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Protocol for Study M20-350

Acute Hepatitis C (HCV) Infection: Safety and Efficacy of Glecaprevir (GLE)/Pibrentasvir (PIB) 8-Week Treatment

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PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

SPONSOR/EMERGENCY MEDICAL CONTACT:*

Therapeutic Area Scientific Director
[redacted] PhD
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
Office:
Mobile: [redacted]
Fax:
Email:

Group Medical Director, Infectious Disease
[redacted] MD
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
Office:
Mobile: [redacted]
Fax:
Email: [redacted]

EMERGENCY 24 hour Number: +1 973 784-6402

*For European Union countries: the sponsor is AbbVie Deutschland GmbH & Co. KG. The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority. Additional study contact information can be found in the Operations Manual (Appendix F).

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1 SYNOPSIS

Title: A Multicenter, Single-Arm Prospective Study to Evaluate Safety and Efficacy of GLE/PIB 8-Week Treatment in Adults and Adolescents with Acute Hepatitis C Virus (HCV) Infection	
Background and Rationale:	Hepatitis C viral infection is a global health problem, with approximately 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 agent 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. 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 recently reported a dramatic increase in HCV within the US, with new HCV cases 4 times higher than they were 10 years ago. This jeopardizes the World Health Organization's 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 initially developed for use in chronically infected HCV treatment-naïve (TN) and treatment-experienced (TE) genotype (GT)1 – GT6-infected adult subjects without cirrhosis or with compensated 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 in the European Union on March 13, 2019. Efficacy of GLE/PIB treatment was also demonstrated in Phase 2 and Phase 3 studies in chronically HCV-infected adults who were self-reported as current/recent PWID. Regulatory approval of antiviral treatment for 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. 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. Initial evidence indicates that GLE/PIB could be an efficacious and safe treatment for this population. 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 (ITT) sustained virologic response 12 weeks post-treatment (SVR_{12}) of 90% and per protocol SVR_{12} of 96%. • 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.

	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 treatment of adults and adolescents (≥ 12 years of age) with acute HCV with GLE/PIB 300 mg/120 mg QD, which is currently approved for patients with chronic HCV. This study aims to provide data to support the treatment of acute HCV patients with GLE/PIB, facilitate HCV management in outreach settings, and improve the HCV care cascade.
Objective(s) and Endpoint(s):	**Primary Objective** The primary objective of this study is to demonstrate the efficacy of 8-week treatment with GLE/PIB in adults and adolescents with confirmed acute HCV infection by comparing the SVR_{12} rate from this study to the historical SVR_{12} rate in subjects with chronic HCV infection who were treated with GLE/PIB. The primary efficacy objective will be assessed based on the ITT population which is defined as all enrolled subjects who received at least 1 dose of study drug. **Secondary Objectives** The key secondary objective of this study is the same as the primary objective of this study except that the key secondary objective will be assessed in the modified ITT – virologic failure (mITT-VF) population. The mITT-VF population is defined as all enrolled subjects who received at least one dose of study drug, excluding those who did not achieve SVR_{12} 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 study drug, and those who were missing HCV RNA data in the SVR_{12} window after backward imputation). The other secondary objectives of this study are to determine the on-treatment virologic failure, post-treatment relapse, and post-treatment reinfection rates in the ITT population. **Safety Objectives** The safety objectives of this study are to examine the safety with respect to alanine aminotransferase (ALT) elevations, adverse events (AEs) leading to study drug discontinuation, SAEs, and AEs of hepatic decompensation during an 8-week treatment with GLE/PIB in adults and adolescents with confirmed acute HCV infection in the Safety Analysis Set (defined as all subjects who received at least 1 dose of study drug). **Primary Endpoint** The primary endpoint is the achievement of SVR_{12} (defined as HCV RNA < the lower limit of quantification [LLOQ] 12 weeks after the last actual dose of study drug) for each subject in the ITT population. **Secondary Endpoints** The key secondary endpoint is achievement of SVR_{12} for each subject in the mITT-VF population. **Supportive Secondary Endpoints** • On-treatment virologic failure for each subject in the ITT population • Post-treatment relapse for each subject in the ITT population who completed treatment as planned with HCV RNA < LLOQ at the end of treatment and with at least 1 post-treatment HCV RNA value

	• Post-treatment reinfection with HCV for each subject in the ITT population **Safety Endpoints** • Alanine aminotransferase elevations of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade 1, 2, 3, or 4 with ALT grade increased from baseline for each subject in the Safety Analysis Set • Post-nadir ALT elevation > 3 × ULN with total bilirubin >2 × ULN for each subject in the Safety Analysis Set • Treatment-emergent hepatic decompensation/hepatic failure events for each subject in the Safety Analysis Set • Treatment-emergent AEs leading to discontinuation of study drug for each subject in the Safety Analysis Set • Treatment-emergent SAEs for each subject in the Safety Analysis Set
Investigator(s):	Multicenter.
Study Site(s):	Approximately 70 sites in approximately 8 countries.
Study Population and Number of Subjects to be Enrolled:	The study population consists of subjects with acute HCV infection. The study will enroll approximately 283 subjects.
Investigational Plan:	This study will be conducted as a Phase 3b, multicenter, single-arm, prospective study to evaluate the safety and efficacy of GLE/PIB 8-week treatment in adult and adolescent subjects with acute HCV infection.

Key Eligibility Criteria:	• Adult or adolescent, age 12 years and older.
	• Subject must have evidence of acute HCV infection prior to enrollment. Evidence of acute HCV infection is defined as physician diagnosis of acute HCV infection, quantifiable HCV RNA at screening, and at least 1 of the following:
	  • Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening;
	  OR
	  • Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 11-month period prior to Screening; AND risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen;
	  OR
	  • 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 all within an 8-month period prior to Screening; AND risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen;

	OR • Negative anti-HCV antibody with a positive HCV RNA or HCV core antigen within a 5-month period prior to Screening. • Subject must be HCV treatment naïve, defined as no prior treatment including interferon for this HCV infection. • Subject must be documented as either having no cirrhosis or as having compensated cirrhosis. If liver diagnostic tests are indeterminate with available diagnostic methods, subject must demonstrate absence of decompensated cirrhosis by evaluating Child-Pugh score. • Absence of hepatocellular carcinoma (HCC), for subjects with cirrhosis or with indeterminate cirrhosis status, as indicated by a negative ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or a negative ultrasound at Screening. Subject who has a positive ultrasound result suspicious of HCC followed by a subsequent negative CT scan or MRI or biopsy result will be eligible for the study. • No history of liver decompensation.
Study Drug and Duration of Treatment:	**Glecaprevir/Pibrentasvir:** Three tablets (i.e., total daily dose of 300 mg/120 mg), taken orally QD at the same time beginning on Study Day 1 for a treatment duration of 8 weeks.
Date of Protocol Synopsis:	26 August 2022

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Hepatitis C viral infection is a global health problem, with approximately 1.75 million new infections worldwide in 2015 and an estimated 44,700 new infections in the United States (US) in 2017.[1,2] There are currently no approved direct acting antiviral agent 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 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's 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 initially developed for use in chronically infected HCV treatment-naïve (TN) and treatment-experienced (TE) genotype (GT)1 – GT6-infected adult subjects without cirrhosis or with compensated 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 in the European Union (EU) on March 13, 2019. Efficacy of GLE/PIB treatment was also demonstrated in Phase 2 and Phase 3 studies in chronically HCV-infected adults who were self-reported as current/recent PWID.[4]

Regulatory approval of antiviral treatment for 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. 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.[5,6] Initial evidence indicates that GLE/PIB could be an efficacious and safe treatment for this population. 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 (ITT) sustained virologic response 12 weeks post-treatment (SVR_{12}) of 90% and per protocol SVR_{12} of 96%.[7]
- 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.[8]

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 treatment of adults and adolescents (≥ 12 years of age) with acute HCV with GLE/PIB 300 mg/120 mg QD, which is currently approved for patients with chronic HCV.

This study aims to provide data to support the treatment of acute HCV patients with GLE/PIB, facilitate HCV management in outreach settings, and improve the HCV care cascade.

2.2 Benefits and Risks to Subjects

The GLE/PIB regimen has been well-studied in chronic HCV infection. The safety and efficacy of the GLE/PIB regimen in chronic HCV TN and/or TE HCV GT1 – GT6-infected adults without cirrhosis or with compensated cirrhosis, including subjects with severe renal impairment or end-stage renal disease (chronic kidney disease Stages 4 or 5), and subjects coinfected with HIV were demonstrated in 9 registrational studies and 3 supportive Phase 2 studies, resulting in regulatory approvals in multiple countries/regions across the globe. Subsequently, the GLE/PIB regimen was studied in a Phase 2/3 study in adolescents 12 to < 18 years of age with chronic HCV GT1 – GT6 infection. The safety and efficacy profile of GLE/PIB in adolescents with chronic HCV GT1 – GT6 infection was shown to be similar to its safety and efficacy profile established in the adult studies. Approvals for extension of the GLE/PIB treatment regimen to adolescents were granted in multiple countries/regions including the EU, US, Japan, and global registrations continue. Efficacy of GLE/PIB treatment was also demonstrated in Phase 2 and Phase 3 studies in chronically HCV-infected adults who were self-reported as current/recent PWID. In clinical trials, the safety and efficacy of GLE/PIB were shown to be similar between subjects who self-identified as current/recent PWID, those who were former PWID, and those who did not report history of injection drug use. The safety and efficacy of GLE/PIB were also similar between subjects who reported concomitant medication-assisted treatment (MAT) for opioid use disorder and those who did not report concomitant MAT.[4] The safety data of GLE/PIB from clinical studies describe a well-tolerated regimen in chronic HCV populations, including adolescents and PWID patients, with very few risks that are mitigated using the product information. Overall, the use of the GLE/PIB regimen as treatment of chronic HCV infection is supported by a favorable benefit-risk profile.

For further details, please see findings from completed studies, including safety data in the current GLE/PIB Investigator's Brochure.

Acute HCV infection is generally benign compared with chronic HCV infection, and it is expected that the same dose of GLE/PIB (300 mg/120 mg) will be effective in treating acute HCV infection. Risks associated with GLE/PIB, including the risks of toxicity, appear to be limited based on the available data.[7] Given the potential for sustained virologic response (SVR) in the acute HCV infection, the risk-benefit assessment is favorable. Given the potential for SVR in the acute HCV infection, the risk-benefit assessment is favorable.

Considering the coronavirus – 2019 (COVID-19) pandemic, the benefit and risk to subjects participating in this study have been re-evaluated. Based on the limited information to date, no additional risk to study participants is anticipated with the use of GLE/PIB. Although there is currently no demonstrated activity/efficacy of GLE/PIB against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), stopping the anti-HCV antiviral treatment may lead to the occurrence of HCV virologic failure and

development of resistance. If a subject in the study has been diagnosed or has symptoms compatible with SARS-CoV-2 infection, study drug administration should be maintained, unless a medication needed for the treatment of the COVID-19 infection is contraindicated with GLE/PIB or is documented to have significant interaction with GLE/PIB.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

The objectives of this study are to assess the safety and efficacy of GLE/PIB 8-week treatment in adults and adolescents with confirmed acute HCV infection.

Glecaprevir/pibrentasvir is expected to achieve a high SVR_{12} rate and an acceptable safety profile in adults and adolescents with acute HCV infection.

Primary

The primary objective of this study is to demonstrate the efficacy of 8-week treatment with GLE/PIB in adults and adolescents with confirmed acute HCV infection by comparing the SVR_{12} rate from this study to the historical SVR_{12} rate in subjects with chronic HCV infection who were treated with GLE/PIB. The primary efficacy objective will be assessed based on the ITT population which is defined as all enrolled subjects who received at least 1 dose of study drug.

The primary hypothesis is that 8-week treatment with GLE/PIB for subjects in the ITT population is superior to an efficacy threshold (described in Section 7.8) based on the historical ITT SVR_{12} rates of treatment with GLE/PIB in subjects with chronic HCV infection.[4] This will be shown if the lower bound of the 2-sided 95% confidence interval (using Wilson's score method) for the percentage of subjects in the ITT population achieving SVR_{12} is greater than the efficacy threshold.

The estimand corresponding to the primary efficacy objective is the percentage of acutely infected HCV subjects assigned 8 weeks of GLE/PIB in the ITT population who achieve SVR_{12}. Subjects who discontinue the study with an unknown SVR_{12} status will be counted as a failure for SVR_{12}.

Key Secondary

The key secondary objective of this study is the same as the primary objective of this study except that the key secondary objective will be assessed in the modified ITT – virologic failure (mITT-VF) population. The mITT-VF population is defined as all enrolled subjects who received at least one dose of study drug, excluding those who did not achieve SVR_{12} 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 study drug, and those who were missing HCV RNA data in the SVR_{12} window after backward imputation).

The key secondary hypothesis is that 8-week treatment with GLE/PIB for subjects in the mITT-VF population is superior to an efficacy threshold (described in Section 7.8) based on the historical mITT-VF SVR_{12} rates of treatment with GLE/PIB in the chronically-infected HCV population.[4] This will be shown if the lower bound of the 2-sided 95% confidence interval (using Wilson's score method) for the percentage of subjects in the mITT-VF population achieving SVR_{12} is greater than the efficacy threshold.

The estimand corresponding to the key secondary efficacy objective is the percentage of acutely infected HCV subjects assigned 8 weeks of GLE/PIB in the mITT-VF population (i.e., excluding those in the ITT population who did not achieve SVR_{12} for reasons other than virologic failure) who achieve SVR_{12}.

Supportive Secondary

The other secondary objectives of this study are to determine the on-treatment virologic failure (OTVF), post-treatment (PT) relapse, and post-treatment reinfection rates in the ITT population.

Safety

The safety objectives of this study are to examine the safety with respect to alanine aminotransferase (ALT) elevations, adverse events (AEs) leading to study drug discontinuation, SAEs, and AEs of hepatic decompensation during an 8-week treatment with GLE/PIB in adults and adolescents with confirmed acute HCV infection in the Safety Analysis Set (defined as all subjects who received at least 1 dose of study drug).

3.2 Primary Endpoint

The primary endpoint is the achievement of SVR_{12} (defined as HCV RNA < the lower limit of quantification [LLOQ] 12 weeks after the last actual dose of study drug) for each subject in the ITT population.

3.3 Secondary Endpoints

Key Secondary Endpoint

The key secondary endpoint is achievement of SVR_{12} for each subject in the mITT-VF population.

Supportive Secondary Endpoints

- On-treatment virologic failure (as defined in Section 7.4) for each subject in the ITT population
- Post-treatment relapse ($Relapse_{12}$: as defined in Section 7.4) for each subject in the ITT population who completed treatment as planned (as defined in Section 7.4) with HCV RNA < LLOQ at the end of treatment (EOT) and with at least 1 post-treatment HCV RNA value
- Post-treatment reinfection with HCV (as defined in Section 7.4) for each subject in the ITT population

3.4 Additional Efficacy Endpoints

Additional efficacy endpoints will be specified in the Statistical Analysis Plan (SAP).

3.5 Safety Endpoints

- Alanine aminotransferase elevations of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade 1, 2, 3 or 4 with ALT grade increased from baseline for each subject in the Safety Analysis Set.
- Post-nadir ALT elevation > 3 × upper limit of normal (ULN) with total bilirubin > 2 × ULN for each subject in the Safety Analysis Set.
- Treatment-emergent hepatic decompensation/hepatic failure events for each subject in the Safety Analysis Set.
- Treatment-emergent AEs leading to discontinuation of study drug for each subject in the Safety Analysis Set
- Treatment-emergent SAEs for each subject in the Safety Analysis Set.

4 INVESTIGATIONAL PLAN

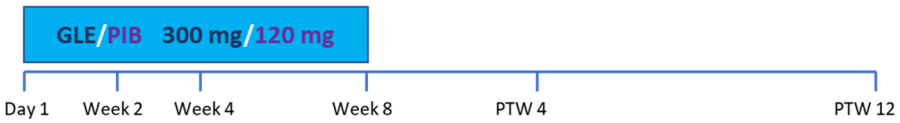
4.1 Overall Study Design and Plan

This study will be conducted as a Phase 3b, multicenter, single-arm, prospective study to evaluate the safety and efficacy of GLE/PIB 8-week treatment in adult and adolescent subjects with acute HCV infection.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual (Appendix F).

See Section 5 for information regarding eligibility criteria.

Figure 1. Study Schematic



GLE = glecaprevir; PIB = pibrentasvir; PTW = post-treatment week

4.2 Discussion of Study Design

Choice of Control Group

An integrated analysis of Phase 2 and Phase 3 studies of GLE/PIB in chronically HCV-infected adults and adolescents who were self-reported as current/recent PWID (referred to hereafter as PWID) versus those who were former/non-PWID (referred to hereafter as non-PWID) was performed, and results of the analysis are presented in the US Package Insert.[4] This analysis will provide the historical efficacy

control for the current trial. The threshold for comparison for the primary efficacy hypothesis will be derived from a weighted average of the ITT SVR_{12} rates in the PWID and non-PWID chronically infected populations of subjects. In the Phase 2 and Phase 3 studies, the overall SVR_{12} rate was 88.7% (55/62) in PWID subjects in the ITT population, with a virologic failure rate of 1.6% (1/62); the overall SVR_{12} rate was 97.8% (4147/4241) in non-PWID subjects in the ITT population, with a virologic failure rate of 1.2% (50/4241). Excluding subjects who failed to achieve SVR_{12} due to reasons other than virologic failure yields SVR_{12} rates of 98.2% (55/56) for PWID subjects and 98.8% (4147/4197) for non-PWID subjects, for the mITT-VF population. Given that the acute HCV population is comprised primarily of PWID patients and the SVR_{12} rates in the PWID subjects with chronic HCV treated with GLE/PIB are high, an active control arm would not provide value in establishing the efficacy of the 8-week GLE/PIB regimen in the acute population. So, the efficacy of GLE/PIB can be established via comparison to a threshold rather than to non-inferiority to an active control. Consequently, the observed SVR_{12} rates from the chronically infected subjects (ITT and mITT-VF populations) will be used as historical controls to provide comparators for assessment of GLE/PIB in acutely infected subjects. A threshold for each of the primary and key secondary efficacy analyses of the 8-week GLE/PIB regimen in acute HCV to the historical control is determined by subtracting a margin of 6% from the weighted average of the PWID and non-PWID historical SVR_{12} rates. A margin of 6% is selected to ensure a minimal loss of efficacy of the 8-week GLE/PIB regimen in acute HCV relative to the historical SVR_{12} rate in subjects with chronic HCV. Details for calculating the efficacy thresholds are provided in Section 7.8.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are standard for assessing disease activity in subjects with acute HCV. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

This study plans to enroll subjects age 12 years or older who have demonstrated evidence of acute HCV infection, who are either without cirrhosis or with compensated cirrhosis and are TN for the current HCV infection, in order to assess the safety and efficacy of GLE/PIB in the acute HCV patient population. Among people with acute HCV infection, PWID are the most prevalent population and PWID are at high risk of community transmission. Current intravenous drug users of the PWID population are eligible to participate in the study. Treatment of people who are at risk to transmit to other people leads to cost-savings for society.

Patients with acute hepatitis will likely have significant fluctuation of ALT levels and the peak ALT elevation can be > 10 times the ULN. In order to allow subjects with acute HCV infection to enroll, eligibility criteria are adjusted to reflect the characteristics of acute HCV infection.

Selection of Doses in the Study

The doses of GLE (300 mg) and PIB (120 mg) are the approved doses for treatment of chronic HCV infection and will be evaluated in the study for acute HCV infection. Acute HCV infection is generally benign compared with chronic HCV infection, and it is expected that the same dose of GLE/PIB (300 mg/120 mg) will be effective in treating acute HCV infection.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects or their legally authorized representative (if permitted per local regulations) must voluntarily **sign and date an informed consent** (and assent for minors as required by applicable regulation), approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult or adolescent, age 12 years and older.
- 3. Subject must be able to understand and adhere to the study protocol and study visit schedule in the opinion of the investigator.
- 4. Subject must not have any of the following abnormal laboratory results at screening:
  - Albumin < 2.8 mg/dL for subjects with cirrhosis, < lower limit of normal for subjects without cirrhosis;
  - International normalized ratio (INR) > 1.5 × ULN, unless subject has known hemophilia or is on a stable anticoagulant regimen affecting INR;
  - Hemoglobin < 10 g/dL;
  - Platelets < 50,000 cells per mm^3 for adult subjects with cirrhosis; < 90,000 cells per mm^3 for adult subjects without cirrhosis; < 40,000 cells per mm^3 for subjects aged < 18 years regardless of cirrhosis status;
  - Calculated creatinine clearance < 30 mL/min.

Subjects who have exclusionary laboratory parameters for hemoglobin and/or calculated creatinine clearance are allowed to retest 1 time within the Screening period and must meet all other eligibility laboratory criteria on the panel that is repeated. If the retest result(s) are also exclusionary, the subject may not be rescreened or retested again.

Disease/Condition Activity

- 5. Subject must have evidence of acute HCV infection prior to enrollment. Evidence of acute HCV infection is defined as physician diagnosis of acute HCV infection, quantifiable HCV RNA at Screening, and at least 1 of the following:
  - Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening;

OR

- Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 11-month period prior to Screening; AND risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen;

OR

- 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 all within an 8-month period prior to Screening; AND risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen;

OR

- Negative anti-HCV antibody with a positive HCV RNA or HCV core antigen within a 5-month period prior to Screening.

- 6. Negative test result for hepatitis B surface antigen (HBsAg).
- 7. No evidence of chronic HCV infection for this HCV infection.
- 8. No known active SARS-CoV-2 infection. All subjects should undergo viral testing to rule out SARS-CoV-2 infection at Screening. Subjects with active SARS-CoV-2 infection may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:
  - At least 10 days since first polymerase chain reaction (PCR) test result have passed in asymptomatic patients; or 10 days have passed since symptom onset and at least 24 hours since resolution of fever without use of antipyretics and other symptoms improvement.
- 9. Subject with HCV/human immunodeficiency virus 1 (HIV-1) co-infection must also meet the following criteria:
  - Naïve to HIV treatment:
    - Must have a cluster of differentiation 4 (CD4+) count ≥ 500 cells/mm^3 (or CD4+ % ≥ 29%) at Screening;
    - Have no plan to initiate HIV-1 antiretroviral therapy (ART) treatment while participating in this study.
  - On a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to Screening:
    - Must have CD4+ count ≥ 200 cells/mm^3 (or CD4+ % ≥ 14%) at Screening, and plasma HIV-1 RNA < 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0).
    - The HIV-1 ART regimen must include at least 1 of the following:
      - Raltegravir orally (*per os)* (PO) twice a day (BID)
      - Dolutegravir PO QD or BID
      - Rilpivirine PO QD
      - Elvitegravir/cobicistat PO QD
      - Bictegravir PO QD

In addition to the above medications, subjects may take a nucleoside/nucleotide reverse transcriptase inhibitor backbone containing any of the following:

- Tenofovir disoproxil fumarate PO QD
- Tenofovir alafenamide PO QD
- Abacavir PO QD or BID
- Emtricitabine PO QD
- Lamivudine (3TC) PO QD or BID

- Alternative HIV-1 ART regimens may be permitted with Sponsor approval.

Subject History

- 10. Subject must be HCV TN, defined as no prior treatment including interferon for this HCV infection.
- 11. Subject must be documented as either having no cirrhosis or as having compensated cirrhosis. If liver diagnostic tests are indeterminate with available diagnostic methods, subject must demonstrate absence of decompensated cirrhosis by evaluating Child-Pugh score.
- 12. Absence of hepatocellular carcinoma (HCC), for subjects with cirrhosis or with indeterminate cirrhosis status, as indicated by a negative ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or a negative ultrasound at Screening. Subject who has a positive ultrasound result suspicious of HCC followed by a subsequent negative CT scan or MRI or biopsy result will be eligible for the study.
- 13. No history of liver decompensation.
- 14. No history of organ transplant.
- 15. No history of severe life-threatening or other significant sensitivity to any excipients of the study drug.
- 16. Subject must not have clinically significant abnormalities, other than HCV infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile, and a 12-lead electrocardiogram (ECG) that make the subject an unsuitable candidate for this study in the opinion of the investigator, including, but not limited to:
  - Uncontrolled diabetes as defined by a glycated hemoglobin (HbA1c) level > 8.5%.
  - Active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
  - Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric, or other medical disease or disorder, which is unrelated to the existing HCV infection.
- 17. Subject must not have cause of liver disease other than HCV infection, including but not limited to the following:
  - Hemochromatosis;
  - Alpha-1 antitrypsin deficiency;

- Wilson's disease;
- Autoimmune hepatitis;
- Alcoholic liver disease;
- Cholestatic liver diseases such as primary biliary cholangitis and primary sclerosing cholangitis;
- Steatosis or steatohepatitis on liver biopsy considered to be the primary cause of the liver disease rather than concomitant/incidental with HCV infection.

✔ 18. Subject must not have uncontrolled drug use that may impair protocol compliance in the opinion of the investigator.

Contraception

✔ 19. Female who is not **pregnant or breastfeeding, and is not considering becoming pregnant or donating eggs** during the study or for approximately 30 days after the last dose of study drug.

✔ 20.For all females of child-bearing potential; a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug.

✔ 21. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is effective from Study Day 1 through at least 30 days after the last dose of study drug. Female subjects of non-childbearing potential do not need to use birth control.

Concomitant Medications

✔ 22. Subject must not require chronic use of systemic immunosuppressants during the study, including but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab).

✔ 23. Subject must not have been treated with **any investigational drug** within 30 days or 10 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another interventional clinical study or was previously enrolled in this study.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, of Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:

- Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
- Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.

- Postmenopausal female
  - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
  - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 30 international units (IU)/L.
- Premenarchal female (has not met the definition of childbearing potential below)
  - Females who have not experienced menarche (at least 1 menstrual period).

- Females, of Childbearing Potential

  Females who have experienced menarche (at least 1 menstrual period) prior to or during the study.
  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 30 days after the last dose of study drug.
  - Females must commit to one of the following methods of birth control:
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device.
    - Intrauterine hormone-releasing system.
    - Male or female condom with or without spermicide.
    - Cap, diaphragm, or sponge with spermicide.
    - A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier method).
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

Contraception Requirements for Males

No contraception is required for male subjects.

5.3 Prohibited Medications and Therapy

Subject must be able to safely discontinue any prohibited medications or supplements listed in Section 5.1 at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of GLE/PIB and not use these during the entire Treatment Period and for 14 days following discontinuation of study drug. Subject must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

In addition to the medications listed in the eligibility criteria, concomitant use of the following is NOT allowed:

- Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort;
- Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin;
- Atorvastatin, lovastatin, simvastatin;*
- Astemizole, cisapride, terfenadine;
- Atazanavir, efavirenz, oxcarbazepine, pitavastatin.

*Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drug. Subjects receiving these statins should either switch to pravastatin or rosuvastatin 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug or may interrupt statin therapy throughout the treatment period beginning at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug and until 14 days after the last dose of study drug, based on investigator's judgment. If switching to or continuing pravastatin or rosuvastatin, it is recommended to reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drug.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines), over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the subject is receiving at the time of enrollment or receives during the study must be recorded from at least 14 days prior to study drug administration through 14 days following discontinuation of study drug. After 14 days post-treatment, antiviral therapies related to the treatment of HCV, medications prescribed in association with an SAE, and opiate substitution therapy must be recorded. Nonprescribed illicit drug use must be recorded throughout the study.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie Medical Director or Scientific Director. Information regarding potential drug interactions with GLE/PIB can be located in the GLE/PIB Investigator's Brochure.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., messenger RNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening or the treatment period, as long as the vaccine is not contraindicated or medically inappropriate.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of GLE/PIB on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- The first dose of study drug GLE/PIB, when possible, is preferred to be given at least ± 7 days from any SARS-CoV-2 vaccine administration.
- GLE/PIB dosing should not be interrupted due to SARS-CoV-2 vaccine administration.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with HCV and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine electronic Case Report Form (eCRF). Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the Sponsor.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug.
- The investigator determines the subject is significantly noncompliant with study procedures.

The following criteria will be considered evidence of **HCV OTVF**, for the purposes of subject management, leading to discontinuation of study drug:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of > 1 log10 IU/mL above nadir) at any time point during treatment; or
- Confirmed HCV RNA ≥ 100 IU/mL (defined as 2 consecutive HCV RNA measurements ≥ 100 IU/mL) after HCV RNA < LLOQ during treatment.

  Confirmatory testing should be completed as soon as possible and the subject should remain on study drug treatment until the OTVF criterion has been confirmed. Subjects with confirmed OTVF will be discontinued from study drug and will continue to be followed in the PT Period for the emergence and persistence of resistant viral substitutions until 12 weeks post-treatment.

  Subjects who completed treatment with HCV RNA < LLOQ at the end of treatment who experience potential virologic failure (HCV RNA ≥ LLOQ) in the PT period should have confirmatory testing completed as soon as possible to determine if the subject relapsed.

For HCV/HIV-1 co-infected subjects on stable ART, the criteria for failure to maintain HIV virologic suppression is as follows:

- HIV-1 RNA ≥ 200 copies/mL confirmed on 2 consecutive tests at least 2 weeks apart, in a subject compliant with their HIV ART therapy.

  During the Treatment Period, subjects with confirmed failure to maintain HIV-1 RNA suppression should continue study drug treatment unless there is a requirement for prohibited concomitant medications. Clinical management of failure to maintain HIV-1 virologic suppression during the study (Treatment Period and PT Period) will be handled by the site investigator according to current HIV treatment guidelines and local standard of care.

If the investigator deems it necessary to change the HIV-1 ART regimen or to initiate ART treatment for a subject due to safety reasons, the AbbVie Medical Director or Scientific Director must be contacted and the change must be approved by AbbVie, unless the change is being made to address an immediate safety concern.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at their site if they have safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix F.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

5.7 Study Drug

Study drugs refer to drugs that are used (or can be used) in this study to assess the safety and the efficacy of the Investigational Product. Investigators will assess the relationship of AEs to the use of study drugs. See Section 6.1 (Adverse Event Severity and Relationship to Study Drug) for the list of study drugs.

Three tablets of GLE/PIB (i.e., total daily dose of 300 mg/120 mg daily dose), manufactured by AbbVie, will be taken orally QD at the same time beginning on Study Day 1 (Baseline) and should be taken at approximately the same time each day for a treatment duration of 8 weeks. The study drug will be dosed together with food. If subjects should forget to take their GLE/PIB at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember as long as it is less than 18 hours from the regularly scheduled dosing time that GLE/PIB should have been taken. Otherwise, they should take the next dose at the next scheduled dosing time.

If the subject vomits within 3 hours after taking a dose, an additional dose of study drug should be taken. If vomiting occurs more than 3 hours after dosing, an additional dose of study drug is not needed.

Where an interruption is required, the study drugs should not be interrupted for more than 7 days. If study drugs need to be interrupted for more than 7 days, the AbbVie Medical Director or Scientific Director should be contacted and consideration should be given to discontinue the subject.

If a subject experiences a severe AE (Grade 3+) or an SAE that the investigator considers to have a reasonable possibility of relationship to study drug, the investigator should assess whether the AE can be managed medically without interruption of study drug, or whether study drugs should be interrupted until the event improves. If study drugs are interrupted and restarted and the AE recurs, then study drugs should be permanently discontinued.

The subject will be instructed to return all drug containers (even if empty) to the study site personnel at Week 4 and Week 8 Visits during the Treatment Period and at the Premature Discontinuation visit (Appendix D). The study site personnel will document compliance.

AbbVie will provide study drug, GLE/PIB. AbbVie provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie. If a subject is unable to come to the study site to pick up their study drug due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to the Operations Manual in Appendix F for details on DTP shipment of study drug.

Glecaprevir/pibrentasvir will be packaged in quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs) will be returned to the sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug accountability procedures.

5.8 Randomization/Drug Assignment

This is a non-randomized, open-label, single-arm study. All eligible subjects will receive the same dosage of study drug for a duration of 8 weeks.

Details regarding the assignment of subject numbers are provided in Section 6.3 of the Operations Manual (Appendix F).

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IEC/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

5.10 Data Monitoring Committee

Not applicable.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) 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 protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is

considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
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 or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
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 subject. 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 subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, 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. 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.

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. After 30 days following the last dose of study drug or completion of study treatment only spontaneously reported SAEs will be collected (nonserious AEs will not be collected). In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an Investigational Medicinal Product (IMP) related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the investigational medicinal product (IMP) was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information) and meets one of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the NCI CTCAE (Version 4.03).

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

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.

Study Drugs That Will Be Assessed for the Relationship to Adverse Events

Study Drug Name: GLE/PIB

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Administration of study drug may be continued at the investigator's discretion after discussion with the subject if the benefit of continuing therapy is felt to outweigh the risk (Section 5.5). If a subject is discontinued, the subject will be monitored for SVR in the Post-Treatment Period as described in Appendix D.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected for pregnancies occurring up to 30 days after the EOT.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Toxicity Management

For the purpose of medical management, all AEs and laboratory abnormalities that occur during the study must be evaluated by the investigator. All AEs and laboratory abnormalities will be managed and followed to a satisfactory clinical resolution. A toxicity is deemed "clinically significant" based on the medical judgment of the investigator. The table of clinical toxicity grades "NCI CTCAE, Version 4.03" is to be used in the grading of AEs and laboratory abnormalities.

The following specific toxicity management guidelines apply to the instances of increases in ALT:

If a subject experiences a post-baseline ALT value ≥ 5 × ULN that is also ≥ 2 × Baseline value, the subject should have a confirmatory test performed. If, the ALT value is confirmed ≥ 5 × ULN, and ≥ 2 × Baseline value, the recommendations below should be followed:

If a subject experiences a post-nadir ALT elevation > 3 × ULN with total bilirubin > 2 × ULN, the recommendations below should also be followed:

- Complete hepatic questionnaire eCRF.

- Evaluate for alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain anti-hepatitis A virus (HAV) immunoglobulin M (IgM), anti-HAV total, anti-hepatitis B virus core (HBc) IgM, anti-HBc total, anti-hepatitis B viruses (HBVs), HBV DNA, HBsAg, anti-hepatitis E virus (HEV) IgM, anti-HEV immunoglobulin G and HEV RNA, and other additional tests, as appropriate.
- Manage the subject as medically appropriate.
- Repeat ALT, aspartate aminotransferase (AST), total and fractionated bilirubin, alkaline phosphatase and INR within 1 week. Repeat liver chemistries as indicated until resolution.
- Discontinue study drugs if any of the following is observed at any time:
  - ALT level is ≥ 20 × ULN in the absence of an alternate etiology.
  - Increasing direct bilirubin or INR or onset of symptoms/signs of hepatitis.
  - At the discretion of the investigator.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and secondary analyses. Complete and specific details of the statistical analysis will be described in the SAP.

SAS (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.

7.2 Definition for Analysis Populations

The ITT population is defined as all enrolled subjects who received at least 1 dose of study drug. The ITT population will be used for the primary efficacy analysis and other secondary efficacy analyses.

The mITT-VF population is defined as all enrolled subjects who received at least 1 dose of study drug, excluding those who did not achieve SVR_{12} 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 study drug, and those who were missing HCV RNA data in the SVR_{12} window after backward imputation). The mITT-VF population will be used for the key secondary efficacy analysis.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug.

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

For the primary efficacy analysis, subjects who discontinue the trial with an unknown SVR_{12} status (after applying backward imputation) will be counted as a failure for SVR_{12}.

7.4 Statistical Analyses for Efficacy

Descriptive statistics will be provided, such as the number of observations, mean, and standard deviation for continuous variables and counts and percentages for discrete variables.

The primary and key secondary efficacy analyses will be performed on the ITT and mITT-VF populations, respectively, as defined in Section 7.2. Supportive secondary efficacy analyses will be performed on the ITT population.

Intercurrent events will be analyzed as described in Section 7.3. For the primary efficacy analysis, subjects who do not have an SVR_{12} result after applying backward imputation will be considered a failure for SVR_{12}.

No data will be imputed for any efficacy analyses except for analyses of SVR endpoints (HCV RNA data) and patient reported outcomes (PRO) questionnaires. Hepatitis C virus RNA values will be selected for the analyses of all SVR endpoints based on defined visit windows. A backward imputation method will be used to impute missing responses for SVR analyses. Details of the backward imputation method and the imputation of missing responses on PRO questionnaires will be described in the SAP.

Summary and Analysis of the Primary Endpoint

The primary endpoint is the achievement of SVR_{12} (defined as HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) for each subject in the ITT population.

For the primary efficacy endpoint analysis, the number and percentage of subjects achieving SVR_{12} will be calculated for the ITT population along with a 2-sided 95% confidence interval using Wilson's score method. The superiority of 8-week treatment with GLE/PIB in acute HCV infection to the weighted efficacy threshold described in Section 7.8, which is based on the historical ITT SVR_{12} rate of treatment with GLE/PIB in PWID and non-PWID subjects with chronic HCV infection, will be demonstrated if the lower bound of the 2-sided 95% confidence interval (using Wilson's score method) for the percentage of subjects achieving SVR_{12} is greater than the weighted efficacy threshold.

In this analysis, subjects who have OTVF, $Relapse_{12}$, or post-treatment reinfection (defined below), are missing SVR_{12} status after backward imputation, or have early premature discontinuation leading to virologic failure will count as SVR_{12} failures. A summary of reasons for SVR_{12} non-response will be provided.

Details of the analysis will be documented in the SAP.

Summary and Analysis of Secondary Endpoints

Summary and Analysis of Key Secondary Endpoint

The key secondary endpoint is achievement of SVR_{12} for each subject in the mITT-VF population.

For the key secondary endpoint analysis, the number and percentage of subjects achieving SVR_{12} will be calculated for the mITT-VF population along with a 2-sided 95% confidence interval using Wilson's score method.

The superiority of 8-week treatment with GLE/PIB in acute HCV infection to the weighted efficacy threshold described in Section 7.8, which is based on the historical mITT-VF SVR_{12} rate of treatment with GLE/PIB for PWID and non-PWID with chronic HCV infection, will be demonstrated if the lower bound of the 2-sided 95% confidence interval (using Wilson's score method) for the percentage of subjects achieving SVR_{12} is greater than the efficacy threshold. The key secondary hypothesis will be tested only if the primary efficacy hypothesis is demonstrated according to the fixed-sequence testing procedure described in Section 7.7. Details of the analysis will be documented in the SAP.

Summary and Analysis of Supportive Secondary Endpoints

Supportive secondary endpoints:

1. On-treatment virologic failure (defined as confirmed increase of > 1 log10 IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the EOT with at least 6 weeks of treatment) for each subject in the ITT population.
2. Post-treatment relapse ($Relapse_{12}$: defined as confirmed HCV RNA ≥ LLOQ between EOT and 12 weeks after the last dose of study drug [up to and including the SVR_{12} assessment time point], excluding cases of reinfection) for each subject in the ITT population who completed treatment as planned (defined as study drug duration ≥ 52 days) with HCV RNA < LLOQ at the EOT and with at least 1 post-treatment HCV RNA value.
3. Post-treatment reinfection with HCV (defined as confirmed HCV RNA ≥ LLOQ in the PT period along with the PT detection of a different HCV genotype, subtype, or clade compared with baseline) for each subject in the ITT population.

For each secondary endpoint, the number and percentage of subjects in the ITT population meeting the endpoint will be calculated along with a 2-sided 95% confidence interval using Wilson's score method.

Details of the analyses will be documented in the SAP.

Summary and Analysis of Additional Efficacy Endpoints

Analysis of additional efficacy endpoints will be described in the SAP.

Subgroup Analysis for Efficacy

Subgroup analyses on the percentage of subjects achieving SVR_{12} will be performed. For each subgroup, the number and percentage of subjects achieving SVR_{12} will be calculated for the ITT and mITT-VF populations. For subgroups with at least 5 subjects, a 2-sided 95% confidence interval for the percentage will be calculated using Wilson's score method in the ITT and mITT-VF populations. Analysis of SVR_{12} will be provided for the following subgroups:

- HCV genotype and subtype;
- Sex;
- Age;
- Race;

- Body mass index;
- Baseline HCV RNA level;
- Baseline platelet count;
- Baseline serum albumin;
- Baseline ALT;
- Baseline total bilirubin;
- Geographic region;
- Baseline creatinine clearance/estimated glomerular filtration rate;
- History of diabetes;
- Stable opiate substitution status;
- Non-prescribed drug use status;
- Baseline aspartate aminotransferase to platelet ratio index (APRI);
- Baseline FibroTest;
- Baseline Fibrosis-4;
- Baseline ALT/AST ratio;
- Baseline risk behaviors;
- HIV status;
- Estimated acute HCV infection duration;
- Primary versus re-infection status;
- Baseline fibrosis stage;
- Baseline cirrhosis status;
- Study treatment duration;
- Study treatment compliance.

Details of the analyses will be documented in the SAP.

7.5 Statistical Analyses for Safety

The safety endpoints specified in Section 3.1, where AE endpoints will be based on treatment-emergent AEs and laboratory endpoints will be based on values collected during treatment, will be analyzed 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. Treatment-emergent hepatic decompensation/hepatic failure events will be identified using the AbbVie Product Medical Dictionary for Regulatory Activities (MedDRA) query, including events such as ascites, hepatic encephalopathy, esophageal variceal bleeding, and spontaneous bacterial peritonitis. For each safety endpoint, the number and percentage of subjects meeting the criteria will be calculated.

7.6 Interim Analysis

Not applicable for this study.

7.7 Overall Type I Error Control

In order to control the family-wise Type I error rate, a fixed-sequence testing procedure will be used for the primary and key secondary efficacy analyses of SVR_{12} as listed below. The fixed-sequence testing procedure will utilize the sequence of the primary analysis followed by the key secondary analysis.

The multiplicity-controlled efficacy analyses will be performed sequentially in the following order:

1. Primary: Superiority of the SVR_{12} rate of 8-week treatment with GLE/PIB for subjects in the ITT population to the efficacy threshold. If superiority is demonstrated, then proceed to the key secondary efficacy analysis. If superiority is not demonstrated in the primary analysis, then stop the testing procedure (i.e., do not perform the key secondary analysis).
2. Key Secondary: Superiority of the SVR_{12} rate of 8-week treatment with GLE/PIB for subjects in the mITT-VF population to the efficacy threshold. If superiority is demonstrated, then declare superiority for both the mITT-VF and ITT populations. If not, then declare that superiority was demonstrated only for the ITT population.

7.8 Sample Size Determination

The threshold for comparison for the primary efficacy estimand will be derived from a weighted average of the ITT SVR_{12} rates in the PWID and non-PWID chronically infected populations of subjects who received GLE/PIB in Phase 2 and 3 trials. The ITT SVR_{12} rate among chronically infected HCV PWID (current/recent PWID) is 88.7% and is 97.8% among chronic non-PWID (former/non-PWID) (Mavyret US Prescribing Information 2020, Section 14.9[4]). The threshold for comparison will be calculated by (proportion of PWID in the ITT population of this study × 88.7%) + (proportion of non-PWID in the ITT population of this study × 97.8%) minus a margin of 6%. Therefore, the threshold would be 82.7% if all subjects in the ITT population of this study are PWID, and it would be 91.8% if all subjects in the ITT population of this study are non-PWID. Similarly, the threshold for the comparison of the key secondary 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% and is 98.8% among chronic non-PWID. The threshold for comparison will be calculated by (proportion of PWID in the mITT-VF population of this study × 98.2%) + (proportion of non-PWID in the mITT-VF population of this study × 98.8%) minus a margin of 6%. It follows that the threshold would be 92.2% if all subjects in the mITT-VF population of this study are PWID, and it would be 92.8% if all subjects in the mITT-VF population of this study are non-PWID.

It is planned to enroll approximately 283 subjects. Assuming all of the subjects in the ITT population of this study are PWID, 283 subjects will provide 80% power to show that an 88.7% SVR_{12} rate among acutely infected HCV subjects in the ITT population is superior to a threshold of 82.7% based on the historical ITT SVR_{12} rate among chronically infected HCV subjects, using a 2-sided 95% confidence

interval. Assuming all of the subjects in the ITT population of this study are non-PWID, 283 subjects will provide greater than 95% power to show that a 97.8% SVR_{12} rate among acutely infected HCV subjects in the ITT population is superior to a threshold of 91.8% based on the historical ITT SVR_{12} rate among chronically infected HCV subjects, using a 2-sided 95% confidence interval.

Assuming that approximately 10% of the ITT subjects will not be included in the mITT-VF population and that all of the subjects in the mITT-VF population of this study are PWID, a total of 255 subjects will provide greater than 95% power to show that a 98.2% SVR_{12} rate among acutely infected HCV subjects in the mITT-VF population is superior to a threshold of 92.2% based on the historical mITT-VF SVR_{12} rate among chronically infected HCV subjects using a 2-sided 95% confidence interval. Assuming all of the subjects in the mITT-VF population of this study are non-PWID, 255 subjects will provide greater than 95% power to show that a 98.8% SVR_{12} rate among acutely infected HCV subjects in the mITT-VF population is superior to a threshold of 92.8% based on the historical mITT-VF SVR_{12} rate among chronically infected HCV subjects, using a 2-sided 95% confidence interval.

Additionally, the proposed sample size of 283 will provide greater than 94% probability to detect any toxicity that has a true incidence rate of at least 1% in subjects with acute HCV infection. Table 1 shows the probability that a given AE or laboratory toxicity would be observed with a sample size of 283 subjects in the Safety Analysis Set.

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

True Toxicity Rate	Sample Size	Probability of at Least 1 Subject with Toxicity
0.5%	283	75.8%
1%	283	94.2%
2%	283	99.7%
3%	283	100%

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines,

applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 START AND COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of end of study participation by the last subject in the last country where the study was conducted.

12 REFERENCES

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
APRI	Aminotransferase to platelet ratio index
aPTT	Activated partial thromboplastin time
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
BID	Twice a day
BUN	Blood urea nitrogen
CD4+	Cluster of differentiation 4
COVID-19	Coronavirus – 2019
CS	Clinically significant
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D/C	Discontinuation
DNA	Deoxyribonucleic acid
DTP	Direct-to-patient
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
EQ-5D-5L	EuroQol-5 Dimensions-5 Level
EU	European Union
EudraCT	European Clinical Trials Database
FSH	Follicle-stimulating hormone
FSS	Fatigue Severity Scale
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GLE	Glecaprevir
GLE/PIB	Glecaprevir and Pibrentasvir
GT	Genotype

HAV	Hepatitis A virus
HbA1c	Glycated hemoglobin
HBc	Hepatitis B virus core
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus 1
IASL	International Association of the Study of the Liver
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IgM	Immunoglobulin M
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intention-to-treat
IU	International unit
LDL	Low density lipoprotein
LLOQ	Lower limit of quantification
MAT	Medication-assisted treatment
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT-VF	Modified intention-to-treat analysis set excluding those who did not achieve SVR_{12} due to reasons other than virologic failure
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NCS	Not clinically significant
OTVF	On-treatment virologic failure
PCR	Polymerase chain reaction

PIB	Pibrentasvir
PO	Orally (*per os*)
PRO	Patient reported outcomes
PT	Post-treatment or pro-thrombin time
PTW	Post-treatment week
PWID	People who inject drugs
QD	Once daily
RBC	Red blood cell
RNA	Ribonucleic acid
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SUSAR	Suspected unexpected serious adverse reactions
SVR	Sustained virologic response
SVR_{12}	Sustained virologic response 12 weeks post-treatment
TE	Treatment-experienced
TN	Treatment-naïve
ULN	Upper limit of normal
US	United States
WBC	White blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M20-350: A Multicenter, Single-Arm Prospective Study to Evaluate Safety and Efficacy of GLE/PIB 8-Week Treatment in Adults and Adolescents with Acute Hepatitis C Virus (HCV) Infection

Protocol Date: 26 August 2022

Clinical research studies sponsored by AbbVie are subject to the ICH GCP and local laws and regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate IRB/IEC, except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly (within one [1] calendar day to AbbVie, the ethics committees/institutional review boards [as required] and other appropriate individuals [e.g., coordinating investigator, institution director]):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Development
[redacted]	[redacted]	Statistics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities for this study. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed in the Operations Manual.

Study Activities Table

Activity	Screening (Day –30 to Day –1)	Baseline (Day 1)	Week 2	Week 4	Week 8 (EOT) or Premature D/C from Treatment	PT Week 4	PT Week 12 or PT Premature D/C
INTERVIEWS & QUESTIONNAIRES							
Informed consent	✓						
Eligibility criteria	✓	✓					
Medical/surgical history (update on Day 1)	✓	✓					
Alcohol and nicotine use	✓						
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓
Patient Reported Outcomes (EQ-5D-5L, FSS)		✓			✓		✓
Questions on hepatitis C risk behaviors	✓						
Questions on experience with opioid substitutes and non-prescribed illicit drug use		✓			✓		✓
EXAMS							
12-lead ECG	✓						
Height (screening only) and weight	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓
Physical examination	✓	✓			✓		✓
Child-Pugh score (cirrhotic subjects and subjects with indeterminate cirrhosis status only)	✓	✓			✓		
Hepatic decompensation assessment	✓	✓					
HCC screen by ultrasound, if cirrhotic or indeterminate cirrhosis status	✓						
LOCAL LABS							
SARS-CoV-2 testing (e.g., PCR)	✓						
Review of signs/symptoms of SARS-CoV-2 infection at Day 1, then as suspected		✓					

Activity	Screening (Day –30 to Day –1)	Baseline (Day 1)	Week 2	Week 4	Week 8 (EOT) or Premature D/C from Treatment	PT Week 4	PT Week 12 or PT Premature D/C
CENTRAL LABS							
HIV-1 RNA (only for HCV/HIV coinfected subjects)	✓	✓	✓	✓	✓	✓	✓
Anti-HCV antibody, HIV antibody, and HBsAg	✓						
Hematology, clinical chemistry, urinalysis, coagulation panel	✓	✓	✓	✓	✓	✓	✓
Pregnancy test (for female confirmed to have child-bearing potential [S-serum; U-urine])	✓(s)	✓(u)		✓(u)	✓(u)	✓(u)	✓(u)
FSH (female with no menses for > 12 months)	✓						
HCV genotype/subtype	✓						
Hepatitis B Panel	✓						
HbA1c	✓						
Total Insulin		✓					✓
Fibrotest and APRI (or Fibroscan or Liver Biopsy)	✓						
HCV RNA	✓	✓	✓	✓	✓	✓	✓
HCV resistance sample		✓	✓	✓	✓	✓	✓
Archive sample	✓	✓	✓	✓	✓	✓	✓
Drug/Alcohol Screen	✓						
Flow cytometry CD4+ (only for HCV/HIV coinfected subjects)	✓						
TREATMENT							
Drug Assignment		✓					
Dispense study drug		✓		✓			
Perform drug reconciliation				✓	✓		

APRI = aminotransferase to platelet ratio index; CD4+ = cluster of differentiation 4; D/C = discontinuation; ECG = electrocardiogram; EOT = end of treatment; EQ-5D-5L = EuroQol-5 Dimensions-5 Level; FSH = follicle-stimulating hormone; FSS = Fatigue Severity Scale; HbA1c = glycated hemoglobin; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus 1; PCR = polymerase chain reaction; PT = post-treatment; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	01 March 2021
Version 2.0	02 April 2021
Version 3.0	23 April 2021
Administrative Change 1	01 June 2021
Version 4.0	14 October 2021

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following:

- *Title page: Added Sponsor name for EU countries.*

  Rationale: *To clarify Sponsor name for EU countries.*

- *Section 5.1: Added text to Eligibility Criterion 5 to indicate that subjects must have quantifiable HCV RNA at Screening.*

  Rationale: *To clarify definition of acute HCV infection.*

- *Section 5.1: Added bictegravir to Eligibility Criterion 9 as a permitted ART.*

  Rationale: *To clarify that bictegravir is an acceptable component of a qualifying HIV-1 ART regimen.*

- *Section 5.1: Added instructions to Eligibility Criterion 11 for determining absence of decompensated cirrhosis.*

  Rationale: *To clarify subject eligibility if liver diagnostic tests are indeterminate.*

- *Section 5.1: Added text to Eligibility Criterion 12 to indicate that subjects with indeterminate cirrhosis status must demonstrate absence of HCC.*

  Rationale: *To clarify subject eligibility if liver diagnostic tests are indeterminate.*

- *Section 5.1: Edited text in Eligibility Criterion 23 to update the length of time that subjects must not have been treated with any investigational drug prior to the first dose of study drug.*

  Rationale: *To align the length of time with what is allowed for discontinuation of prohibited medications prior to the first dose of study drug.*

- *Section 5.3: Added text to describe timing of discontinuation of prohibited medications and to indicate that concomitant use of certain medications is not allowed.*

  Rationale: *To clarify safe discontinuation of prohibited medications and clarify that concomitant use of certain medications is not allowed.*

- *Section 5.7: Added text to describe handling of study drug upon completion or discontinuation from study treatment.*

Rationale: *To clarify study drug return or destruction procedures.*

- *Section 5.7 and Section 6.1: Added text and table to define study drugs.*

  Rationale: *To clarify study drugs that will be assessed for their relationship to adverse events.*

- *Section 6.1: Added text to describe collection of SAEs after 30 days following last dose of study drug or completion of study treatment.*

  Rationale: *To clarify what types of AEs will be collected after 30 days following last dose of study drug or completion of study treatment.*

- *Section 7.4: Added subgroups to the list for analysis of efficacy.*

  Rationale: *To align the subgroups for analysis of efficacy with the SAP.*

- *Section 11: Added definition of study start and updated definition of end-of-study.*

  Rationale: *To clarify definitions of study start and end-of-study.*

- *Appendix F: Removed collection of respiratory rate.*

  Rationale: *To remove unnecessary vital sign determination.*

- *Appendix B: Added text describing reporting responsibilities of the investigator.*

  Rationale: *To clarify the reporting responsibilities of the investigator.*

- *Appendix C and Appendix F: Modified the list of protocol signatories.*

  Rationale: *To align with the current team composition and relevant standard operating procedures.*

- *Appendix F: Updated Section 1 contact information.*

  Rationale: *To reflect current team contact information.*

- *Appendix F: Added text to describe testing procedures for subjects with indeterminate cirrhosis status.*

  Rationale: *To align with clarified eligibility criteria for subjects with indeterminate cirrhosis status.*