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.