Title Page

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
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Research Question and Objectives	Glecaprevir (GLE) 300 mg and pibrentasvir (PIB) 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.
Countries of Study	US/PR, UK, Spain, Italy, France, Canada and Australia
Author	[redacted] Principal Medical Writer AbbVie

This study will be conducted in compliance with this protocol.

Confidential Information

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Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	AbbVie Deutschland GmbH & Co. KG; AbbVie Inc.
MAH Contact Person	Not applicable

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2.0 Abbreviations

AE	adverse event
ALT	alanine aminotransferase
CTCAE	Common Terminology Criteria for Adverse Events
DAA	direct acting antiviral agent
eCRF	electronic Case Report Form
EDC	electronic data capture
EMR	electronic medical record
EOT	end of treatment
FAS	Full Analysis Set
GLE	glecaprevir
GT	genotype
HCV	hepatitis C virus
HIV	human immunodeficiency virus
INR	International normalized ratio
mFAS	modified Full Analysis Set
mITT-VF	modified intention-to-treat analysis set excluding those who did not achieve SVR_{12} due to reasons other than virologic failure
NCI	National Cancer Institute
PIB	pibrentasvir
PR	Puerto Rico
PWID	people who inject drugs
QD	once daily
RNA	ribonucleic acid
SAE	serious adverse event
SAS	Statistical Analysis System
SVR	sustained virologic response
SVR_{12}	sustained virologic response 12 weeks after the last dose of the drug
SVR_{24}	sustained virologic response 24 weeks after the last dose of the drug
UK	United Kingdom
ULN	upper limit of normal
US	United States

3.0 Responsible Parties

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*The specific details of the AbbVie legal entity within the relevant country are provided within the Non-Interventional Study Agreement with the Investigator/Institution.

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4.0 Abstract

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

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 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 and Objectives:

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.

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 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 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.

Study Design:

This is a non-interventional, single-arm, retrospective study (patient chart review) including sufficient patients (≥ 250) with documented acute HCV, such that at least 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.

Population:

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:

- History of liver decompensation.
- Liver or kidney transplant history.

Variables: 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) or not for each patient in the modified Full Analysis Set (mFAS) population.

The secondary efficacy endpoints are:

- Achievement of SVR_{12} or not 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) or not 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) or not 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) or not for each patient in the FAS population.

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 Product Medical Dictionary for Regulatory Activities Query.
- AEs leading to discontinuation of study drug and SAEs.

Data Sources: To avoid sampling, all patients who are documented in their medical record as meeting the inclusion/exclusion criteria and treated at each site between 26 Jul 2017 through end dates that are 5 months prior to site initiation. The data source for eligible patients includes all sources of study-relevant information that are available to the investigator at the clinical study site and will be referred to as "patient charts." This may include, but is not limited to, paper medical charts, Electronic Medical Records (EMRs), and clinical laboratory records. This study will only collect retrospective information recorded in patient charts prior to the start of data collection from 6 months prior to the first dose of GLE/PIB, through the duration of GLE/PIB treatment, and for up to 210 days after the end of GLE/PIB treatment. No information that would enable the identification of any patients will be recorded in the study's electronic Case Report Forms (eCRFs). In addition, all actual dates will be anonymized prior to entry into the eCRFs. Only the clinical study sites' personnel can review the patient charts. Neither AbbVie nor AbbVie's designee can review the patient charts.

Study Size: The threshold for comparison for the primary efficacy estimand will be derived from a weighted average of the intention-to-treat analysis (ITT) set modified to exclude those who did not achieve SVR due to reasons other than virologic failure (mITT-VF) SVR_{12} rates in the people who inject drugs (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 mFAS population of this study × 98.2%) + (the proportion of non-PWID in the mFAS population of this study × 98.8%) minus a margin of 6%. The situation that is associated with the lowest power, 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 at least 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.

Data Analysis:

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.

Data Analysis (continued):

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 in the chronically infected HCV population assigned 8 weeks of treatment with GLE/PIB in Phase 2 and 3 clinical trials.

Milestones:

Start of Data Collection: May 2021

End of Data Collection: August 2022

Study Progress Report: Not Applicable

Interim Report: Not Applicable

Registration in the EU PAS register: 19 April 2021

Final Report of Study Results: December 2022

5.0 Amendments and Updates

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	04 May 2022	Entire H20-315 protocol	Amendment	• Protocol converted to post-marketing observational study (PMOS) template
		Various	Update	• Updates added from the Administrative Change 1 Document
		Various	Update	• Clarified that at least 250 patients would be enrolled in the Principal Safety Stratum
		3.0	Update	• Updated the AbbVie contact details
		9.5	Update	• Clarified that the comparator population for the primary endpoint is the population with chronic HCV treated in GLE/PIB clinical trials that is represented in Section 14.9 of the Mavyret USPI 2020, and deleted statement that the Safety Analysis Set and the FAS would be the same in this study because that may not be accurate based on analysis population definitions
		9.8.1	Update	• Clarified that confidence intervals will be calculated for efficacy endpoints only
		9.8.2	Update	• Deleted jaundice from the list of medical conditions included in the definition of a history of hepatic decompensation

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1 (con't)		9.8.6	Update	• Clarified that the subgroup analysis of SVR_{12} based on non-prescribed drug use is non-prescribed illicit drug use; added subgroups for analysis of SVR_{12} based on baseline fibrosis stage, baseline cirrhosis status, and treatment duration; and clarified that descriptive comparisons for safety endpoints will be conducted for patients with and without on-treatment safety laboratory values and patients with and without post-treatment HCV RNA or safety laboratory values.

6.0 Milestones

Major study milestones and their planned dates are as follows:

Start of Data Collection:	May 2021
End of Data Collection:	August 2022
Study Progress Report:	Not Applicable
Interim Report:	Not Applicable
Registration in the EU PAS register:	19 April 2021
Final Report of Study Results:	December 2022

7.0 Rationale and Background

7.1 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 in 2017.[1,2] There are currently no approved direct acting antiviral agents (DAA) options for use in patients with acute hepatitis C virus (HCV) infection. Because of this, treatment is

frequently delayed by 6 months (i.e., until the HCV infection is considered chronic). The majority of new HCV infections today are in people who inject drugs (PWID) and men who have sex with men.[3] Since PWID are often disconnected from care, waiting 6 months to confirm chronic infection results in the loss of many such patients to care and accelerates community transmission of HCV as the patients infect others during the acute phase. The Centers for Disease Control and Prevention (CDC) recently reported a dramatic increase in HCV within the US, with new HCV cases 4 times higher than they were 10 years ago.[2] This jeopardizes the World Health Organization goal of HCV elimination by 2030.

The combination treatment regimen of 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) was developed for use in chronically infected HCV treatment-naïve and treatment-experienced genotype (GT)1 – GT6-infected adult patients with compensated liver disease (with or without cirrhosis). The safety and efficacy of the GLE/PIB regimen were demonstrated in 9 registrational and 3 supportive Phase 2 studies in adults with chronic HCV. Subsequent studies have demonstrated the safety and efficacy of GLE/PIB in adolescents, and an update to the indication to include adolescents (12 to < 18 years of age) was approved by the Food and Drug Administration on April 30, 2019, and within the European Union on March 13, 2019.

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. Initial evidence indicates that GLE/PIB could be an efficacious and safe treatment for this population. The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver practice guidelines recommend treatment of acute HCV to prevent progression to chronic HCV.[4,5] Additionally, 2 recent clinical studies also support that GLE/PIB treatment may be efficacious and safe for use in patients with acute HCV:

- Martinello et al evaluated GLE/PIB treatment of 6 weeks duration in 30 acute/recent acquired HCV patients, and reported an intention-to-treat sustained virologic response 12 weeks after the last dose of the drug (SVR_{12}) of 90% and per-protocol SVR_{12} of 96%.[6]
- Chromy et al evaluated GLE/PIB treatment of 8 weeks duration in 11 patients with acute HCV who were also positive for human immunodeficiency virus (HIV), and demonstrated a 100% SVR_{12} rate.[7]

The GLE/PIB regimen was well-tolerated in both studies, with no treatment-emergent serious adverse events (SAEs) observed.

This study is designed to support a new indication to treat adult and adolescent patients (≥ 12 years of age) with acute HCV with the fixed-dose co-formulated tablet combination regimen of GLE/PIB 300 mg/120 mg QD, which is currently approved for patients with chronic HCV.

7.2 Rationale

This study aims to demonstrate safety and efficacy for QD GLE/PIB at the dose of GLE 300 mg and PIB 120 mg in patients with acute HCV infection.

8.0 Research Question and Objectives

8.1 Research Question

Glecaprevir (GLE) 300 mg and pibrentasvir (PIB) 120 mg will achieve a high SVR_{12} rate in patients acutely infected with HCV, with an acceptable safety profile.

8.2 Study Objectives

8.2.1 Primary Objective

The primary objective of this study is:

- To demonstrate the efficacy of GLE/PIB for acute HCV infection by comparing the SVR_{12} rate in patients with acute HCV GT1 – GT6 infection to the historical rate in patients with chronic HCV infection.

The primary efficacy objective will be assessed based on a modified Full Analysis Set (mFAS) population which includes all eligible patients (adults or adolescents with confirmed acute HCV GT1 – GT6 infection treated with GLE/PIB excluding patients who fail to achieve SVR_{12} for reasons other than virologic failure; Section 9.5).

The primary hypothesis is that treatment with GLE/PIB for 8 weeks for patients in the mFAS population is superior to an efficacy threshold which is based on the historical rate of GLE/PIB in adults with chronic HCV infection. This will be shown if the lower bound of the 2-sided 95% confidence interval for the percentage of patients achieving SVR_{12} is greater than the efficacy threshold.

The estimand corresponding to the primary efficacy objective is the percentage of patients achieving SVR_{12} among the study population infected with acute HCV treated with GLE/PIB, excluding those who did not achieve sustained virologic response (SVR) due to non-virologic reasons (mFAS population).

8.2.2 Secondary Objectives

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.

8.2.3 Safety Objectives

The safety objectives of this study are:

- To examine the safety with respect to alanine aminotransferase (ALT) elevations, 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.

8.3 Study Endpoints

8.3.1 Primary Endpoint

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 mFAS population.

8.3.2 Secondary Endpoints

The secondary efficacy endpoints are:

- Achievement of SVR_{12} for each patient in the FAS population.
- On-treatment virologic failure (defined as at least 1 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.

8.3.3 Safety Endpoints

The safety endpoints examined among all patients in the Safety Analysis Set (all patients treated with GLE/PIB) and in the Principal Safety Stratum (all patients in the Safety Analysis Set with baseline and on-treatment ALT and bilirubin results) 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.
- AEs of hepatic decompensation/failure according to the Product Medical Dictionary for Regulatory Activities query.
- AEs leading to discontinuation of study drug and SAEs.

The Safety Analysis Set will include all patients who are prescribed 8 weeks of GLE/PIB and receive at least 1 dose of GLE/PIB, without restriction by level of testing performed, to provide rates of safety endpoints in a generalizable population reflecting real-world practice. The Principal Safety Stratum will include all patients who have a baseline and during-treatment ALT value and bilirubin value to provide rates of safety endpoints among patients who received this minimum level of testing as part of their clinical care and for whom ALT elevations can be assessed.

9.0 Research Methods

9.1 Study Design

Study P20-315 is a non-interventional, single-arm, retrospective study (patient chart review) designed to include a sufficient number of patients with documented acute HCV, treated with GLE/PIB (8 weeks of prescription) in order to enroll at least 250 patients with baseline and on-treatment ALT and bilirubin values (Principal Safety Stratum) for comparison to historical safety and efficacy results for chronic HCV patients.

At each site, all patients who are documented in their medical record as meeting the inclusion/exclusion criteria and treated at each site between 26-Jul-2017 through end dates that allow collection of SVR determination before site initiation will be included in the study. If significantly fewer than 135 patients have SVR_{12} status or fewer than 250 patients have been included in the Principal Safety Stratum, additional sites may be opened and they must include in the study all patients meeting the inclusion/exclusion criteria as stated above.

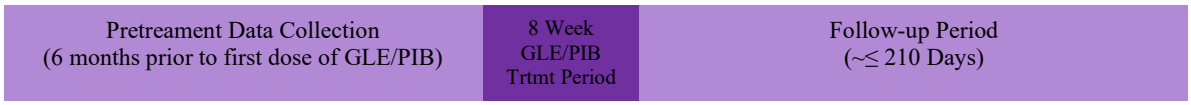
Data collection will consist of retrospective data collected for all of the following study epochs (Figure 1):

- the Pretreatment Data Collection, which will consist of the 6 months prior to and through the day of the first dose of GLE/PIB;
- the 8-week Treatment Period, which starts on the day of the first dose of GLE/PIB and ends on the day of the last dose of study drug;
- the Follow-up Period, which starts the day after the last dose of GLE/PIB and ends after HCV RNA data collection (12 to 24 weeks post-treatment).

The date of the first dose of GLE/PIB is the index date; if it is not available, the physician-reported start date or the fill date of the first prescription will be used as the date of the first dose of GLE/PIB.

If the date of the last dose of GLE/PIB is not known, then the physician-reported date of the last dose of GLE/PIB or the date that would correspond to the end of the last prescription based on the days supplied will be used.

Figure 1. Study P20-315 Study Epochs for Retrospective Data Collection



GLE = glecaprevir; PIB = pibrentasvir; Trtmt = Treatment

9.2 Setting

This study will include data from sufficient adolescent and adult acutely HCV infected patients (≥ 250) treated with GLE/PIB whose data are collected through retrospective chart review such that at least 250 patients have baseline and on-treatment ALT and bilirubin values to be included in the Principal Safety Stratum.

9.2.1 Inclusion Criteria

The charts of patients that meet the following eligibility criteria will be included:

- 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 within** 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 within** 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.

- Age 12 or older.
- Treatment naïve, i.e., no prior treatment, including interferon, for this HCV infection.
- Evidence of 8 weeks total of GLE/PIB prescription provided to patient.
- Patient received treatment with GLE/PIB, as confirmed by investigator.

9.2.2 Exclusion Criteria

Exclusion criteria:

1. History of liver decompensation.
2. Liver or kidney transplant history.

9.3 Variables

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) or not for each patient in the modified Full Analysis Set (mFAS) population.

The secondary efficacy endpoints are:

- Achievement of SVR_{12} or not 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) or not 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) or not 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) or not for each patient in the FAS population.

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 Product Medical Dictionary for Regulatory Activities Query.
- AEs leading to discontinuation of study drug and SAEs.

9.4 Data Sources

9.4.1 Retrospective Data Component

Patient demographics, clinical characteristics, and treatment information, as well as outcome data, will be retrospectively collected by chart review. In particular, the following variables will be collected by eCRF as available:

- Medical record duration: the date of the first event and the last event in the patient medical record.
- Demographics: age, weight, height, sex, race, and ethnicity.
- Baseline laboratory values and characteristics (closest to or on index date): HCV GT, HCV RNA level, baseline laboratory tests including ALT, aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, serum creatinine, creatinine clearance/estimated glomerular filtration rate (eGFR), platelets, serum albumin and International normalized ratio (INR).
- Tobacco, alcohol, opiate substitution, and non-prescribed drug use status and history.
- Diagnosis: HCV antibody test results, HCV RNA results, HCV core antigen date and results, date of physician diagnosis of acute HCV infection and risk behaviors to document acute HCV infection, fibrosis stage, and liver cirrhosis assessment (and Child Pugh Score if cirrhotic).
- HCV history : whether ever previously infected with HCV and cured or not.
- Relevant medical history, including any history of liver decompensation, liver or kidney transplant (which are exclusionary), diabetes, and HIV infection.
- GLE/PIB treatment: number of prescriptions and length of each prescription, physician attestation of GLE/PIB treatment, treatment duration, interruptions, or early termination.
- Safety laboratory tests results during treatment through 2 weeks after GLE/PIB treatment: documented laboratory test date and results for ALT, AST, (total, direct, and/or indirect) bilirubin, alkaline phosphatase, serum creatinine, creatinine clearance/eGFR, platelets, serum albumin, and INR.
- Prior and concomitant medications include medication administered within 30 days prior to GLE/PIB treatment through 30 days after GLE/PIB treatment. Other post-treatment HCV medications taken after GLE/PIB treatment will be collected throughout the post-treatment period.
- Treatment-emergent AEs: all AEs during and through 30 days post-GLE/PIB treatment, including but not limited to any AEs of hepatic decompensation. Relationship to GLE/PIB treatment will be assessed by the investigator as having a "reasonable possibility" or "no reasonable possibility" of being related to GLE/PIB treatment.

- Outcome data: HCV RNA values during treatment and post-treatment, specifically achievement of SVR_{12} (or SVR_{24} if SVR_{12} is not available), relapse, breakthrough, or EOT failure, if applicable, reinfection, and method of determination of any reinfection, if applicable.

The following site-specific data will be collected by eCRF:

- Completeness of medical capture in the patient chart.
- Evidence of such completeness (e.g., electronic medical record, site is in a country of local region with universal health system or site is part of a closed healthcare system).
- Frequency of ALT testing during DAA treatment.

9.4.2 Data Collection Methods

Each center will document patient data in eCRFs.

Diagnostic measures that have been performed in patients and observations from patients included in this study as part of routine medical practice will be entered into the AbbVie eCRFs by the site physician (or staff under the physician's supervision), according to the Section 9.4.1 Of note, all laboratory results specified in Section 9.4.1 for baseline should be reported in the eCRFs from 6 months prior to start of GLE/PIB dosing. All laboratory results specified in Section 9.4.1 for collection during GLE/PIB treatment should be reported in the eCRFs. Normal ranges will also be reported in the eCRF per laboratory used. Prior to entry of any actual date (other than birth year) the center must use the tool provided by AbbVie to anonymize the dates. A second site staff will be required to check all the data entered into the eCRFs and verify its correctness and completeness.

Neither AbbVie nor any agents acting on behalf of AbbVie may complete the eCRFs. Neither AbbVie nor AbbVie's designee will monitor data entered in the eCRFs versus the chart data. Queries will be issued in electronic data capture (EDC) based only on logical data verification checks within the EDC system.

To avoid sampling, all patients who are documented in their medical record as meeting the inclusion/exclusion criteria and treated at each site between 26-Jul-2017 through end dates that are 5 months prior to site initiation. The data source for eligible patients includes all sources of study-relevant information that are available to the investigator at the clinical study site and will be referred to as "patient charts." This may include, but is not limited to, paper medical charts, EMRs, and clinical laboratory records. This study will only collect retrospective information recorded in patient charts prior to the start of data collection from 6 months prior to the first dose of GLE/PIB, through the duration of GLE/PIB treatment, and for up to 210 days after the end of GLE/PIB treatment. No information that would enable the identification of any patients will be recorded in the study's eCRFs. In addition, all actual dates will be anonymized prior to entry into the eCRFs. Only the clinical study sites' personnel can review the patient charts. Neither AbbVie nor AbbVie's designee can review the patient charts.

9.5 Analysis Populations

The FAS population includes all patients in the study population (per eligibility criteria) who were treated with GLE/PIB. The FAS population will be used for all secondary efficacy analyses as well as for baseline analyses.

The mFAS population includes all patients in the FAS, excluding patients who did not achieve SVR for reasons other than virologic failure (i.e., those with HCV reinfection, those who did not achieve SVR_{12} due to early premature discontinuation of GLE/PIB, and those who do not have an SVR status available in the patient chart). The mFAS population will be used for the primary efficacy analysis. The mFAS definition matches the definition of the modified intention-to-treat analysis set which excludes those who did not achieve SVR due to reasons other than virologic failure (mITT-VF) for the GLE/PIB Integrated Summary of Efficacy (ISE) analysis set. The mFAS SVR rate in this study is being compared to the mITT-VF SVR rate in the population with chronic HCV treated in GLE/PIB clinical trials and represented in the "Phase 2/3 Analysis Set" included in the Mavyret USPI 2020, Section 14.9[8] for the primary endpoint.

The Safety Analysis Set consists of all patients who were treated with GLE/PIB. The same definition will be used for the summary of safety data from the patients assigned 8 weeks of treatment with GLE/PIB in Phase 2 and 3 clinical trials to which the safety results will be compared.

The Principal Safety Stratum consists of all patients in the Safety Analysis Set who have ALT and bilirubin values at baseline and during GLE/PIB treatment.

9.6 Study Size

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)[8] and is 98.8% among chronic non-PWID. The threshold for comparison will be calculated by the (proportion of PWID in the mFAS population of this study × 98.2%) + (the proportion of non-PWID in the mFAS population of this study × 98.8%) minus a margin of 6%. The situation that is associated with the lowest power, 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 at least 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. Table 1 shows the

probability that a given AE or laboratory toxicity would be observed with a sample size of 250 or 300 patients.

Table 1. Sample Size Justification Based on Probability of Observing Any Toxicity

True Toxicity Rate	Sample Size	Probability of Not Observing Any Toxicities
0.5%	250	71.4%
	300	77.8%
1%	250	91.9%
	300	95.1%
2%	250	99.4%
	300	99.8%
3%	250	100%
	300	100%

9.7 Data Management

Data for this study will be recorded in English by each participating center via an electronic data capture (EDC) system using a web-based eCRF.

Case report forms must be completed for each patient enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an EDC system called Rave® provided by the technology vendor Medidata Solutions, Inc., a Dassault Systèmes company. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

Pre-existing patient files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be made available to each site via a password protected secure internet link at the end of the study. It will be possible for the investigator to make paper printouts.

9.8 Data Analysis

9.8.1 General Approach

Continuous data will be summarized using descriptive statistics including count (n), mean, median, standard deviation, range, and inter-quartile range. Categorical data will be summarized using count (n) and percentage. Also for proportions used to summarize efficacy data, a 95% 2 sided confidence interval will be computed using Wilson's score method.

Statistical Analysis System (SAS Institute, Inc., Cary, NC) for the UNIX operating system will be used for all analyses. All confidence intervals will be 2-sided with an alpha level of 0.05.

A separate Statistical Analysis Plan (SAP) will be issued for this study. The SAP will follow the statistical analysis strategy and procedures as outlined in the study protocol, but will provide more details of the statistical methods and related procedures.

There will be no interim analyses.

There is only one primary efficacy endpoint comparison. The secondary efficacy endpoints are not included in the Type I error control as no hypothesis is being tested for the secondary efficacy endpoints.

9.8.2 Patients' Demographics, Disease Characteristics, Treatment Patterns, and Treatment Discontinuation

All available demographics and baseline characteristics will be summarized for all patients in the FAS, Safety Analysis Set, mFAS, and Principal Safety Stratum populations. Demographics include age, weight, height, BMI, sex, race, and ethnicity. Baseline characteristics include HCV GT, baseline HCV RNA level, cirrhosis status, tobacco use, alcohol use, nonprescribed drug use, stable opiate substitution therapy use, and renal and hepatic impairment. The history of varices or hepatic decompensation (broken down by ascites, variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome), Child Pugh score (if cirrhotic), baseline fibrosis stage, diabetes, and HIV infection will be summarized, if available. Mode of acute HCV infection, which criteria of acute HCV definition, and history of whether ever previously infected with HCV and cured or not will be summarized, if available.

9.8.3 Primary Efficacy Analysis

For the primary efficacy endpoint analysis, the number and percentage of patients 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. All patients in the mFAS will have SVR_{12} status by definition of mFAS. The superiority of the 8-week treatment duration in HCV acute infection to the efficacy threshold derived as

described in Section 9.6 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 in Section 9.8.4. 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 at least 52 days of drug. If the appropriate HCV RNA levels are not available, physician attestation of relapse will suffice.

9.8.4 Secondary Efficacy Analysis

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, determined to be reinfected, or reported to 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.

9.8.5 Safety Analysis

The safety endpoints specified in Section 8.3.3, where AE endpoints will be based on treatment-emergent AEs and laboratory endpoints will be based on values collected during treatment, will be analyzed based on the Safety Analysis Set. 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 meeting the criteria will be summarized beside the number and percentage of patients in the chronically infected HCV population assigned 8 weeks of GLE/PIB in Phase 2 and 3 clinical trials.

In addition, the safety endpoints specified in Section 8.3.3 will be analyzed based on the Principal Safety Stratum and on the mFAS specified in Section 9.5. Side-by-side comparison of the safety endpoint outcomes in the FAS/Safety Analysis Set, mFAS, and Principal Safety Stratum populations will be made.

9.8.6 Subgroup and/or Sensitivity Analysis

Sensitivity Analyses of Demographics and Baseline Characteristics

The demographic and baseline characteristics of patients who had no safety laboratory tests drawn at baseline, no laboratory tests drawn during treatment or no safety laboratory tests drawn at baseline or during treatment will be compared descriptively to patients who did have laboratory tests drawn in order to assess the possible differences between these 2 groups of patients.

Demographic and baseline characteristics of the patients with acute HCV infection will be categorized and compared descriptively to the percentage of patients in each category in the chronically infected HCV population assigned 8 weeks of GLE/PIB in Phase 2 and 3 clinical trials.

Subgroup and Sensitivity Analyses of Efficacy (SVR_{12})

Subgroup efficacy analyses on the percentage of patients achieving SVR_{12} will be performed. For each subgroup, the number and percentage of patients achieving SVR will be summarized along with a 2-sided 95% confidence interval using Wilson's score method in the FAS and mFAS populations. Analysis of SVR will be provided for the following subgroups:

- HCV genotype;
- Sex;
- Age;
- Race;
- BMI;
- Baseline HCV RNA level;
- Baseline platelet count;
- Baseline serum albumin;
- Baseline ALT;

- Geographic region;
- Baseline creatinine clearance/eGFR;
- History of diabetes;
- Stable opiate substitution status;
- Non-prescribed illicit drug use status;
- Estimated acute HCV infection duration;
- Prior HCV infections (yes or no);
- Baseline fibrosis stage (equivalent to Metavir F0 – F1, F2, F3, or F4);
- Baseline cirrhosis status (cirrhotic or non-cirrhotic);
- Treatment duration (< 52 days, ≥ 52 days)

Subgroup analyses will provide the efficacy endpoint results for each categorized baseline characteristic for the acutely infected HCV population with the same results by category for the chronically infected HCV population. In addition, descriptive comparisons will be conducted for efficacy endpoints for patients with and without on-treatment laboratory values.

Sensitivity and Subgroup Analyses of Safety Endpoints

Sensitivity analysis of the safety endpoints will be conducted including only sites that are likely to have all medical care during GLE/PIB treatment captured in the patient chart (e.g., sites that are part of a closed healthcare system or sites that are in a country or local region with universal healthcare system).

Sensitivity analysis of safety endpoints of ALT elevation will be conducted including only centers that more routinely/frequently test ALT on treatment.

Subgroup analyses by the intrinsic factors of sex, age, race, ethnicity, BMI, cirrhosis status, first infection status, and pre-treatment ALT and creatinine clearance, by the extrinsic factors of geographic region, and by concomitant statin and contraceptive use will be conducted for the safety endpoints.

A descriptive comparison will be conducted for safety endpoints for the following groups: patients with and without on-treatment safety laboratory values; patients with and without post-treatment HCV RNA or safety laboratory values; and by discontinuation status – discontinued, did not discontinue, and unknown, and by HCV treatment switch or not (if sufficient patients switch to another HCV therapy). Since analyses of safety outcomes that are stratified by post-baseline factors (such as on-treatment laboratory values or discontinuation status) may be additionally confounded by factors that are associated with these post-treatment factors, we will explore predictors of each of these post-baseline factors and further stratify by as many such factors as possible for evaluation of these relevant groups of patients.

Subgroup analyses will provide the safety endpoint results for each categorized baseline characteristic for the acutely infected HCV population with the same results by category for the chronically infected HCV population.

Further details about subgroup analyses will be described in the SAP.

9.8.7 Feasibility/Acceptability Assessment

In order to assess the fitness of the data collected in the study for labelling changes, the following analyses will be conducted:

1. Amount of laboratory data as assessed by the percentage of patients in the Principal Safety Stratum with each of the laboratory values of interest (in Section 9.4.1) at baseline and during treatment with GLE/PIB, separately.
2. The frequency of follow-up overall will be summarized for all patients in the Safety Analysis Set and the Principal Safety Stratum by counting the number of touchpoints with health care professionals during the time period of the chart review for each included patient.
3. The validity of the acute definition by determining the proportion of patients with a physician diagnosis of acute infection (all) meeting each of the bulleted criteria regarding laboratory values in Inclusion Criteria #1.

4. Assess the homogeneity of the study population across sites and countries by examining efficacy and safety outcomes by site and by country.

Additional details and additional analyses for the feasibility/acceptability assessment will be specified in the SAP.

9.9 Quality Control

9.9.1 Data Protection

Data will be collected in an anonymized manner in the study's eCRF following approval of the responsible Ethics Committee. No data that would enable identification of any patient will be recorded in the eCRFs that are provided to AbbVie, nor will AbbVie receive a linking list that would allow AbbVie to re-identify the patients.

9.9.2 Data Storage and Access

AbbVie will store the data that it receives in a limited access, secure storage space.

9.10 Limitations of the Research Methods

Retrospective chart review data are fit for the purpose of establishing efficacy and safety of the regimen for the following reasons:

- Includes patients who have been treated in the real world during the acute phase of HCV infection, without protocol-driven restrictions based on baseline characteristics. The intention is to enroll patients who were treated with GLE/PIB within 6 months of their likely time of acute infection per Inclusion Criterion 1.
- Short treatment window (8 weeks), with low potential for loss-to-follow-up for evaluating safety events on treatment.
- Efficacy and important safety outcomes are laboratory-based measures with high internal and external validity.

Limitations of the retrospective chart review data and study design include:

- For the primary efficacy estimand, the study is limited to patients who underwent follow-up HCV RNA testing to assess SVR.
- For safety, collection of safety events is limited to those that occurred within the healthcare system with HCV care captured within the medical chart.
- There is a lack of a direct comparator to untreated acute HCV patients. It is unknown how rates of safety events of interest while on treatment with GLE/PIB differ from such rates for patients with acute HCV who are not treated during the acute phase.
- Mitigation includes side-by-side comparison of the rates of SVR and the rates of safety events from the chronic HCV program for patients treated with 8 weeks of GLE/PIB.

Possible sources of bias, and ways to address these sources:

- Bias related to the selection of charts/patients to be evaluated for entry in the study.
  - Sites will be requested to include all acute HCV patient charts for evaluation against the eligibility criteria during a period of time from 26 Jul 2017 (approval of Maviret in EU) through end dates which are 5 months prior to site initiation (to allow for enrolled patients to have SVR_{12} data prior to site initiation).
- Bias due to physician selection of acutely HCV infected patients to be treated with GLE/PIB due to baseline factors.
  - Subgroup analyses by baseline characteristics, including pre-treatment ALT.
- Bias due to inadequate capture of relevant safety events because they occur outside of the system captured in the treating physician's medical chart.
  - Sensitivity analysis of the safety endpoints will be conducted and restricted to sites that are likely to have all medical care during GLE/PIB treatment captured in the patient medical chart (e.g., sites that are part of a closed healthcare system or sites that are in a country or local region with

universal healthcare system) to see if safety in these sites is similar or different from the safety across all sites.

- Bias due to inadequate performance of laboratory testing to assess for elevations/abnormal results.
    - Sensitivity analysis of safety endpoints of ALT restricted to centers that more routinely/frequently test ALT during treatment.
    - The demographic and baseline characteristics from subjects with and without laboratory data will be examined to see if any baseline factors appear to be associated with missing laboratory data. Then sensitivity analyses will be performed to examine whether the safety and effectiveness outcomes are associated with those baseline factors. In addition, sensitivity analyses will be performed to examine whether the safety and efficacy outcomes are associated with the factors that were predictive of safety and efficacy outcomes in AbbVie's chronic HCV clinical program outcomes.
    - Clinical safety endpoints will be compared for patients with and without on-treatment laboratory values. Clinical and laboratory-based (if available) safety endpoints will be compared for patients with and without post-treatment laboratory values (including HCV RNA), and by discontinuation or switch status. These comparisons will allow for an understanding of AE and laboratory safety endpoints in the context of patients with limited information.
    - The electronic Case Report Form (eCRF) will collect whether the patient was lost to follow-up in the opinion of the site. The results for the safety endpoints for patients who are listed in the eCRF as lost to follow-up will be compared to all other patients to see if there are different results in those lost to follow-up.
- Survivorship bias (e.g., patients with satisfactory response to previous DAA treatment are more likely to be treated again) as it applies to inclusion of patients who were treated for a previous HCV infection.
    - Potential survivorship bias among those previously treated and cured (expected to enroll very few such patients) will be examined by comparing

the efficacy and safety outcomes among those previously treated and cured and those not.

10.0 Protection of Human Subjects

The guidelines for good pharmacoepidemiology practices in non-interventional studies will be respected along with any applicable local laws and regulations. This study is not in the scope of Good Clinical Practice studies. Any Competent Authority and Institutional Review Board/Independent Ethics Committee notification or approval will be obtained prior to the initiation of the study as necessary per local Regulation.

This study is a retrospective cohort study using only pre-existing patient chart information, and no information that would enable the identification of any patients will be recorded in the study's eCRFs. Therefore, no patient study consent is needed.

11.0 Reporting of Safety Data

This study is based on secondary use of data previously collected by healthcare professionals for other purposes. Any safety information collected for the purposes of the research will be summarized in the final report.

The following AE and safety information definitions and further information are provided for reporting safety information to AbbVie in the eCRFs.

11.1 Medical Complaints

11.1.1 Adverse Event Definition and Serious Adverse Event Categories

An AE is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the labeling, as well as from "special situations" as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, lack of efficacy, or drug withdrawal, all which must be reported whether associated with an adverse event or not. Any worsening of a pre-existing condition or illness is considered an AE and should be reported as a new AE.

Laboratory abnormalities and changes in vital signs are considered to be AEs only if they resulted in discontinuation of GLE/PIB, necessitated therapeutic medical intervention, meet protocol specific criteria, and/or if the treating physician considers them to be AEs.

The table of clinical toxicity grades modified from the NCI CTCAE Version 4.03 (available on the Cancer Therapy Evaluation Program home page http://ctep.cancer.gov) is to be used in the grading of AEs and laboratory abnormalities that are reported as AEs.

If an AE meets any of the following criteria, it is considered a **serious adverse event (SAE)**:

Death of Patient:	An event that results in the death of a patient.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization:	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity:	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event, and any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.1.2 Relationship to Pharmaceutical Product

The following definitions will be used to assess the relationship of the AE to the use of GLE/PIB:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.

No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship

11.1.3 Serious and Nonserious Adverse Event Reporting

Adverse events recorded in patient charts for patients included in this study will be entered into the AbbVie eCRFs by the site physician (or site staff under the physician's supervision). Neither SAEs nor suspected adverse reactions identified during the course of the retrospective review of the data need to be reported to AbbVie in an expedited manner.

Any suspected adverse reactions considered to be related to a non-AbbVie product should be reported in accordance with local laws and regulations to the relevant regulatory authority and/or drug marketing authorization holder.

12.0 Plans for Disseminating and Communicating Study Results

At the end of the study, a report or publication will be written by AbbVie. This report/publication will contain a description of the objectives of the study, the methodology and its results and conclusions. The completed Case Report Forms and the final study output are the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without the express written approval from AbbVie.

13.0 References

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Annex 1. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	Principal Medical Writer	Medical Writing
	Scientific Director	Medical Affairs
	Director, Statistics	Statistics
	Senior Director, and Statistics Therapeutic Area Head, General Medicine and Infectious Disease	Statistics
	Program Leader	Clinical

Annex 2. Study Activities Table

This table encompasses all of the patient chart data to be collected as available in the designated time periods.	Pretreatment Data Collection	Baseline	During Treatment	During 30 Days Post Treatment	During Post-Treatment Day 31 to Day 56	SVR_{12} Window	SVR_{24} Window
Activity	Within 6 months prior to GLE/PIB treatment	Day 1 of GLE/PIB treatment	>Day 1 through Day 56 (EOT)	PT Day 1 to PT Day 30	PT Day 31 to PT Day 56	PT Day 57 to PT Day 126	PT Day 127 to PT Day 210
INTERVIEWS & QUESTIONNAIRES - as available							
Eligibility criteria	✓						
Medical record duration	✓						
HCV and medical history	✓						
Alcohol, nicotine, OST, and non-prescribed drug use	✓						
Adverse event assessment[a]		✓	✓	✓			
Prior/concomitant therapy[a]	✓	✓	✓	✓			
Post-treatment HCV therapy				✓	✓	✓	✓
LOCAL LABS & EXAMS - as available							
HIV	✓						
Height and weight (only 1 data collection at either time point is required for each)	✓	✓					
All LFTs (ALT, AST, Tbili, direct bili, indirect bili, alk phos)[b]	✓		✓				
Serum albumin, serum creatinine clearance, eGFR, INR and platelet counts[b]	✓		✓				
HCV GT, HCV RNA,HCV antibody, HCV core antigen, and SVR status – pretreatment data collection eligibility[c]	✓[a]	✓[a]	✓	✓	✓	✓	✓
TREATMENT - required							
Prescription for GLE/PIB for 8 weeks		✓					
GLE/PIB administration, interruption, or completion		✓	✓				

This table encompasses all of the patient chart data to be collected as available in the designated time periods.	Pretreatment Data Collection	Baseline	During Treatment	During 30 Days Post Treatment	During Post-Treatment Day 31 to Day 56	SVR_{12} Window	SVR_{24} Window
Activity	Within 6 months prior to GLE/PIB treatment	Day 1 of GLE/PIB treatment	>Day 1 through Day 56 (EOT)	PT Day 1 to PT Day 30	PT Day 31 to PT Day 56	PT Day 57 to PT Day 126	PT Day 127 to PT Day 210
Physician attestation that GLE/PIB was administered		✓	✓				

alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; bili = bilirubin; eGFR = estimated glomerular filtration rate; EOT = end of treatment; GLE = glecaprevir; GT = genotype; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LFT = liver function test; OST = opiate substitution; PIB = pibrentasvir; PT = post treatment; RNA = ribonucleic acid; SVR = sustained virologic response; SVR_{12} = sustained virologic response 12 weeks after the last dose of the drug; SVR_{24} = sustained virologic response 24 weeks after the last dose of the drug; Tbili = total bilirubin

a. Adverse event collection includes adverse events occurring during GLE/PIB treatment through 30-days post dosing. Prior/concomitant therapy collection includes therapies administered within 30 days prior to GLE/PIB treatment through 30 days after GLE/PIB treatment.

b. Enter laboratory values within 6 months prior to the first dose of GLE/PIB, through the duration of GLE/PIB treatment, and for up to 2 weeks after the end of GLE/PIB treatment.

c. Including HCV RNA, HCV core antigen, and/or HCV antibody data sufficient to satisfy Inclusion Criteria 1