraindicated medications.

The HCV-TARGET disease registry is a longitudinal, observational study of patients in a consortium of academic and community settings undergoing HCV therapy which can provide data to address important clinical questions that remain incompletely answered from registration trials. Patients being prescribed an AbbVie regimen outside of a clinical trial will be eligible for enrollment. The TARGET registry will be used to evaluate and characterize ALT elevations and obtain more information regarding off-label use, contraindicated medication use, and data in populations with limited information for the AbbVie DAA regimen in the real world setting. The impact of ALT elevation on outcome of treatment including specific hepatic outcomes will be examined. This proposed study will enhance pharmacovigilance by AbbVie with the results disseminated to regulatory agencies, health care professionals, and communications to the public as appropriate.

Research Question and Objectives:

Primary Objectives:

To evaluate and characterize the clinical impact of ALT elevations in patients who have received the AbbVie 2-DAA or 3-DAA regimen in a real world setting:

- Determine the difference in proportions of clinical outcomes (liver failure, liver transplantation, hospitalization for liver injury, liver decompensation, and all cause death) between patients with and without Grade 3+ ALT elevations and by each grade of ALT elevations (Grades 1, 2, 3, 4) versus no such elevation during treatment through a 6-month follow-up period.
- Determine the proportion of Grade 3+ALT elevations during treatment and the difference in proportions of clinical outcomes during treatment through a 6-month follow-up period between patients with and without Grade 3+ ALT elevations by age, sex, race, cirrhosis status, DAA administration with or without RBV, HCV genotype/subtype, non ethinyl estradiol estrogen-containing medication use, any contraindicated medication use, time interval of Grade 3+ ALT onset (within 2, > 2 – 4, > 4 – 12, and > 12 – 24 weeks), geographic region, response to treatment (SVR_{12}), and duration of treatment (< 12 weeks, 12 – < 24 weeks, 24 weeks). These variables will also be examined by other potential risk factors including baseline ALT, baseline MELD score, HIV co-infection, HBV co-infection, current alcohol use, body mass index (BMI, kg/m^2) and concomitant drug use.
- Determine the difference in proportions of treatment decisions (treatment interruption, discontinuation or completion) between patients with and without Grade 3+ ALT elevations.
- To determine the difference in proportions of clinical outcomes during treatment through a 6-month follow-up period adjudicated by the Expert Hepatic Panel as at least possibly related to treatment between patients with and without Grade 3+ ALT elevations.

Secondary objectives:

To assess the frequency of off-label use in patients who have received the AbbVie 2-DAA or 3-DAA regimen in in a real world setting:

- Use of the DAA regimen in patients with genotypes other than HCV GT1 or GT4.
- Use in other DAA combinations.

To assess the frequency of use of contraindicated medications in patients who have received the AbbVie 2-DAA or 3-DAA regimen in a real world setting:

To evaluate populations with limited data in patients who have received the AbbVie 2-DAA or 3-DAA regimen in a real world setting:

- Patients with renal impairment (creatinine clearance < 60 mL/min),
- Patients aged 65 years or older,
- Patients who are co-infected with HIV or HBV,
- Patients who are post liver transplant, or with moderate hepatic impairment (based on the MELD score),
- Use in patients with prior DAA treatment failure.

Study Design: This study is a prospective, longitudinal observational cohort design which will be conducted using data from the HCV-TARGET disease registry to examine patients who have been treated in a real-world setting with the AbbVie HCV 2-DAA or 3-DAA regimen. This design allows the determination of the differences in clinical outcomes related to hepatotoxicity in patients with ALT elevations and those without ALT elevation identification of associated risk factors, and assessment of the clinical impact of these elevations. The planned enrollment is 4269 patients who will be prospectively enrolled into the HCV TARGET registry and followed for up to 6 months after treatment completion. All data available during treatment and clinical outcomes for 6 months post-treatment will be abstracted and analyzed according to study protocol.
Population: Individuals diagnosed with HCV who have been treated with the AbbVie 2-DAA or 3-DAA regimen in a real world setting. This includes men and women, aged 18 years and older who have been enrolled in the HCV-TARGET registry. The study population will be derived from academic and community centers in the North America, Europe, and Israel. All AbbVie 2-DAA and 3-DAA regimen users in the HCV-TARGET registry will be included regardless of prior treatment status – naïve or treatment experienced, treatment duration with or without ribavirin or other concomitant medications used to treat HCV who meet the admission criteria. Since the frequency of collection of ALT values during treatment and during follow-up will be determined by physician practice styles and patient characteristics, an important inclusion criterion is the collection of baseline and at least one ALT sample during treatment. All patients enrolled in the registry are treated at participating sites per local standard of care.
Variables: Outcome variables include: events of ALT elevation during treatment, treatment disposition (continuation, interruption, discontinuation), liver-related outcomes (no serious outcome or severe/serious hepatic outcome of hepatic failure, liver transplantation, hospitalization for liver injury or drug-induced liver injury, presence of hepatic decompensation events, or death from any cause). The exposure variable is treatment with the AbbVie 2-DAA or 3-DAA regimens.
Data Sources: Anonymized data from the HCV-TARGET: Hepatitis C Therapeutic registry and Research Network – A Longitudinal, Observational registry. The patient data are derived from original medical records, clinic and telephone notes, safety data, and efficacy labs collected during the HCV treatment and follow-up intervals from the referring sites. Enrollment will begin at the signing of the protocol and retrospective data from the beginning of data collection from patients treated with the AbbVie 2-DAA or 3-DAA regimen (since January 2015) will be included and will continue until the required sample size is reached (approximately October 2019). The source documents are abstracted and entered into the central HCV-TARGET database by registry staff. Electronic medical records where available are mapped for transfer directly into the registry database. Demographic, clinical, adverse event, and virologic data are collected through treatment and follow-up. Data quality is continuously monitored.
Study Size: A total sample size of 4269 patients (approximately 43 with a Gr 3+ ALT elevation and 4226 without) will provide a 95% confidence interval width (from lower limit to upper limit) of 6% on the difference in patients with a clinical outcome between those with and without Grade 3+ ALT elevations or a half width (from point estimate to either limit) of 3%.

Data Analysis: For the statistical analysis of the primary objectives, difference of proportions of subjects with each grade of ALT elevation (Grades 1, 2, 3, 4) versus no such elevation and of patients with clinical outcomes and treatment decisions by Grade 3+ ALT elevation versus no such elevation will be reported along with their 95% confidence intervals (CIs). Wilson's score method will be used for computing the CIs. Subgroup analysis of the difference in the proportion of subjects with Grade 3+ elevation versus no such elevation and the difference in proportions of subjects with clinical outcomes according to potential risk factors affecting treatment response included in the primary objective above will be performed. The frequency and proportion of severe hepatic clinical outcomes, individually (hepatic failure or liver transplantation indicated or performed or hepatic decompensation or hospitalization for liver injury or drug-induced liver injury or death from any cause, or no severe liver-related outcome) and as a composite occurring within 6 months of stopping the AbbVie regimen will be compared between those who had each grade of ALT elevations (Grades 1, 2, 3, 4) versus no such elevation within the treatment interval. A sensitivity analysis will be performed comparing the difference of proportion of subjects with severe hepatic clinical outcomes determined by the EHP to be at least possibly related to the treatment with an AbbVie regimen to coded hepatic clinical outcomes in the HCV TARGET database.

The variables included in the analysis of the secondary objectives will be characterized descriptively.

Milestones: The study is planned to commence following approval of the AbbVie 2-DAA and 3-DAA regimens and final approval of the study protocol by the CHMP. It is estimated that following approval of the protocol, data collection will commence, and including patient follow-up, will end by 2019. An interim analysis will be generated in 2018. Study updates on enrollment and data collection will be provided in the PSUR submissions. The final analysis and report will be in 2020.

5.0 Amendments and Updates

None.

6.0 Milestones

Major study milestones and their planned dates are as follows:

Milestone	Planned Dates (Note: Dates will be Modified Based Upon Approval Date)
Start of data collection	March 2016 if protocol approved by February 2016
Registration in the EU PAS register	March 2016 if protocol approved by February 2016
Progress report 1, Feasibility assessment (PSUR)	September 2016
Progress report 2 (PSUR)	March 2017
Interim Report (PSUR)	March 2018
End of data collection	October 2019
Final report of study results	September 2020

7.0 Rationale and Background

Hepatitis C virus (HCV) infection affects persons worldwide and is a leading cause of chronic liver disease and liver-related mortality.[1] Treatment with direct acting antiviral agents without interferon represents a significant advance associated with high cure rates for HCV and without the side-effects associated with interferon. AbbVie's 3-DAA regimen (paritaprevir/r, ombitasvir, dasabuvir) has been developed for treatment of genotype 1 HCV and is used with or without RBV. The regimen includes paritaprevir, a NS3/NS4A HCV protease inhibitor, ombitasvir, a nonstructural NS5A HCV inhibitor, and dasabuvir, a nonstructural protein 5B (NS5B) polymerase inhibitor. Ritonavir (denoted "r") is used as a pharmacokinetic enhancer for paritaprevir and has no anti-HCV activity. AbbVie's 2-DAA regimen (paritaprevir/r, ombitasvir) with RBV is being developed for the treatment of genotype 4 HCV.

Over 2,600 subjects were treated in Phase 2 – 3 clinical trials during development of the 3-DAA regimen. Transient alanine aminotransferase (ALT) Grade 3 (5 × ULN) or higher elevations (Gr 3+ ALT) were observed in approximately 1% of subjects in randomized Phase 2 and 3 clinical trials of AbbVie's 3-DAA HCV treatment regimen. The ALT elevations in these subjects were asymptomatic and generally occurred within the first 4 weeks of DAA treatment. Improvement typically occurred with ongoing DAA treatment with resolution by Post-Treatment Week 4. Paritaprevir/r is a known inhibitor of bilirubin transporters and can cause elevations in total and indirect bilirubin. In addition, RBV can cause elevation in total and indirect bilirubin due to RBV-associated hemolytic anemia. Despite this, the ALT elevations were not synchronous with bilirubin elevations. When they occurred, the ALT elevations occurred after or during resolution of elevations in total (predominantly indirect) bilirubin. There were no clinically significant hepatic-related outcomes related to DAA treatment. Evaluation of these elevations revealed two risk factors for ALT elevations: 1) ethinyl estradiol use and 2) administration of higher doses of paritaprevir/r, which had been previously evaluated in the Phase 2 program (i.e., 200 mg or higher). In the absence of these two identified risk factors (i.e., by excluding paritaprevir/r doses of 200 mg or higher and excluding subjects receiving EE-containing medications) an incidence of Grade 3+ ALT elevations of 0.8% was observed. There was no evidence of an increased risk of ALT elevation among patients with compensated cirrhosis. EE-containing medication use was determined to be a major risk factor for Grade 3+ ALT elevations among subjects who used the 150 mg dose of paritaprevir (Table 1).

Table 1. Stepwise Logistic Regression Analysis of Grade 3+ Serum ALT Elevations in the Expanded Phase 2/3 Analysis Set Excluding Subjects Taking a Higher Dose of Paritaprevir/r (200 mg or Higher)

Variable	Odd Ratio Estimate	95% CI	*P* value
Baseline ALT (U/L)	1.01	(1.01, 1.02)	< 0.001
Baseline BMI (kg/m^2)	0.90	(0.82, 0.99)	0.037
Estrogen use (EE vs. no estrogen)	37.59	(11.19, 126.30)	< 0.001
Estrogen use (other estrogen vs. no estrogens)	2.01	(0.26, 15.39)	0.50

Note: Stepwise logistic regression with significance level of 0.10 for entering and for staying in the model resulted in the choice of the first 3 significant factors. When Estrogen use (other versus no) was then forced into the model it was not significant with an OR = 2.01.

Based on these observations, ethinyl estradiol (EE)-containing medications have been contraindicated with the AbbVie 2-DAA or 3-DAA regimen. Use of non EE estrogens is permitted during therapy. In addition, important signs and symptoms of which patients should be aware of are contained within the Warnings and Precautions section of product labeling.

The incidence rate and risk factors for Gr 3+ ALT elevation in real-world settings remains unknown. This prospective, observational cohort study utilizing a disease registry (HCV-TARGET) is being designed to provide additional characterization of the identified risk of serum ALT elevation and possible risk factors associated with it in a real world setting. In addition, although no serious hepatic outcomes have been linked to these Grade 3+ ALT elevations during clinical trials, this study will also evaluate the clinical impact of these ALT elevations as they may affect treatment duration as well as the occurrence of acute liver outcomes during a 6-month follow-up after cessation of treatment with the AbbVie DAA regimen in a real world setting. All data available during treatment and for 6 months post-treatment will be abstracted and analyzed according to study protocol.

The EU risk management plan (RMP) details the identified and potential risks, and areas of missing information for the AbbVie DAA regimen. Off-label use and use in

populations with limited data, including the elderly (age ≥ 65 years), patients with renal impairment, patients co-infected with HIV or hepatitis B (HBV), and patients post liver transplant may be potential risks. This study will also be used to evaluate the frequency of off-label use of the AbbVie 2-DAA and 3-DAA regimens and to identify frequency of use in populations with limited data.

Lastly, product labeling for the AbbVie 3-DAA regimen specifies medications that are contraindicated for use during treatment. To evaluate compliance with the contraindicated medication section of product labeling, this study will also collect and summarize the proportion of patients receiving the AbbVie 2-DAA or 3-DAA regimens who use contraindicated medications. TARGET is a longitudinal, observational study of patients in a consortium of academic (approximately 38) and community (approximately 13) medical centers undergoing HCV therapy designed to specifically address important clinical questions that remain incompletely answered from registration trials. Patient populations under represented or not included in clinical trials (except pediatrics) as well as those being prescribed anti-HCV therapy outside of a clinical trial, will be eligible for enrollment. Treatment algorithms will follow each site's local standard of care and no specific treatments, assessments, and/or laboratory tests will be dictated by enrollment in HCV-TARGET.

The TARGET registry will be used to evaluate and characterize the impact of ALT elevations on clinical outcomes (liver failure, liver transplantation, hospitalization for liver injury, liver decompensation, and all cause death) and treatment decisions (treatment interruption, discontinuation or completion) and to obtain more information regarding off label use, contraindicated medication use, and use in populations with limited information (including patients who have failed prior DAA treatments) for the AbbVie DAA regimen in the real world setting.

8.0 Research Question and Objectives

Research Question and Objectives

Primary Objective

To evaluate and characterize the clinical impact of ALT elevations in patients who have received the AbbVie 2-DAA or 3-DAA regimen in a real world setting:

- Determine the difference in proportions of clinical outcomes (liver failure, liver transplantation, hospitalization for liver injury, liver decompensation, and all cause death) during treatment through a 6-month follow-up period between patients with and without Grade 3+ ALT elevations and by each grade of ALT elevations (Grades 1, 2, 3, 4) versus no such elevation.
- Determine the proportion of Grade 3+ ALT elevations during treatment and the difference in proportions of clinical outcomes during treatment through a 6-month follow-up period between patients with and without Grade 3+ ALT elevations, by age, sex, race, cirrhosis status, DAA administration with or without RBV, HCV genotype/subtype, non-ethinyl estradiol estrogen-containing medication use, any contraindicated medication use, time interval of Grade 3+ ALT onset (within 2, > 2 – 4, > 4 – 12, and > 12 – 24 weeks), geographic region, response to treatment (SVR_{12}), and duration of treatment (< 12 weeks, 12 – < 24 weeks, 24 weeks). These endpoints will also be examined by other potential risk factors including baseline ALT, baseline MELD score, HIV co-infection, HBV co-infection, current alcohol use, body mass index (BMI, kg/m^2) and concomitant drug use.
- Determine the difference in proportions of treatment decisions (treatment interruption, discontinuation or completion) between patients with and without Grade 3+ ALT elevations.
- To determine the difference in proportions of clinical outcomes during treatment through a 6-month follow-up period adjudicated by the Expert Hepatic Panel as at least possibly related to treatment between patients with and without Grade 3+ ALT elevations.

Secondary Objectives

To assess the frequency of off-label use in patients who have received the AbbVie 2-DAA or 3-DAA regimen in in a real world setting:

- Use of the DAA regimen in patients with genotypes other than HCV GT1 or GT4.
- Use in other DAA combinations.

To assess the frequency of use of contraindicated medications in patients who have received the AbbVie 2-DAA or 3-DAA regimen in a real world setting:

To evaluate populations with limited data in patients who have received the AbbVie 2-DAA or 3-DAA regimen in a real world setting:

- Patients with renal impairment (creatinine clearance < 60 mL/min),
- Patients ≥ 65 years,
- Patients who are co-infected with HIV or HBV,
- Patients who are post liver transplant, or with moderate hepatic impairment (based on the MELD score),
- Use in patients with prior DAA treatment failure.

9.0 Research Methods

9.1 Study Design

This is a prospective, observational cohort study of patients with HCV treated with the AbbVie 2-DAA or 3-DAA regimens and enrolled in an HCV disease registry with patients from both the USA and outside the US (Europe, Canada, Israel). This design allows the determination of the differences in clinical outcomes related to hepatotoxicity between patients with ALT elevations and those without ALT elevations, identification of associated risk factors, and assessment of the clinical impact of these elevations. The longitudinal design also allows for the examination of the clinical impact on treatment

course as well as for exploring potential risk factors for the risk of the clinical events of interest. Patients are to be followed in TARGET for SVR_{12}, potential relapse, and the clinical outcomes of interest for 6 months after the end of treatment. Anonymized patient records from the HCV-TARGET registry will be the source of the cohort.

9.2 Setting

The HCV-TARGET: Hepatitis C Therapeutic Registry and Research Network is a consortium of 44 academic and 17 community medical centers in North Americas (including 1 site in Toronto, Canada), Europe (4 centers) and Israel (which also follows the EU SmPC) – where HCV patients are evaluated and treated with antiviral therapies. HCV treatment at participating centers is administered according to the local standard of care. Regimen selection is made by the patient's health care provider. Data from sequentially enrolled patients treated with the AbbVie regimens will be captured from medical records and entered into a central database by registry staff. In addition to medical history, clinical and laboratory evaluations routinely performed in the management of HCV treatment are collected. These evaluations and clinical management are recorded as part of a patient's medical record. Site staff will de-identify and submit all clinic notes, nursing/staff telephone notes, evaluations and lab results collected to monitor the HCV baseline condition and treatment safety and efficacy to the trained TARGET Centralized Chart Data Abstraction team in their respective country core. During this observational study, all available safety and efficacy data submitted in the patient's de-identified medical records will be recorded in the database, regardless of treatment regimen, dosing, or duration. The schedule of observations is a guide for the HCV treatment data that are collected in HCV-TARGET and is provided in Table 2. HCV treatment is not dictated by the protocol. Dosing, treatment/side effect management, and duration will be at the discretion of the provider according to the site standard of care.

As of 01 December 2015, the TARGET registry had enrolled 452 patients administered the AbbVie 2-DAA or 3-DAA regimen, of whom 190 were from outside the US (42%). The distribution of enrolled patients from outside the US was as follows: Canada, 3;

Germany, 106; and, Israel, 81. In this study, the goal is to enroll at least 10% of the total sample size from the EU (approximately 400 patients).

Criteria for the selection of patients are as follows:

Inclusion Criteria:

- Anonymized records of consecutive patients in the HCV-TARGET database who are at least 18 years of age, males and females, all races and ethnicities.
- Have a diagnosis of hepatitis C virus infection and be treated with the AbbVie 2-DAA or 3-DAA regimen.
- Have at least one dose of the AbbVie 2-DAA or 3-DAA regimen outside of a clinical trial.
- Have a baseline ALT laboratory value as defined by HCV-TARGET prior to start of the AbbVie 2-DAA or 3-DAA regimen and a least one ALT laboratory value after the date of the start of the regimen and during the treatment interval.
- Treated for hepatitis C infection at a site in the US, EU, Canada, or Israel.

Exclusion Criteria:

- Had been treated with AbbVie's 2-DAA or 3-DAA regimen during AbbVie's clinical trials for hepatitis C.
- Receiving pegylated interferon.

Enrollment will begin at the signing of the protocol and will continue until the required sample size is reached (approximately October 2019). Each eligible patient will be followed for 6 months after treatment for the assessment of the presence or absence of study hepatic outcomes as well as the other clinical data defined in this protocol. Retrospective data from the patients enrolled in TARGET and treated with an AbbVie HCV regimen prior to initiation of this protocol, but meeting all eligibility criteria, will also be eligible for inclusion in the study from the beginning of data collection (January 2015).

The HCV-TARGET registry does not contain data in pediatric patients. The pediatric population is currently primarily treated through enrollment in HCV clinical trials. Only adult patients currently not on clinical trials are enrolled in the HCV-TARGET Registry.

Table 2. Schedule of Selected Observations (Derived from TARGET 2.0 Protocol Amendment 3, 24 September 2013)

Assessments	Baseline	ON TREATMENT OBSERVATIONS Through Follow-Up	SVR
Informed Consent	X		
Demographics	X		
Medical History/Co-Morbid Conditions	X		
Fibrosis Staging – All Methods Applicable	X		
Prior HCV Treatment Response, if Applicable	X		
IL-28B Genotype	X		
HCV Genotype (Most Recent Genotyping)	X		
CBC	X	Submit ALL CBC results/reports collected during treatment including at least one post-treatment evaluation.	
Serum Chemistries	X	Submit ALL chemistries to monitor patient health and safety collected including at least one post-treatment evaluation.[a]	
HCV RNA	X	Submit ALL HCVRNA results collected during treatment and follow-up until SVR outcome is determined.	X[b]
HCV Medications	X	Submit ALL clinic/telephone notes during treatment including at least one post treatment evaluation. Medication data to be abstracted from notes.	
Concomitant Medications	X	Submit ALL clinic/telephone notes recorded during treatment including at least one post-treatment note – concomitant medication data to be abstracted from notes. To be supplemented by data enrichment for complete concomitant medication information.	
Adverse Events		Submit ALL clinic/telephone notes recorded during treatment including at least one post-treatment note – adverse event data to be abstracted from notes.[c]	
Year of Transplant (for Post-Transplant Subjects Only)	X		

Table 2. Schedule of Selected Observations (Derived from TARGET 2.0 Protocol Amendment 3, 24 September 2013) (Continued)

a. Lab results documenting hepatic/organ insufficiency or failure OR other events of special interest may be requested from the site after Week 4 follow-up to fully characterize HCV treatment safety outcomes.

b. May be performed anytime at or beyond the Week 12 post-treatment time point. In instances where patient is identified with virologic failure – NON-RESPONSE, VIROLOGIC BREAKTHROUGH, or RELAPSE, the HCV RNA that confirms that virologic failure outcome will satisfy SVR, even if collected prior to 12 weeks post-treatment.

c. Lab results documenting hepatic/organ insufficiency or failure OR other events of special interest may be requested from the site after Week 4 follow-up to fully characterize HCV treatment safety outcomes.

9.3 Variables

The variables included in this study are all derived from the HCV-TARGET database. The variable definitions and their measurements are described below.

9.3.1 Outcomes Variables

The clinical impact of an AbbVie DAA regimen will be examined in both terms of the clinical outcomes (the frequency of severe hepatic events occurring during treatment and within 6-months following treatment and incidence of Gr 3+ ALT during the treatment interval) as well as the impact upon clinical decision-making (treatment interruption, discontinuation or completion). All data available during treatment and for 6 months post-treatment will be abstracted and analyzed according to study protocol.

Severe Hepatic Outcomes

Severe hepatic events are those occurring within the AbbVie treatment interval or within 6 months following treatment cessation:

- Hepatic failure
- Liver transplant
- Hospitalization for liver injury or drug-induced liver injury
- Hepatic decompensation
- Death due to any cause

Severe hepatic events are defined as follows:

- Hepatic failure will be defined as any patient who has an event coded with the MedDRA preferred terms of acute hepatic failure, hepatic failure, hepatorenal failure, or subacute hepatic failure (regardless of whether they were hospitalized).
- Hepatic transplant will be defined as any patient who has an event coded with the MedDRA preferred term liver transplant or renal and liver transplant.
- Hospitalization for liver injury or drug induced liver injury will be defined as any patient who is hospitalized for an event meeting the standardized MedDRA query (SMQ) search criteria of Drug-related Hepatic Disorders (severe events only).
- Hepatic decompensation during therapy will be defined as any patient who has a new onset or worsening from baseline of any of the following: 1) ascites, 2) variceal hemorrhage, or 3) hepatic encephalopathy (Source: ENCEPP Protocol WEUSKOP 7135), using the MedDRA preferred terms of ascites, variceal hemorrhage, or hepatic encephalopathy.
- Death due to any cause.

Incidence of Gr 3+ ALT Elevation During Treatment

Alanine aminotransferase (ALT) laboratory values will be evaluated in units per liter. Common Terminology Criteria for Adverse Events (CTCAE) criteria[2] will be used for grading and laboratory values will be categorized into ALT Grades as follows:

Normal/≤ Reference units per liter
Grade 1/> ULN – 3 × ULN
Grade 2/> 3 – 5 × ULN
Grade 3/> 5 – 20 × ULN
Grade 4/> 20 × ULN

Note: ULN is based on the reference intervals of 33 U/L for adult females and 45 U/L for adult males if not provided for the laboratory used for a patient.[3]

A Grade 3+ ALT elevation refers to alanine aminotransferase value > 5.0 × ULN.

A baseline ALT laboratory value is the value occurring prior to the start of the AbbVie 2-DAA or 3-DAA regimens, using the value closest to or on the start date of the AbbVie 2-DAA or 3-DAA Regimen. Assignment of an ALT grade during treatment and will be based upon the highest actual laboratory value after the day of the start of the AbbVie regimen though 2 days after the end of the AbbVie regimen. For individuals who have an ALT value at baseline categorized at Gr 3+, a Gr 3+ during treatment will be assigned only if there is a decreased ALT lab value before the identification of a Gr 3+ during treatment with the AbbVie 2-DAA or 3-DAA regimens or if the Gr 3+ value is higher than baseline.

HCV-TARGET Staff either abstract ALT values and other pertinent laboratory values or they are entered into the TARGET database through an electronic data importer. The number of patients for each treatment interval who had undergone liver enzyme and liver function testing will be documented. ALT values are not measured at a centralized lab because data in TARGET are from a variety of real world settings. Therefore, if an upper limit of normal (ULN) is provided by the lab, this will be utilized. If the ULN is not collected or provided, then standard reference ranges for ULN based on the normal ranges provided by Laboratory Corporation of America (2013) will be utilized (See Annex 1, ABBV-PASS-2 for both ALT cut-offs and CTCAE grading and applicable references).

Clinical Decision Making

Clinical decision making is defined as the status of treatment duration and categorized as:

- AbbVie 2-DAA or 3-DAA regimen completed according to the labelled recommendation for the specific genotype and cirrhosis status of each patient
- AbbVie 2-DAA or 3-DAA regimen interrupted
- AbbVie 2-DAA or 3-DAA regimen discontinued

9.3.2 Exposure Variable

Exposure is defined as the appropriate regimens and treatment durations for the AbbVie 2-DAA and 3-DAA have been determined for each patient population sub genotype and

cirrhosis status according to the Summary of Product Characteristics (SmPC). The AbbVie 2-DAA and 3-DAA regimens allow for both naïve and treatment-experienced patients to be treated. Start and stop dates recorded in the HCV-TARGET database are those listed on the medical record. Exposure will be measured by the number of days on treatment (treatment time interval – days of treatment interruption) and categorized as (< 12 weeks, 12 – < 24 weeks, 24 weeks).

9.3.3 Other Variables

Demographics: Year of birth, Sex, Race, Ethnicity.

Clinical factors: Weight, Height (BMI will be calculated in database from weight and height recorded in the medical record), current alcohol use and smoking.

HCV related factors: HCV RNA levels (The baseline value will be used to calculate change in HCV RNA during therapy); HCV genotype and sub genotype; IL28B genotype (any historical result, if available); Prior treatment status will be ascertained as either naïve to therapy or treatment-experienced, post-liver transplant or moderate hepatic impairment (based on MELD score); Response to treatment will be assessed by sustained virologic response 12 weeks post dosing (SVR_{12}: HCV RNA < lower limit of quantification on or after Post Treatment Day 64); Use of the DAA regimen in patients with genotypes other than HCV GT1 or GT4; Use of other DAA regimens concurrent with an AbbVie regimen.

Comorbidities: HIV, HBV, Depression, Diabetes mellitus, Cardiovascular or cardiac disease/conditions, Lipid disorders, Neurological disorders, pulmonary diseases/conditions.

Laboratory values: Complete blood cell count including platelets; Measures of hepatic disease and function: (ALT, AST, total and direct bilirubin, albumin, prothrombin time/INR); Measures of renal disease and function: creatinine, creatinine clearance.

Medications: All prescription medications used at baseline including the indication for use. A detailed list of the ethinyl estradiol (EE) and non-EE hormones that will be abstracted and categorized is in Annex 1, ABBV-PASS-1. A detailed list of the contraindicated medications is listed in Annex 1, Template Table 2.

Other variables: Cirrhosis (absence/presence) defined by biopsy and/or a combination of clinical, laboratory, and imaging criteria established a priori. Patients were determined to have cirrhosis if they had: (1) evidence of stage 4 fibrosis by liver biopsy at any time prior to therapy; or (2) evidence of stage 3 fibrosis by liver biopsy at any time prior to therapy with any of the following criteria: platelets count < 140,000 per µL, presence of oesophageal varices on oesophagogastroduodenoscopy, evidence of cirrhosis and/or portal hypertension and/or of ascites by imaging studies, FibroSure test or equivalent, compatible with stage 4 fibrosis; or (3) in the absence of liver biopsy, any two of the following criteria: platelet count < 140,000 per µL, presence of oesophageal varices on oesophagogastroduodenoscopy, evidence of cirrhosis and/or portal hypertension and/or ascites by imaging studies, FibroSure test or equivalent, compatible with stage 4 fibrosis.[4] For subjects with an outcome of hepatic decompensation during treatment, collection of the baseline Child-Pugh status will be attempted.

Coagulation disorders; Prior/Current Malignancies including Hepatocellular carcinoma; Chronic skin disease, including dermatologic extra hepatic manifestation of chronic hepatitis C; Pre-existing complications of liver disease if present or being treated at baseline (ascites, encephalopathy, esophageal varices); Prior kidney transplant (date); Prior liver transplant (date).

9.4 Follow-Up

Follow-up time intervals will be computed from the day after the last dose of the AbbVie 2-DAA or 3-DAA regimens through 6 months post completion of the treatment regimen or last dose for those individuals not completing the regimen. This follow-up interval was determined to allow for adequate time for capture of severe hepatic outcomes which may

be associated with an ALT elevation. All data available for 6 months post-treatment will be abstracted and analyzed according to study protocol.

9.5 Data Sources

The source of the data will be HCV-TARGET: Hepatitis C Therapeutic Registry and Research Network – A Longitudinal, Observational Study. The HCV-TARGET database is derived from a longitudinal, observational study of patients undergoing HCV-therapy. It is available as an anonymized database for data analysis. HCV-TARGET is an international cooperative academic consortium of principal investigators from academic institutions and community-based sites affiliated with the academic sites in geographic proximity. The Clinical Coordinating Center (CCC) resides at the University of Florida (PI: David R. Nelson, MD) and the Data Coordinating Center (DCC) resides at the University of North Carolina at Chapel Hill (PI: Michael W. Fried, MD). HCV-TARGET will provide unique opportunities to engage networked physician teams in evidence-based evaluation of HCV therapy and to involve these teams in the conduct of clinical research. The HCV-TARGET Registry abstracts a large amount of information from medical records and electronic laboratory data. The categories of variables are: demographic, clinical, medical history, alcohol and tobacco use, prior HCV treatment types and response, IL28B/HCV genotypes, fibrosis staging, laboratory testing with dates and values (CBC, chemistry, INR, HCV RNA results), current treatment regimen and any associated adverse events and their outcome(s) and resolution or death, concomitant medications, transfusions, and post-treatment liver transplant.

The HCV Treatment related data collected in HCV-TARGET are: All anti-HCV therapies used (product names for each anti-HCV product used in the treatment regimen); Doses (starting doses of all products); Dose changes (any adjustments during treatment, if applicable); Reasons for dose adjustments and/or premature discontinuation; Treatment start and end dates; Treatment status (ongoing, complete, interrupted, prematurely discontinued).

Enrollment will begin at the approval of the protocol and will include data retrospectively compiled from patients who were treated with the AbbVie 2-DAA or 3-DAA regimens since January 2015 and will continue until the required sample size is reached (approximately October 2019).

The HCV-TARGET Registry will characterize the population of HCV patients treated with any anti-HCV regimen outside of a clinical trial. On-treatment visits will coincide with local standard of care visits for participants in HCV-TARGET. Sites submit de-identified medical records to document HCV treatment safety and efficacy. To support comprehensive centralized chart data abstraction of HCV treatment safety and efficacy, all on-treatment clinic notes and nursing/staff telephone notes are submitted for abstraction. Clinical medication and laboratory data results must have been collected on or before the HCV treatment start date to be considered baseline. Subsequent laboratory results collected will be those closest to the treatment date.

For the AbbVie DAA products, appropriate regimens and treatment durations have been determined for each patient population and are included in all SmPCs according to HCV subgenotype and cirrhosis status. Treatment time intervals will be computed from the date of the first dose of the AbbVie DAA Regimen to the date of the last dose. In the case of interrupted doses, the date the treatment was interrupted and the date the treatment resumed will be abstracted.

Because the current TARGET registry data abstraction process does not contain the level of specificity required for all the variables in the proposed study, registry procedures will abstract additional information required for the proposed study. HCV-TARGET will enhance data collection where more detailed data are required for the proposed study such as for the specific names of hormones and their coding and the External Hepatic Panel (EHP) reviews. The process is referred to as "enriched" TARGET.

Specifically, the enriched abstraction of additional detail for medications which are contraindicated for use with the AbbVie 2-DAA or 3-DAA treatment regimens will be performed as below.

- A list of medications contraindicated for use with the AbbVie regimen will be used for comparison to a patient's list of concomitant medications; if one or more contraindicated medications are on the patient's list, it will trigger a query to sites for start and stop dates of the medication(s) (See Annex 1, Sample Template Table 2 and Sample Template Table 3).
- Based on start and stop dates of the AbbVie regimen, it will be determined if the contraindicated medication was taken during treatment with the AbbVie regimen, or stopped prior to treatment, or initiated after treatment completion.
- Since medications containing ethinyl estradiol (EE) are contraindicated with the AbbVie DAA regimen, if a medication is categorized as an estrogen, sites will be queried not only for start and stop dates, but also for the specific type of estrogen used. Determination of EE versus non-EE versus unknown will be made using this additional information. To aid in the abstraction and classification process, the "Guide for Abstractors: Estrogen Medication Classification," was developed and is displayed in Annex 1, ABBV-PASS-1.

TARGET registry personnel will set up both a manual and automatic query process for the determination of contraindicated medication use. All contraindicated medications are programmed into system queries so when contraindicated medications are abstracted, a flag will be triggered. This flag will go to the sites for them to confirm the use of contraindicated medications and will go into the database for analysis of the primary objective by this flag. In addition, the abstractors have been given a list of contraindicated medications against which all concomitant medications will be checked during abstraction.

Another area of specific focus of chart abstraction will be information on specific hepatic outcomes of interest (hepatic failure, hospitalization for a liver injury or drug-related liver injury, liver transplantation, hepatic decompensation, deaths from any cause) reported to have occurred within 6 months after the last dose of an AbbVie regimen.

An External Hepatic Panel (EHP) will plan to meet up to 4 times a year (including 2 times which are to be aligned with database lock of the Periodic Safety Update Report [PSUR]). They will review all severe hepatic outcomes of interest as described in the EHP Draft

Charter (Annex 1, ABBV-PASS-4). Sites with patients meeting the criteria for review by the EHP will be queried by HCV-TARGET to obtain additional relevant information required for EHP review. The primary role of the Expert Hepatic Panel is to evaluate hepatic outcomes from patients in this TARGET protocol and provide Drug Induced Liver Injury Network (DILIN) causality as to whether the AbbVie DAAs caused the hepatic outcome. This will occur by an assessment of available information from patients, including any information on all available HCV RNA data. A sensitivity analysis of the primary efficacy analysis will determine the difference in proportions of clinical outcomes adjudicated by the Expert Hepatic Panel as at least possibly related to treatment between patients with and without ALT elevations, particularly Gr 3+.

9.6 Study Size

The computation of sample size is based upon the primary objective, to determine the difference in proportions of severe hepatic clinical outcomes between patients with and without Grade 3+ ALT elevations during treatment through a 6-month follow-up period. The incidence of Gr 3+ ALT elevation is based upon data from AbbVie Phase 2 and 3 trials. There were no severe hepatic outcomes observed in these clinical trials. The estimation of the incidence of severe hepatic outcomes among persons with chronic hepatitis C was derived from a report of Hepatitis C in the UK.[5]

If we assume that 1% of the patients will have a Grade 3+ ALT elevation and 1% of patients (both with and without a Grade 3+ ALT elevation) will have a serious hepatic event, then a total sample size of 4269 patients (approximately 43 with an ALT elevation and 4226 without) will provide a 95% confidence interval width (from lower limit to upper limit) of 6% on the difference in patients with a clinical outcome between those with and without Grade 3+ ALT elevations or a half width (from point estimate to either limit) of 3%.

The HCV-TARGET investigators report that as of 28 October 2015, 5274 patients have been entered in the registry database regardless of previous or current treatment status. Approximately 300 HCV patients per month have been enrolled regardless of treatment or

HCV severity from 55 sites. Each site enrolls about 50 – 250 patients per year. Enrollment into the AbbVie Regimen during Phase 2 and 3 trials was approximately 97 patients per month. Based upon AbbVie's sample size estimates and optimal uptake of an AbbVie DAA Regimen in in HCV-TARGET, it is anticipated that an adequate sample for the proposed study will be enrolled within a 44-month timeframe.

9.7 Data Management

Several clinical and laboratory evaluations are routinely performed in the management of HCV treatment. These evaluations and clinical management are recorded as part of a patient's medical record. Staff at the referring clinical sites de-identify and submit all clinic notes, nursing/staff telephone notes, evaluations and lab results collected to monitor the HCV baseline condition and treatment safety and efficacy to the trained Centralized Chart Data Abstraction (CCDA) team in their respective country core. During this observational study, all available safety and efficacy data submitted in the patient's de-identified medical records are recorded in the database, regardless of treatment regimen, dosing, or duration.

A dedicated web-based Research Electronic Data Capture (REDCap) data management software package, which is utilized extensively throughout the national Clinical and Translational Science Award (CTSA) program and beyond, will be implemented and supported by the TraCS Institute Data Management team for the HCV-TARGET registry program. The "FDA regulation 21 CFR Part 11" details recommendations for electronic records and electronic signatures. According to this regulation, systems generating electronic records which are to be considered equivalent to paper records, should be validated, produce a time-stamped audit trail of data modifications, require electronic signatures and restrict access to authorized users. The REDCap based data management system implemented for the HCV-TARGET registry is being adapted to the specified FDA recommendations, and annual internal audits will be performed to ensure compliance is achieved. HCV-TARGET is also Clinical Data Interchange Standards Consortium (CDISC) compliant allowing transfer of electronic data with the FDA.

9.8 Data Analysis

The characteristics of enrolled HCV patients will be summarized with proportions or means as appropriate, with corresponding measures of variability. The demographic and baseline characteristics statistically summarized include: Age (birth year), Sex, Race, Ethnicity, Body mass Index, Current smoking, Current alcohol use, Geographic region, Baseline HCV RNA levels, HCV genotype and subtype, Fibrosis stage, MELD score, Hematology values, Serum chemistries of hepatic and renal function, Previous HCV treatments and response, History of/or current cirrhosis, Medical comorbidities. The number and percentage of subjects with ALT values in treatment Weeks 0 – 2, > 2 – 4, > 4 – 12, and > 12 – 24 and post treatment Weeks 0 – 4, > 4 – 12, and > 12 – 24 will be summarized. Data will be pooled across geographic region, but may be examined by country depending on the size of samples in the countries. A complete list of the baseline characteristics along with their measurement categories is displayed in Annex 1, ABBV-PASS-3, Template Table 1.

Concomitant drug use at baseline will be descriptively summarized by drug class. Hormone preparations will be grouped as appropriate (such as, non-ethinyl estradiol estrogen use, ethinyl estradiol use, no estrogen use) and descriptively summarized. Subgroup analysis by non-ethinyl estradiol estrogen-containing medication use and any contraindicated medication use are included in the primary objectives above. Contraindicated medications used will be descriptively summarized individually and by drug class. Groupings by class may be considered for examination of risk factors.

The analysis of any individual concomitant or contraindicated drug or drug class as a covariable in a multivariate model for sensitivity analysis will depend upon the frequency of patients using a drug.

The primary endpoints are:

- the difference in proportions of patients with severe clinical outcomes (liver failure, liver transplantation, hospitalization for liver injury, liver decompensation, and all cause death) during treatment through a 6-month

follow-up period between patients with and without Grade 3+ ALT elevations and by each maximum Grade (1, 2, 3, or 4) ALT elevation versus no such elevation.

- the proportions of patients with and without Grade 3+ ALT elevations during treatment by age, sex, race, cirrhosis status, DAA administration with or without RBV, HCV genotype/subtype, non ethinyl estradiol estrogen-containing medication use, any contraindicated medication use, time interval of Grade 3+ ALT onset (within 2, > 2 – 4, > 4 – 12, and > 12 – 24 weeks), geographic region, response to treatment (SVR_{12}), and duration of treatment (< 12 weeks, 12 – < 24 weeks, 24 weeks), baseline ALT, baseline MELD score, HIV co-infection, current alcohol use, body mass index (BMI, kg/m^2) and concomitant drug use.
- the differences in proportions of patients with severe clinical outcomes during treatment through a 6-month follow-up period between patients with and without Grade 3+ ALT elevations, by age, sex, race, cirrhosis status, DAA administration with or without RBV, HCV genotype/subtype, non-ethinyl estradiol estrogen-containing medication use, any contraindicated medication use, time interval of Grade 3+ ALT onset (within 2, > 2 – 4, > 4 – 12, and > 12 – 24 weeks), geographic region, response to treatment (SVR_{12}), and duration of treatment (< 12 weeks, 12 – < 24 weeks, 24 weeks), baseline ALT, baseline MELD score, HIV co-infection, current alcohol use, body mass index (BMI, kg/m^2) and concomitant drug use.
- the differences in proportions of patients completing, discontinuing or interrupting treatment will be calculated between patients with and without Grade 3+ ALT elevations.
- the difference in proportions of patients with clinical outcomes during treatment through a 6-month follow-up period adjudicated by the Expert Hepatic Panel as at least possibly related to treatment between patients with and without Grade 3+ ALT.

The difference in proportions of patients with each severe hepatic clinical outcome (hepatic failure or liver transplant indicated or performed or hepatic decompensation or hospitalization for liver injury or drug-induced liver injury or death from any cause, or no

severe liver-related outcome) and any of the severe hepatic outcomes occurring during treatment or within 6 months of stopping the AbbVie regimen will be calculated between those who had a Gr 3+ ALT elevation and those who did not have a Gr 3+ ALT elevation.

Similarly for each of the subgroups in the second primary endpoint, the difference in proportions of subjects with each and any severe hepatic clinical outcome will be calculated between those who had a Gr 3+ ALT elevation and those who did not have a Gr 3+ ALT elevation. Similarly for each grade of ALT elevation, the outcomes of interest will be compared between those that had at least that grade of ALT elevation or higher, and those that did not.

The proportion of patients with at least maximum ALT elevations (Grades 1, 2, 3, 4) during treatment and the difference in proportions of patients with severe hepatic clinical outcomes between patients with at least each ALT Grade (1, 2, 3, or 4) elevation versus no such elevation will be calculated along with 95% confidence intervals using Wilson's score method for a single proportion and a difference in proportions, respectively.

The proportion of patients with Grade 3+ ALT elevations during treatment will be examined for all factors listed in the fourth primary endpoint will be calculated along with 95% confidence intervals using Wilson's score method for a single proportion.

A sensitivity analysis of the first primary endpoint will be performed comparing the difference of proportion of subjects with severe hepatic clinical outcomes determined by the EHP to be at least possibly related to the treatment with an AbbVie regimen to coded hepatic clinical outcomes in the HCV TARGET database.

Additional sensitivity analyses of the first primary endpoint will be performed using the difference in the number of subjects with clinical outcomes per patient days of exposure and per patient days of follow-up in the study.

The difference in proportions of subjects completing, discontinuing or interrupting treatment will be calculated between those who had had a Gr 3+ ALT elevation and those who did not have a Gr 3+ ALT elevation.

The difference of proportions of patients with clinical outcomes and treatment decisions between those will and without Gr 3+ ALT elevations will be reported along with their 95% confidence intervals (CIs). Wilson's score method will be used for computing the CIs.

The secondary endpoints are

- the frequency of patients with off-label use of the AbbVie 2-DAA or 3-DAA regimen in in a real world setting:
  - use of the DAA regimen in patients with genotypes other than HCV GT1 or GT4.
  - use in combination with other DAAs.
- the frequency of patients using each and any contraindicated medication during treatment with the AbbVie 2-DAA or 3-DAA regimen in a real world setting:
- the frequency of patients who have received the AbbVie 2-DAA or 3-DAA regimen among populations with limited data in patients in a real world setting:
  - patients with renal impairment at baseline (creatinine clearance < 60 mL/min),
  - patients aged 65 years or older years at baseline,
  - patients who are co-infected with HIV or HBV,
  - patients who are post liver transplant, or with moderate hepatic impairment (based on the MELD score) at baseline,
  - patients with prior DAA treatment failure.

Among patients administered an AbbVie 2 DAA or 3 DAA regimen, the number and proportions of subjects in the patient subgroups of off-label use, using each and any contraindicated medication, or in population with limited data (fifth, sixth and seventh secondary endpoints listed above) will be calculated.

Subgroup analyses will examine the impact of potential confounding variables and effect modifiers and are included in the primary or secondary objectives above. The results of these analyses will guide the selection of variables used in the multivariate logistic regression sensitivity analyses. Strategies for determining exposures, outcomes and other variables relevant to the objectives are described in the variables Section 9.3 above. The TARGET data abstraction protocol provides for granularity of information concerning exposure to a treatment regimen including start and stop dates and reasons for any treatment stop or interruptions. However, the multiple logistic regression analysis of serious hepatic clinical outcomes with Grade 3+ ALT elevation (yes/no) and all other stratification factors included in the primary objectives determined to be statistically significant will be attempted as a sensitivity analysis. It will not be used as the primary analysis as separation or quasi-separation of the model is likely to occur when many factors are included when the outcome variable is of low frequency.

9.8.1 Handling of Missing Data

Procedures are used by HCV-TARGET staff to ensure the completeness of data abstracted. A review of the periodic data reports provided by HCV-TARGET for other DAAs affirms this.

Only subjects who have a pre-treatment ALT measurement and a post-baseline ALT measurement will be included in the study to ensure the possibility of capturing an ALT elevation post baseline for all patients. The number of patients excluded using this criterion is expected to be small, and the proposed sample size will be met excluding these patients.

To ensure that excluding subjects without a pre-treatment and post-baseline ALT value doesn't introduce significant bias into the study, the subjects in the HCV-TARGET database who have not met the study criteria but who have received at least one dose of an AbbVie DAA regimen will be summarized and compared to those in study with respect to age, sex, baseline comorbidities, prior treatment and response, and liver severity.

Because frequency of collection of laboratory data is determined by physician practice styles and patient characteristics, the frequency of collection ALT values during treatment and during follow-up will vary. Thus, the number of subjects with ALT values in treatment Weeks 0 – 2, > 2 – 4, > 4 – 12, and > 12 – 24 and post treatment Weeks 0 – 4, > 4 – 12, > 12 – 24 will be summarized. As the majority of ALT elevations in clinical trials with the AbbVie regimen occurred during the first 4 weeks, sensitivity analyses of the primary efficacy analysis will determine the difference in proportions of clinical outcomes between patients missing ALT values during treatment Weeks 0 – 4 and those with ALT elevations during treatment Weeks 0 – 4 and with those without ALT elevations during treatment Weeks 0 – 4.

All potential confounding variables and effect modifiers will be examined for their completeness. For any variable with more than 10% missing data, a sensitivity analysis of the primary efficacy analysis will determine the difference in proportions of clinical outcomes between patients with and without ALT elevations by that variable with a category for missing data.

Clinical outcomes will be collected in all patients (including patients without ALT elevations).

Also, determination of any pattern, cause, or mechanism of missingness may be performed and guided by methods outlined in Graham 2009.[6]

9.9 Quality Control

HCV-TARGET has standardized data collection tools, study monitoring, and protocol implementation in order to increase the efficiency and minimize costs associated with performing clinical research. To help minimize the frequency of errors, the Data Manager will conduct regular conference calls with the Clinical Monitoring and Abstraction Core staff to discuss any consistently observed deficiencies in the use of the data management system. The CRA will maintain regular contact with the Central Data Abstraction Services (CDAS) staff and will address identified deficiencies. Also, the provision of

timely data quality reports is an important aspect of the Data Management function. In addition to documenting exemplary performance, these reports provide a basis for setting goals for high-quality data collection, and for tracking progress towards achieving those goals. Data queries will be generated by the Data Manager or CRA in order to identify problems on an on-going basis. Such data checks include, but are not limited to:

- Frequencies on selected variables by CDAS, to identify differences in the application or interpretation of study protocol or abstraction conventions;
- Tabulations and listings of incomplete or inconsistent responses on data collection forms; tabulations and listings of expected forms not received in a timely manner; and tabulations of clinical center error rates in data entry;
- Analyses of digit preferences for clinical measurements (e.g., blood pressure, weight, height) and other evidence suggesting inadequate or erroneous data entry; and
- The collection of repeated measures for quality control purposes as selectively implemented.

The HCV-TARGET registry team commissions qualified resources to conduct monitoring of the data. Clinical site visits and data monitoring are performed in accordance with the Clinical Monitoring Plan (CMP) Monitors will inspect the operations to ensure that:

- The protocol is followed and implemented in compliance with Good Clinical Practices;
- Accurate and complete records are maintained;
- Staff are trained, certified, and are performing the agreed-upon activities and not delegating to other unspecified staff.

All monitoring activities are expected to be completed with a written report. The report will summarize the findings and highlight all recommendations and action items.

9.10 Limitations of the Research Methods

The main outcome of this study is serious hepatic outcomes and these outcomes will be collected for all patients receiving the AbbVie 2-DAA or 3-DAA regimens. Genotype is not expected to impact the occurrence of hepatic outcomes. In addition, the study will include serious hepatic outcomes through 6 months post DAA dosing, regardless of DAA dosing duration. Thus, follow-up for hepatic outcomes will be consistent regardless of treatment duration. AbbVie acknowledges that the majority of sites in the TARGET disease registry are located in the US. However, amongst patients in the US, the majority are HCV genotype 1, similar to patients in the EU. HCV genotype 1 subtype differs between the US and EU, so patients captured in TARGET would predominantly (~70%) be HCV genotype 1a compared to those who may be enrolled in the EU who would be approximately 50% HCV genotype 1b.[1] HCV genotype 1 is expected to form the majority of genotypes reflected in TARGET and is believed to be representative of the EU population. Nonetheless, analyses by subgroups; including, genotype, subgenotype, duration of treatment, administration with or without RBV, and geographic region will be explored to determine if any differences could impact the interpretation of the analysis of the primary and secondary objectives.

Due to the nature of observational study conducted in real world clinical practice studies, collection of all ALT measurements through a centralized laboratory is not warranted and not feasible. ALT measurements from all patients will be collected through routine practices from local laboratories. Analysis of data, including laboratory data analysis from the TARGET database has been used for publication purposes and has been accepted in peer reviewed journals and presented at international meetings both in the US and EU.[4,7] The sponsor will compare the ALT values to standardized reference level upper limits of normal for males and females regardless of normal range at the laboratory from which the values were obtained to minimize this bias and ALT grade classification.

Hepatic outcomes for all treated HCV patients will be examined, regardless of ALT values; collection of hepatic outcomes will not be limited to patients meeting a Grade 3+ ALT measurement. This will ensure that all hepatic outcomes are captured. Strategies

already used by TARGET will minimize either selection or ALT recording or measurement bias and ensure generalizability of the study of results.

The following summarizes the strengths and limitations of the proposed study.

Strengths:

- HCV patients with longitudinal detailed information on laboratory and clinical measurements, medications and hospitalizations, eliminating recall or interviewer bias.
- Because the data are longitudinal, the risk of the events of interest can be directly measured.
- HCV patients are from a wide geographical area (both US and international).
- An established platform for data collection and referrals rendering the feasibility of conducting the proposed study in a manner quicker than with the initiation of a de novo study.
- Comprehensive computerized data on medication usage and morbidities (hospitalization data) and laboratory values are available, hence no recall or interview bias.
- Completeness of primary dependent variable of interest – The HCV-TARGET registry reports for the first 1100 patients enrolled, baseline ALT value was present in 98% of patients.
- Disease registry provides HCV disease management in a real-life setting of patients treated with the AbbVie 3-DAA or 2-DAA regimens in routine clinical care from multiple clinical sites integrated into one database.
- Follow-up adequate for study objectives – The HCV-TARGET registry reports a loss to follow-up not exceeding 5% for currently approved DAAs.

Limitations:

- The majority of patients are currently from US sites however approximately 400 patients are expected to be enrolled from European sites.
- Generalizability – registries depend upon voluntary enrollment, hence this may limit their generalizability.

- Length of time of follow-up (6 months post treatment) – registries and longitudinal observational studies take considerable time to collect information particularly outcomes, and may be limited in the completeness of follow-up data and number of patients observed over time. All data available for 6 months post-treatment will be abstracted and analyzed according to study protocol.
- Data sources outside HCV-Target registry – If a patient's data are captured outside the data collection scope of the registry (i.e., another hospital, clinic or physician practice), they may not be included in the registry's database.
- Differential follow-up – There may be differential follow-up of patients, such that more ill patients may be followed up more closely than less sick patients. Because the mobility of this population is not known, reasons for losses to follow-up may not be able to be obtained.
- Differences in local or standard health care practices – Treatment and follow-up algorithms may vary by each participating site's local standard of care and may impact the timing of laboratory monitoring of patients receiving treatment. Thus, laboratory values for all time intervals immediately before and during the AbbVie regimens may not be available or available in any consistent time intervals.
- Selection bias may occur if sites offer enrollment in TARGET only to certain patients – To avoid selection bias, sites enrolling patients in HCV-TARGET make every effort to offer enrollment to all patients being prescribed HCV treatment from the time of IRB approval at their respective center. This approach to sequential enrollment is essential to accurately characterize the outcomes of the HCV patients receiving the AbbVie 2-DAA or 3-DAA regimen.
- Channeling bias may occur if only patients with more severe disease and/or co-morbidities are given the AbbVie 2-DAA or 3-DAA regimen resulting in the possibility of a higher incidence of Gr 3+ ALT and more liver-related outcomes occurring in this group.
- Laboratory tests from local labs will be used for measurement of liver enzyme and liver function tests. As the normal ranges will vary between laboratories, manual standardization will be required.

Summary of Strengths and Limitations

Although there are limitations to the proposed study, the many strengths point to the study's ability to generate meaningful information for the conduct of the proposed real world study of the AbbVie DAA regimens. Conclusions from the study will be interpreted considering the identified limitations.

9.10.1 Study Closure/Uninterpretability of Results

Owing to the expected rarity of the two primary hepatic event categories of interest (ALT elevations and severe hepatic events), the potential for low enrollment rates into the HCV TARGET registry of patients receiving an AbbVie DAA regimen, the increasing availability of multiple new alternative therapies emerging for the treatment of HCV, and a potentially increasing pool of individuals who have failed prior therapies, the likelihood of not achieving enrollment increases with each year of the study. Thus, if the enrollment fails to achieve at least half of the desired sample at study midpoint in the proposed study duration, the study will be declared not feasible to continue due to the reasons aforementioned.

10.0 Protection of Human Subjects

10.1 Ethical Approval and Subject Consent

This study will be conducted in accordance with the Good Pharmacovigilance Practices (GVP) issued by the EMA (EMA 2013), the Declaration of Helsinki and its amendments (Declaration of Helsinki 2008), Guide on Methodological Standards in Pharmacoepidemiology (EMA 2010),[8] and any applicable guidelines of participating nations.

Each participating site will be responsible for ensuring that the study protocol and its associated documents, consistent with local regulations, are submitted to the responsible IRB/Ethics Committee for review and approval prior to enrollment of patients at that site.

Given the epidemiology of HCV infection, patients enrolled in the HCV-TARGET Registry will include adults of all races. It is anticipated that males will be more frequently enrolled than women also reflecting the epidemiology of this disease. Patients will be recruited from multiple sources and multiple nations, including community and tertiary referral populations, which will capture the entire spectrum of HCV infection.

HCV-TARGET is solely an observational, prospective, longitudinal cohort study and does not specify any treatment paradigm nor dictate management or follow-up of patients, including the duration of follow-up. This study specifies a post-treatment follow-up period of 6 months, and every effort will be made to collect data through this treatment period. However, consent for study participation and sharing of the anonymized data for research from the patient is the responsibility of the referring study site. Clinical information will not be released without the approval of the local IRB and the written consent of the patient. Consent procedures and forms, and the transmission and storage of patient data are compliant with HIPAA regulations. US Federal regulations govern and are followed regarding the protection of patients' rights relative to the use of the data for research and for confidentiality.

10.2 Patient Confidentiality

Study sites and the Chart Data Abstraction team will be responsible for the confidentiality of the data associated with participants in HCV-TARGET in the same manner they are responsible for the confidentiality of any patient information within their spheres of responsibility. All study personnel have completed training in Protection of Human Subjects and other local requirements, where applicable to the staff member activities such as The Health Insurance Portability and Accountability Act (HIPAA). All forms used for the study data will be only identified by coded identifiers to maintain subject confidentiality. All records will be kept in locked files at study sites and CCC with access limited to HCV-TARGET study staff. All study staff will identify patients by the patient identifier number generated at the study site. Clinical information is not released without written permission of the participant, except as necessary for monitoring by the IRB or DCC and centralized abstraction at the CCC. Participants grant permission to share

research data with these entities in the consent document. Federal regulations govern the protection of patient's rights relative to data confidentiality and use of research data. Consent forms for procedures and survey forms, and the communication, transmission and storage of patient data will comply with individual site IRB and federal requirements for compliance with HIPAA.

Additionally, every effort will be made to protect participant confidentiality according to the EU legislation on personal data protection, Directive 95/46/EC (1995) and in compliance with the provisions of the Safe Harbor privacy principles (US Department of Commerce, 2000).

11.0 Management and Reporting of Adverse Events/Adverse Reactions

The HCV-TARGET registry protocol specifies reporting to regulatory authorities such as the FDA and AbbVie simultaneously receiving serious adverse events/adverse reactions identified by the registry study team during the acquisition and/or abstraction of data received. All adverse experiences recorded in the medical record during treatment for HCV are routinely abstracted by registry staff and reported to the appropriate sponsor or regulatory authority. Reporting to the EU will come from AbbVie per AbbVie's usual pharmacovigilance practices. All adverse events will be collected and coded utilizing MedDRA dictionary.

12.0 Plans for Disseminating and Communicating Study Results

12.1 Target Audience

Interim and final reports will be submitted to the EMA, the FDA and other regulatory agencies as well as the marketing authorization holder's Product Safety Team, Safety Review Board (governance board of AbbVie). Subsequent to the approval of the final report, study findings will be disseminated in professional journals and at professional

society meetings. Communication to the lay public will be prepared after the completion of the final study report.

13.0 References

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