1.0 Synopsis

Title	A Single-Arm Retrospective Study to Evaluate Safety and Efficacy in Patients with Acute Hepatitis C Virus (HCV) Infection Treated with 8 Weeks of Glecaprevir/Pibrentasvir
Sponsor (Responsible Party)	**AbbVie*** *The specific details of the AbbVie legal entity within the relevant country are provided within the Non-Interventional Study Agreement with the Investigator/Institution.
Rationale and Background	Hepatitis C viral infection is a global health problem, with 1.75 million new infections worldwide in 2015 and an estimated 44,700 new infections in the United States (US) in 2017. There are currently no approved direct acting antiviral agents (DAA) options for use in patients with acute HCV infection. Because of this, treatment is frequently delayed by 6 months (i.e., until the HCV infection is considered chronic). Regulatory approval of antiviral treatment in patients with acute HCV would prevent loss of patients to care, simplify decision-making for clinicians in the community setting, shorten the time to treatment of HCV infection, and would decrease the risk of community transmission. This study aims to demonstrate safety and efficacy for once-daily (QD) glecaprevir (GLE) and pibrentasvir (PIB) at the dose of GLE 300 mg and PIB 120 mg (hereafter referred to as GLE/PIB) in acute HCV patients.
Research Question	Glecaprevir 300 mg and pibrentasvir 120 mg will achieve a high sustained virologic response 12 weeks after the last dose of the drug (SVR_{12}) rate in patients acutely infected with HCV, with an acceptable safety profile.
Objectives and Endpoints	The primary objective of this study is to demonstrate the efficacy of GLE/PIB prescribed for 8 weeks in patients with acute HCV genotype (GT)1 – GT6 infection by comparing the SVR_{12} rate from this study to the historical SVR_{12} rate in people with chronic HCV infection who were treated with GLE/PIB. The primary efficacy endpoint is the achievement of SVR_{12} (defined as HCV ribonucleic acid [RNA] < 50 IU/mL between Day 57 and Day 126 after the last dose of study drug if available, or sustained virologic response 24 weeks after the last dose of the drug [SVR_{24}], defined as HCV RNA < 50 IU/mL between Day 127 and Day 210 after the last dose of study drug if SVR_{12} result is not available) for each patient in the modified Full Analysis Set (mFAS) population. The secondary objectives of this study are: • To determine the SVR_{12} rate among patients with acute HCV GT1 – GT6 infection following treatment with GLE/PIB (prescribed 8 weeks) based on all patients treated with GLE/PIB (the Full Analysis Set [FAS]). • To determine the on-treatment virologic failure, relapse, and reinfection

	rates among patients with acute HCV GT1 – GT6 infection based on the FAS population. The secondary efficacy endpoints are: • Achievement of SVR_{12} for each patient in the FAS population. • On-treatment virologic failure (defined as at least one HCV RNA ≥ 100 IU/mL after HCV RNA < 50 IU/mL during treatment, or no HCV RNA < 50 IU/mL during treatment provided the last on-treatment value was on or after 36 days of treatment for a patient who received at least 6 weeks of treatment) for each patient in the FAS population. • Post-treatment relapse (defined as HCV RNA < 50 IU/mL at end of treatment [EOT] or at the last on-treatment HCV RNA measurement, followed by HCV RNA ≥ 50 IU/mL post-treatment, excluding cases of reinfection) for each patient in the FAS population who completed treatment as planned. • Post-treatment reinfection with HCV (defined as post-treatment relapse along with the post-treatment detection of a different HCV genotype, subtype, or clade compared with baseline) for each patient in the FAS population. The safety objectives of this study are: • To examine the safety with respect to alanine aminotransferase (ALT) elevations, serious adverse events (SAEs), adverse events (AEs) leading to study drug discontinuation, and AEs of hepatic decompensation during treatment with GLE/PIB (8-week prescription) in patients with acute HCV GT1 – GT6 infection in the Safety Analysis Set compared to historical safety results in patients with chronic HCV infection. The safety endpoints will also be examined on the Principal Safety Stratum which consists of patients in the Safety Analysis Set that have ALT and bilirubin results both at baseline and during treatment with GLE/PIB. The safety endpoints are: • ALT elevations of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 Grade 1, 2, 3, or 4 and increased from baseline. • ALT > 3 × upper limit of normal (ULN) with total bilirubin > 2 × ULN. • AE of hepatic decompensation/failure according to the standardized Medical Dictionary for Regulatory Activities query. • AEs leading to discontinuation of study drug and SAEs.
Study Design	Overall Study Design: This is a non-interventional, single-arm, retrospective study (patient chart review) including sufficient patients (>250) with documented acute HCV, such that 250 patients are in the Principal Safety Stratum (have both baseline and on-treatment ALT and bilirubin values), treated with GLE/PIB (8 weeks of prescription) for comparison to historical safety and efficacy results for

	chronic HCV patients treated with GLE/PIB. Inclusion/Exclusion Criteria for study population: The charts of patients that meet the following eligibility criteria will be included: 1. Evidence of acute HCV infection is defined as physician diagnosis of acute HCV infection and 1 of the following: a. negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen followed by initiating GLE/PIB treatment within a 9-month period OR b. negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen followed by initiating GLE/PIB treatment within a 12-month period; AND risk behavior 6 months prior to positive HCV RNA or HCV core antigen OR c. clinical signs and symptoms compatible with acute hepatitis (ALT > 5 × ULN and/or jaundice) in the absence of a history of chronic liver disease or other cause of acute hepatitis and positive HCV RNA or HCV core antigen followed by initiating GLE/PIB treatment within a 9-month period; AND risk behavior 6 months prior to positive HCV RNA or HCV core antigen OR d. negative anti-HCV antibody with a positive HCV RNA or HCV core antigen followed by initiating GLE/PIB treatment within a 6-month period 2. Age 12 years or older. 3. Treatment-naïve, i.e., no prior treatment, including interferon, for this HCV infection. 4. Evidence of 8 weeks total of GLE/PIB prescription provided to patient. 5. Patient received treatment with GLE/PIB, as confirmed by investigator. Exclusion criteria: 1. History of liver decompensation. 2. Liver or kidney transplant history.
Sample size and Justification	The threshold for comparison for the primary efficacy estimand will be derived from a weighted average of the mITT-VF SVR_{12} rates in the PWID and non-PWID chronically infected populations. The mITT-VF SVR_{12} rate among chronically infected HCV PWID is 98.2% (Mavyret US Prescribing Information 2020, Section 14.9) and is 98.8% among chronic non-PWID. The threshold for comparison will be calculated by the (proportion of PWID in the mITT-VF population of this study × 98.2%) + (the proportion of non-

	PWID in the mITT-VF population of this study × 98.8%) minus a margin of 6%. The most stringent threshold in this setting, assuming the true SVR_{12} rate is the threshold plus 6%, would be 92.2% as if all patients were PWID. If a total of 135 patients enroll in the mFAS population, there will be 90% power to show that a 98.2% SVR_{12} rate among acutely infected HCV patients is superior to a threshold of 92.2% based on the historical SVR_{12} rate among chronically infected HCV patients using a 2-sided 95% confidence interval (that is, the lower confidence bound of the Wilson's score confidence interval will be above 92.2%). Sufficient adolescent and adult acutely HCV infected patients who meet the admission criteria will be enrolled such that 250 patients have baseline and on-treatment ALT and bilirubin values to be included in the Principal Safety Stratum. A sample size of 250 patients in the Principal Safety Stratum provides > 91% probability and a sample size of 300 in the Safety Analysis Set provides > 95% probability to detect any toxicity which occurs in ≥ 1% of patients with acute HCV.
Statistical methods	For the primary efficacy endpoint analysis, the number and percentage of patients assigned to 8 weeks of GLE/PIB achieving SVR_{12} will be summarized for the mFAS population along with a 2-sided 95% confidence interval using Wilson's score method. A summary of reasons for SVR_{12} non-response (e.g., on-treatment virologic failure or relapse) will be provided. The superiority of the 8-week treatment duration in HCV acute infection to the efficacy threshold described above will be established if the lower bound of the 2-sided 95% confidence interval for the percentage of patients achieving SVR_{12} is greater than that threshold. A patient will be considered to have on-treatment virologic failure if they have **breakthrough** (at least one HCV RNA ≥ 100 IU/mL after HCV RNA < 50 IU/mL during treatment) or **EOT failure** (no HCV RNA < 50 IU/mL during treatment provided the last on-treatment value was on or after 36 days of treatment for a patient who received at least 6 weeks of treatment). If the appropriate HCV RNA levels are not available, physician attestation of breakthrough or EOT failure will suffice. A patient will be considered to have post-treatment HCV virologic relapse if they had HCV RNA < 50 IU/mL at EOT or at the last on-treatment HCV RNA measurement followed by HCV RNA ≥ 50 IU/mL post-treatment, excluding reinfection as described below. A patient who starts another treatment before SVR_{12} status has been obtained will be considered to have experienced relapse. Completion of treatment is defined as study drug duration of 52 days or greater. If such completion of treatment data is not available, then completion of treatment will include physician testimonial that the patient received drug for at least 52 days. If the appropriate HCV RNA levels are not available, physician attestation of relapse will suffice. For the secondary efficacy endpoint analysis, the number and percentage of patients assigned to 8 weeks of GLE/PIB achieving SVR_{12} will be

	summarized for the FAS population along with a 2-sided 95% confidence interval using Wilson's score method. In this analysis, patients who are missing SVR_{12} status, have reinfection, or have early premature discontinuation leading to relapse or EOT failure will be imputed as having virologic failure. A summary of reasons for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse, reinfection, other) will be provided. For the secondary endpoint of on-treatment virologic failure, the number and percentage of patients with on-treatment virologic failure in the FAS population will be summarized along with a 2-sided 95% confidence interval using Wilson's score method. For the secondary endpoint of virologic relapse, the number and percentage of patients with relapse among the appropriate patients in the FAS population will be summarized along with a 2-sided 95% confidence interval using Wilson's score method. For the secondary endpoint of post-treatment reinfection, a patient will be considered to have reinfection if they have HCV virologic relapse along with the post-treatment detection of a different HCV genotype, subtype, or clade compared with baseline. The number and percentage of patients with reinfection among the appropriate patients in the FAS population will be summarized along with a 2-sided 95% confidence interval using Wilson's score method. The safety endpoints will be analyzed based on both the Safety Analysis Set and the Principal Safety Stratum. Treatment-emergent AEs are defined as those with onset during GLE/PIB treatment through 30 days post-dosing. Laboratory values during treatment are those collected during GLE/PIB dosing. Adverse events or laboratory abnormalities during a different DAA treatment after a treatment switch would not be attributed to GLE/PIB. For each safety endpoint, the number and percentage of patients in each population meeting the criteria will be summarized beside the number and percentage of patients assigned 8 weeks of treatment with GLE/PIB in Phase 2 and 3 clinical trials.