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Protocol for Study M16-133
Chronic HCV Genotype 1 – 6:
Glecaprevir/Pibrentasvir Once Daily Therapy in Subjects with APRI ≤ 1

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FULL TITLE: A Single Arm, Open Label, Multicenter Study to Evaluate the Efficacy and Safety of Glecaprevir(GLE)/Pibrentasvir(PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotypes 1 – 6 Infection and Aspartate aminotransferase to Platelet Ratio Index (APRI) ≤ 1

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1 SYNOPSIS

Title: A Single Arm, Open Label, Multicenter Study to Evaluate the Efficacy and Safety of Glecaprevir(GLE)/Pibrentasvir(PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotypes 1 – 6 Infection and Aspartate aminotransferase to Platelet Ratio Index (APRI) ≤ 1	
Background and Rationale:	The advent of direct-acting antivirals (DAAs) has dramatically changed the hepatitis C virus (HCV) treatment outcomes, with sustained virologic response (SVR) rates over 90% with shorter treatment durations and improved tolerability compared to peginterferon based regimens. However with the first generation DAAs, there is still a need for a comprehensive patient assessment, including determination of fibrosis status, genotype (GT) and subtype, and baseline characteristics (such as quantitative viral load) in order to determine the best treatment strategy (regimen, duration, addition of ribavirin). AbbVie's next generation DAAs include glecaprevir (GLE), an HCV nonstructural (NS) 3/4A protease inhibitor (PI) and pibrentasvir (PIB), an HCV NS5A inhibitor. Each DAA has potent antiviral activity against the major HCV GTs in vitro with no or little loss of potency against common single-position NS3 and NS5A resistance-associated substitutions. Glecaprevir/pibrentasvir fixed-dose combination tablets have been developed for the treatment of chronic HCV infection. While a pangenotypic regimen that has high efficacy across all treatment-naïve non-cirrhotic patients with 8 week treatment duration is very attractive for treatment simplification and scaling up therapy, the need for a comprehensive patient evaluation with more complex diagnostic tests such as liver biopsy and transient elastography to identify cirrhosis can still be a barrier to access to treatment. Several serum biomarkers have been evaluated to identify patients with cirrhosis or advanced fibrosis. Among these, the Aspartate aminotransferase to Platelet Ratio Index (APRI) has been extensively studied and a meta-analysis including more than 16,000 patients has shown mean accuracy of 0.84 to identify non-cirrhotic patients with a cut off ≤ 1. The negative predictive value, i.e., the probability of identifying non-cirrhotic patients when in a population with an estimated cirrhosis prevalence of around 18% for APRI ≤ 1 using sensitivity and specificity reported in this meta-analysis was calculated to be around 94%. In addition, APRI is a widely available low cost test that is very easy to perform. This study is being conducted to further assess the safety and efficacy of 8 weeks of GLE/PIB combination regimen (300 mg GLE/120 mg PIB, once daily [QD]) in treatment naïve adults with chronic HCV GT1 – 6 infection and APRI ≤ 1.

Objective(s) and Endpoint(s):	The primary objective of this study is: • To demonstrate the efficacy (by achieving high sustained virologic response 12 weeks post dosing [SVR_{12}] rate) and safety of 8 weeks of treatment with the GLE/PIB combination regimen in treatment naïve adults with HCV GT 1 – GT6 infection with APRI ≤ 1. The primary efficacy objective will be assessed based on modified intention-to-treat (mITT) population across genotypes HCV GT1 – GT6. The primary efficacy endpoint is the percentage of subjects who achieve SVR_{12} (HCV RNA < lower limit of quantification [LLOQ] 12 weeks after the last actual dose of study drug) across genotypes in adults with HCV GT1 – GT6 based on mITT population.
Investigator(s):	Multicenter
Study Site(s):	Approximately 43 sites worldwide.
Study Population and Number of Subjects to be Enrolled:	Approximately 230 subjects with chronic HCV GT1 – 6 (maximum of 20% [46] enrollment of GT3 subjects) and APRI ≤ 1, who meet all eligibility criteria.
Investigational Plan:	Non-randomised, open label, Phase 3b study.
Key Eligibility Criteria:	**Demographic and Laboratory Assessments** ✓ Adult male or female, at least 18 years old at the time of screening. ✓ Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug: • Platelets ≥ 150,000 cells/mm^3 • Alanine aminotransferase (ALT) ≤ 10 × upper limit of normal (ULN) • Aspartate aminotransferase (AST) ≤ 10 × ULN • Direct bilirubin ≤ ULN • Albumin ≥ lower limit of normal (LLN) • Calculated creatinine clearance (using Cockcroft-Gault method) ≥ 30 mL/min • A negative hepatitis B surface antigen (HBsAg), and negative anti-hepatitis B core (HBc) or; hepatitis B virus (HBV) DNA < LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti hepatitis B surface [HBs]) **Disease Activity** ✓ Positive anti- HCV antibody (Ab) AND Plasma HCV RNA viral load ≥ 1000 IU/mL at Screening and for at least 6 months before Screening. ✓ Any HCV GT allowed, including HCV GT1-, 2-, 3-, 4-, 5-, and/or 6-infection. Mixed GT and indeterminate GT may be acceptable. ✓ APRI SCORE ≤ 1, at time of Screening.

Key Eligibility Criteria (continued):	**Subject History** ✅ No history of hepatocellular carcinoma (HCC). ✅ No evidence of cirrhosis described as: • previous histologic diagnosis of cirrhosis on liver biopsy, e.g., METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of > 3, Ishak score of > 4 in any liver biopsy conducted prior to screening, OR • Any previous transient elastography score of ≥ 12.5 kPa, OR • Any current or historical clinical evidence of cirrhosis or decompensated cirrhosis, including any current or past evidence of Child-Pugh B or C classification, hepatic encephalopathy or variceal bleeding; radiographic evidence of ascites; or use of lactulose and/or rifaximin for hepatic encephalopathy prophylaxis or treatment. ✅ Subject is treatment naïve, e.g., has never received any other investigational or commercially available anti-HCV agents (e.g., interferon, peginterferon, ribavirin [RBV], telaprevir, boceprevir, simeprevir, asunaprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, dasabuvir, voxilaprevir or any other anti-HCV agent that is approved during the study).
Study Drug and Duration of Treatment:	Subjects will receive GLE/PIB combination (300 mg/120 mg) QD for 8 weeks and followed for an additional 12 week post-treatment period.
Date of Protocol Synopsis:	31 July 2017

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Hepatitis C viral infection is a global health problem, with over 184 million individuals infected worldwide.[1] Successful treatment of HCV has been shown to significantly reduce the risk of disease progression and related mortality.[2,3] The advent of DAAs has dramatically changed the HCV treatment outcomes, with SVR rates over 90% with shorter treatment durations and improved tolerability compared to peginterferon based regimens. However with the first generation DAAs,[4] there is still a need for a comprehensive patient assessment, including determination of fibrosis status, genotype and subtype, and baseline characteristics (such as quantitative viral load) in order to determine the best treatment strategy (regimen, duration, addition of RBV). The next generation DAAs are typically pangenotypic but the optimal treatment duration still depends on fewer key baseline characteristics such as cirrhosis status and GT.[2] Fibrosis status is usually assessed by liver biopsy (an invasive method) or a noninvasive method such as transient elastography which is currently not available worldwide.[5] Due to prior limitations on treatment availability, patients with advanced liver disease were prioritized to receive treatment with DAAs.[5] As these patient populations have consistently achieved SVR, the focus is shifting to patients with milder forms of liver disease (i.e., non-cirrhotic) for whom HCV treatment is also cost effective (as these patients have a low risk of developing cirrhosis after achieving SVR).[3,5-7] In addition, some models have shown that scaling up therapy for the patient population with mild liver disease is a key strategy towards HCV eradication by impacting disease prevalence and transmission.[5]

AbbVie's next generation DAAs include GLE, an HCV NS3/4A PI, and PIB, an HCV NS5A inhibitor. Each DAA has potent antiviral activity against the major HCV GTs in vitro with no or little loss of potency against common single-position NS3 and NS5A resistance-associated substitutions. Glecaprevir/pibrentasvir fixed-dose combination tablets have been developed for the treatment of chronic HCV infection.[8,9]

The GLE/PIB registrational program assessed a broad population including subjects with compensated liver disease and subjects with severe renal insufficiency across all GTs using a single GLE/PIB dose of 300 mg/120 mg QD. Supportive Phase 2 studies used the Phase 2 formulation of separate GLE and PIB tablets, with each tablet containing 100 mg and 40 mg, respectively. Treatment arms from these supportive Phase 2 studies using the regimen selected for registrational studies (GLE 300 mg plus PIB 120 mg) were pooled with arms from the registrational studies for analyses of efficacy and safety. Treatment-naïve and treatment experienced subjects to any combination of pegylated interferon, RBV, sofosbuvir, NS5A inhibitors, or PIs were allowed in the program. In addition, the program included subjects with HIV co-infection (Study M13-590), subjects with chronic kidney disease Stages 4 – 5, including those on hemodialysis (Study M15-462), subjects with compensated cirrhosis (Studies M14-172, M15-462, and M14-868 Part 3), and subjects with or without cirrhosis who failed a previous regimen containing an NS5A inhibitor and/or an NS3/4A PI (Study M15-410).

A total of 2,376 subjects were randomized or enrolled in the registrational studies or supportive Phase 2 studies to receive GLE 300 mg QD and PIB 120 mg QD. Of these, 2,369 subjects received at least 1 dose of study drug.[8-13]

In treatment naïve subjects with compensated cirrhosis GLE/PIB achieved SVR_{12} rates over 98%, including in subjects with GT3, with 12 weeks of therapy as in SURVEYOR II Part 3 (Study M14-868 – GT3).[10]

Based on the efficacy data presented above, the 8-week treatment duration is anticipated to achieve high SVR_{12} rates in GT1 – 6-infected treatment-naïve subjects without cirrhosis.[10,12]

In Phase 3 trial, ENDURANCE-1 (M13-590), that has explored chronic HCV GT1 treatment naïve adult subjects without cirrhosis, the administration GLE/PIB for 8 weeks has shown SVR_{12} rates of 99.1% (348/351 including 1 subject with missing data). This was non-inferior to the 12 week arm data.[11] In the combined analysis from Phase 2, SURVEYOR II-Part 4 study that has explored chronic GT2, 4, 5 and 6 treatment-naïve adult subjects without cirrhosis, the administration GLE/PIB for 8 weeks has shown SVR_{12} rates of 96.5% (196/203, including 3 subjects with missing data).[12] These results were similar to 12 weeks of GLE/PIB in this population. For chronic HCV GT3 treatment-naïve adult subjects without-cirrhosis, the SVR_{12} rate for 8 weeks of therapy was 94.9% (149/157 including 2 subjects with missing data), also non-inferior to 12 weeks of therapy as demonstrated in ENDURANCE-3 (Study M13-594).[13]

While a pangenotypic regimen that has high efficacy across all treatment-naïve non-cirrhotic patients with 8 week treatment duration is very attractive for treatment simplification and scaling up therapy[6,7,14], the need for a comprehensive patient evaluation with more complex diagnostic tests such as liver biopsy and transient elastography to identify cirrhosis can still be a barrier to access to treatment.[5] Some guidelines recommend that serum biomarkers can be used in the absence of transient elastography.[4,5,7,14] The World Health Organization (WHO) guidelines state that non-invasive monitoring is considered to be preferable to invasive testing. The WHO considers that APRI, Fibrosis-4 score (FIB-4) and transient elastography are the most useful tests for assessing the stage of liver disease.[5] Several serum biomarkers have been evaluated to identify patients with cirrhosis or advanced fibrosis. Among these, the APRI has been extensively studied and a meta-analysis including more than 16,000 patients has shown mean accuracy of 0.84 to identify non-cirrhotic patients with a cut off ≤ 1.[6] The negative predictive value, i.e., the probability of identifying non-cirrhotic patients when in a population with an estimated cirrhosis prevalence of around 18% for APRI ≤ 1 using sensitivity and specificity reported in this meta-analysis was calculated to be around 94%. In addition, APRI is a widely available low cost test that is very easy to perform and is validated to diagnose fibrosis and cirrhosis.[5,6] The APRI cut off ≤ 1 is recommended in guidelines to rule out cirrhosis.[6,7,14] Being able to easily identify patients that are eligible for 8 week treatment could simplify treatment algorithms and reserve liver biopsy and transient elastography for those patients who really need a more advanced evaluation.

This study is being conducted to further assess the safety and efficacy of 8 weeks of GLE/PIB combination regimen (300 mg GLE/120 mg PIB, QD) in treatment-naïve adults with chronic HCV GT1 – GT6 infection and APRI ≤ 1.

Clinical Hypothesis

The clinical hypothesis of this study is that 8 weeks of therapy with GLE/PIB in treatment-naïve GT1 – GT6 subjects that have APRI ≤1 will achieve high efficacy rates as observed in treatment-naïve, non-cirrhotic subjects evaluated in Phase 2 – 3 clinical trials for 8 weeks.

2.2 Benefits and Risks to Subjects

Chronic HCV infection is a major global health problem impacting quality of life, morbidity, as well as mortality. Evidence suggests that effective treatment of HCV can cure the infection as well as improve liver function.[1-3]

The GLE/PIB regimen is an oral, RBV-free pangenotypic regimen that provides high SVR_{12} rates ≥ 95% in subjects with compensated liver disease infected with HCV GT1 – GT6, with the majority of subjects treated for 8 – 12 weeks. Low relapse rates < 3% were observed in GT1 – GT6 treatment-naïve subjects without cirrhosis following 8 weeks of treatment, demonstrating no benefit of an additional 4 weeks of treatment. Among these subjects, an 8-week regimen of GLE/PIB achieved SVR rates similar to 12 weeks of treatment and to the only currently approved pangenotypic HCV regimen. However, GLE/PIB achieved similar efficacy with a significant reduction of the duration of treatment, which may improve subjects' adherence, access to treatment, and convenience, and also reduce the burden associated with additional medical visits and procedures.

Based on safety data from the registrational and supportive clinical trials where 2369 HCV-infected subjects were treated, the fixed-dose combination of GLE/PIB demonstrated a favorable safety profile. The most frequent GLE/PIB related adverse events (AEs) include headache, fatigue and nausea, and were mostly Grade 1 (mild) in severity. Grade 3 or higher AEs and serious adverse events (SAEs) were uncommon, occurring in 3.8% and 3.1%, of subjects, respectively. Similarly, the overall rate of study drug discontinuations due to AEs was low (0.5%).[8,9] Safety in subjects with cirrhosis was shown to be similar to subjects without cirrhosis.[8,9]

Potential risks that may occur with GLE/PIB therapy include hepatotoxicity, development of viral resistance, and the development of toxicities from drug-drug interactions (DDIs). The potential risks for GLE/PIB can be monitored, mitigated and managed in clinical practice.

No trends in liver chemistry abnormalities have been observed in Phase 2 and Phase 3 studies, including in subjects with compensated cirrhosis. ALT elevation from nadir to > 5 × ULN occurred in 3/2367 (0.1%) of subjects; none of these subjects prematurely discontinued study drug due to the elevation in ALT. Similarly, Grade 3 increases in bilirubin were rare (0.4%), predominantly indirect, and without bilirubin-related AEs. There were no cases identified consistent with drug-induced liver injury.

While there is a risk for the development of amino acid substitutions conferring resistance to GLE and/or PIB in subjects who fail the therapy, it may be possible to successfully retreat these subjects.

The risk of toxicities from DDIs are addressed and mitigated by the product information, which ensures awareness of these risks by both subjects and healthcare providers. Appropriate recommendations for dose adjustments of certain medications or avoidance of coadministration with other specific medications are provided in the product information.

Pharmacological class risks include Hepatitis B Virus (HBV) reactivation with DAA treatment. As the risk of HBV reactivation in subjects treated with GLE/PIB has not been studied, HBV co-infected subjects will be excluded from the study.

Aminotransferase/platelet ratio index score ≤ 1 has a high negative predictive value in the general chronic hepatitis C population. Additional eligibility criteria of normal platelets and normal albumin as well as the absence of previous diagnosis of cirrhosis have been added to mitigate the risk of including cirrhotic subjects. Also according to WHO analysis, the potential increase in treatment availability resulting from increased access to low-cost, non-invasive monitoring and reduced risk of adverse events from liver biopsy was felt to outweigh the potential harms of false-negative case identification by APRI.[5]

Given the potential for achieving high rates of SVR in naïve non-cirrhotic subjects with HCV GT1 – GT6 infection and the favorable safety profile of GLE/PIB, the overall benefit-risk balance of the GLE/PIB regimen is, therefore, positive and supports the use in subjects with chronic HCV with compensated liver disease, including subjects with renal impairment and HIV-1 co-infection.

For further details, please see findings from completed studies, including safety data in the GLE/PIB Investigator Brochure and addendum.[8,9]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The primary objective of this study is:

- To demonstrate the efficacy (by achieving high SVR_{12} rate) and safety of 8 weeks of treatment with the GLE/PIB combination regimen in treatment-naïve adults with HCV GT1 – GT6 infection with APRI ≤ 1. The primary efficacy objective will be assessed based on mITT population across GTs HCV GT1 – GT6.

The secondary objectives of this study are:

- To demonstrate the efficacy (by achieving high SVR_{12} rate) of 8 weeks of treatment with the GLE/PIB combination regimen in treatment naïve adults with HCV GT1 – GT6 infection with APRI ≤ 1 based on ITT population.
- Assess the percentage of subjects with HCV on-treatment virologic failures across GTs in adults with HCV GT1 – GT6 infection with APRI ≤ 1 based on ITT population.
- Assess the percentage of subjects with HCV virologic relapse across GTs in adults with HCV GT1 – GT6 infection with APRI ≤ 1 based on ITT population.

3.2 Primary Endpoint

The primary efficacy endpoint is the percentage of subjects who achieve SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) across genotypes in adults with HCV GT1 – GT6 based on mITT population.

3.3 Secondary Endpoints

Secondary endpoints are:

- Percentage of subjects who achieve SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) across GTs in adults with HCV GT1 – GT6 based on ITT population
- Percentage of subjects with on-treatment virologic failure based on ITT population
- Percentage of subjects with post-treatment relapse based on ITT population

3.4 Exploratory Endpoints

- SVR_{12} in subjects with APRI ≤ 0.7 and APRI ≤ 0.5 based on ITT population
- Percentage of subjects with virologic failure with Fibrotest > 0.75 based on ITT population
- Percentage of subjects with SVR_{12} by key groups (HCV genotype and subtype; age) based on ITT population
- Adherence to treatment based on ITT population

3.5 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, electrocardiogram (ECG), and clinical laboratory testing (hematology, chemistry including hepatic function parameters) as a measure of safety and tolerability for the entire study duration.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the **Operations Manual**.

This is a Phase 3b, multicenter, non-randomized, open label study to evaluate the efficacy and safety of GLE/PIB in HCV treatment-naïve adult subjects with chronic HCV GT1 – 6 and APRI ≤ 1 for 8 weeks.

The study is designed to enroll approximately 230 subjects (maximum of 20% [46] enrollment of GT3-infected subject) at approximately 43 sites worldwide.

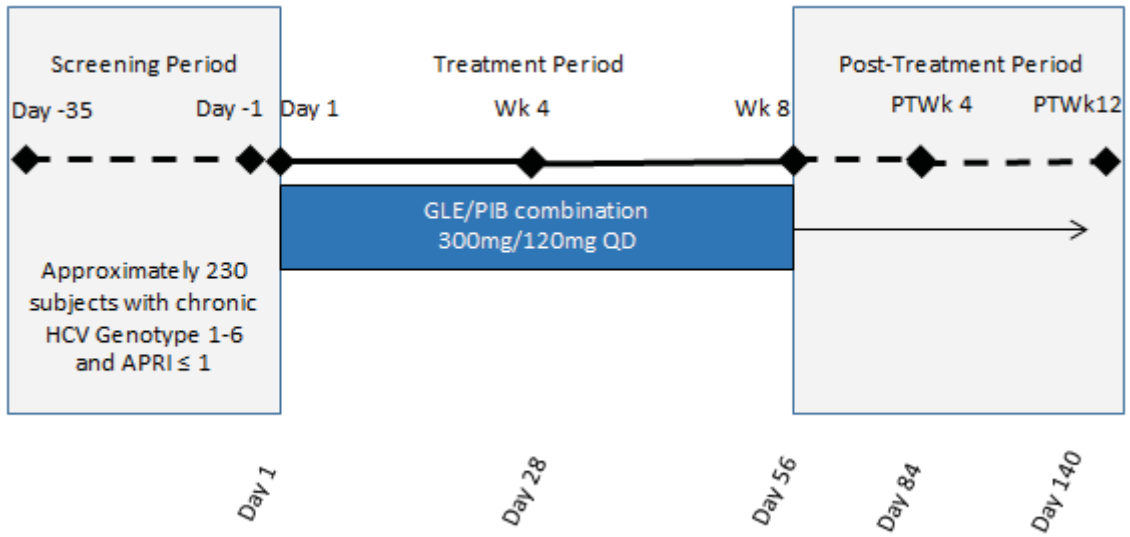
This study will consist of a Screening Period, a Treatment Period, and a Post-Treatment Period.

Screening Period: Subjects have up to 35 days following the Screening Visit to confirm eligibility and enroll into the study.

Treatment Period: Eligible subjects will be enrolled to receive GLE/PIB 300 mg/120 mg QD for 8 weeks.

Post-Treatment (PT) Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 12 weeks (Wks) after their last dose of study drug to evaluate efficacy and to monitor HCV RNA, and the emergence and persistence of viral substitutions.

Figure 1. Study Design Schematic



4.2 Discussion of Study Design

Appropriateness of Measurements

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

Suitability of Subject Population

This subject population will include treatment-naïve subjects only. While data from registrational and Phase 2 supportive trials shows that high SVR_{12} rates can be achieved with 8 weeks of GLE/PIB, slightly lower rates were achieved in treatment-experienced subjects across all GTs. To reduce the risk of Post-Treatment relapse, treatment-experienced subjects will be excluded from this study.

Aminotransferase/platelet ratio index ≤ 1 has been shown to have high sensibility and therefore high predictive negative value in ruling out cirrhosis. It is very likely that the population that will be included in this study using this biomarker will be non-cirrhotic. However, in order to decrease the risk of

enrolling truly cirrhotic subjects, subjects with clinical signs of cirrhosis, history of decompensation, or with lab abnormalities compatible with cirrhosis (low platelets and/or low albumin) will be excluded from this study.

Hepatitis C virus-infected subjects with chronic HCV infection have moderate stable elevations of AST and ALT levels and are considered representative of the population who will receive anti-HCV therapy. This study will include stable subjects with HIV/HCV co-infection, as this sub-population is shown to have similar results as mono-infected treatment-naïve non cirrhotic subjects with 8 weeks treatment duration in Study M14-730. As HBV co-infected subjects may have some alteration in APRI scores (due to inflammation) and it is difficult to interpret the APRI score in HBV/HCV co-infected population, subjects co-infected with HBV will be excluded from the population.

The age range selected for this study, 18 years of age or older, is also intended to be representative of the target population. Similarly, a substantial portion of the HCV-infected population have a relatively high body mass index, and given the acceptable safety and pharmacokinetic profiles of GLE/PIB in previous studies, this protocol will enroll subjects without a body mass index restriction.

Glecaprevir/pibrentasvir has shown similar efficacy and safety in subjects at all stages of renal impairment, including subjects with chronic kidney disease Stage 4 or 5 and in dialysis. However, as subjects with creatinine clearance < 30 mL/minute can show falsely low APRI levels which may increase the risk of enrolling a truly cirrhotic subject. Therefore, subjects with creatinine clearance < 30 mL/minute will be excluded from this study.

Selection of Dose in the Study

The dose of GLE/PIB (300 mg/120 mg by mouth QD) to be used in this study is the proposed label-recommended dose. These doses have been administered to over 2,300 subjects in the registrational program, and have shown high SVR_{12} rates with a favorable safety profile. The maximum dose of GLE/PIB will not exceed 300 mg/120 mg per day for up to 8 weeks.

Selection of Treatment Duration

Treatment duration was selected based on available data (SVR_{12} rates) from 12-week and 8-week treatment groups receiving GLE/PIB combinations (Studies M13-590, M15-464, M13-594, M13-583, and M14-868) in HCV GT1 – GT6-infected non-cirrhotic subjects as well as exposure-response modeling and simulations. With robust antiviral activity demonstrated in in vitro and in vivo studies, the 8-week GLE/PIB 300 mg/120 mg combination is predicted to be optimal across HCV non-cirrhotic, treatment-naïve GT1 – GT6-infected subjects.

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 statements below will result in exclusion from study participation.

Consent

- 1. Subjects must voluntarily sign and date an informed consent, 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 male or female, at least 18 years old at the time of screening.
- 3. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug:
  - Platelets ≥ 150,000 cells/mm^3
  - ALT ≤ 10 × ULN
  - AST ≤ 10 × ULN
  - Direct bilirubin ≤ ULN
  - Albumin ≥ LLN
  - Calculated creatinine clearance (using Cockcroft-Gault method) ≥ 30 mL/min
  - A negative HBsAg, and negative anti-HBc or; HBV DNA < LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti HBs)

Disease Activity

- 4. Positive anti- HCV Ab AND Plasma HCV RNA viral load ≥ 1000 IU/mL at Screening and for at least 6 months before Screening.
- 5. Any HCV GT allowed, including HCV GT1-, 2-, 3-, 4-, 5-, and/or 6-infection. Mixed GT and indeterminate GT may be acceptable.
- 6. APRI SCORE ≤ 1, at time of Screening.

Medical History

- 7. No history of HCC.
- 8. No evidence of cirrhosis described as:
  - previous histologic diagnosis of cirrhosis on liver biopsy, e.g., METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of > 3, Ishak score of > 4 in any liver biopsy conducted prior to Screening, OR
  - Any previous transient elastography score of ≥ 12.5 kPa, OR
  - Any current or historical clinical evidence of cirrhosis or decompensated cirrhosis, including any current or past evidence of Child-Pugh B or C classification, hepatic encephalopathy or variceal bleeding; radiographic evidence of ascites; or use of lactulose and/or rifaximin for hepatic encephalopathy prophylaxis or treatment.
- 9. Subject is treatment-naïve, e.g., has never received any other investigational or commercially available anti-HCV agents (e.g., interferon, peginterferon, RBV, telaprevir, boceprevir, simeprevir, asunaprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, dasabuvir, voxilaprevir or any other anti-HCV agent that is approved during the study).

- 10. Human Immunodeficiency Virus type 1 co-infection (as documented in the medical record) is allowed if the subject is naïve to treatment with any anti-retroviral therapy (ART) and has no plans to initiate ART treatment while participating in this study, or is on a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to Screening. The HIV-1 ART regimen must include at least 1 of the following anti-retroviral (ARV) agents:
  - Raltegravir by mouth twice daily (PO BID)
  - Dolutegravir PO QD or PO BID
  - Rilpivirine PO QD

  In addition to the above medications, subjects may take a nucleoside/nucleotide reverse transcriptase inhibitor (N(t)RTI) backbone containing any of the following:
  - Tenofovir disoproxil fumarate (TDF) PO QD
  - Tenofovir alafenamide (TAF) PO QD
  - Abacavir PO QD or BID
  - Emtricitabine PO QD
  - Lamivudine PO QD or BID

  Substituting TDF for TAF as part of the combination regimen is allowed at any time.

  Subjects receiving any other HIV-1 ART in addition to those noted above would not be eligible for enrollment in the study.

  In addition HIV-1 co-infected subjects must have the following:

  Subjects naïve to ART:
  - CD4+ count ≥ 500 cells/mm^3 (or CD4+ % ≥ 29%) at Screening

  or

  Subjects on a stable ART regimen must have the following:
  - CD4+ count ≥ 200 cells/mm^3 (or CD4+ % ≥ 14%) at Screening; and
  - Plasma HIV-1 RNA below < 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once (HIV-1 < 50 copies/mL) during the 12 months prior to Screening (by an approved plasma HIV-1 RNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTime HIV-1 assay).
- 11. No history of clinically significant abnormalities or co-morbidities, or recent (within 6 months prior to study drug administration) alcohol or drug abuse that make the subject an unsuitable candidate for this study in the opinion of the investigator.
- 12. Subject must not have been a previous recipient of an organ transplant.
- 13. No history of severe, life-threatening or other significant sensitivity to any excipients of the study drug.

Contraception

- 14. A negative serum pregnancy test for all female subjects of childbearing potential at the Screening Visit and a negative urine pregnancy test at Study Day 1 prior to the first dose of study drug.
- 15. If female, the subject must be either postmenopausal (Age > 55 years with no menses for 12 months or more without an alternative medical cause, or age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an follicle stimulating hormone (FSH) level > 40 IU/L), OR permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) OR for women of childbearing potential practicing at least one specified method of birth control (refer to Section 5.2) that is effective from Study Day 1 through at least 30 days after the last dose of study drug.
- 16. If female, the subject must not be pregnant, breastfeeding, or considering becoming pregnant during the study and for 30 days after the last dose of study drug.

Concomitant Medications

- 17. Subject is able and willing to safely discontinue the prohibited medications or supplements listed below at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of GLE/PIB.
  - Red yeast rice (monacolin K), St. John's Wort
  - Carbamazepine, Dabigatran, efavirenz, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
  - Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drug. Subjects receiving these statins should either (a) switch to pravastatin or rosuvastatin at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug or (b) 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 5 mg QD when taking with the study drug
  - Astemizole, cisapride, terfenadine
  - Ethinyl estradiol

5.2 Contraception Recommendations

Contraception Requirements for Females

Postmenopausal is defined as:

- 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 an FSH level > 40 IU/L.

If female, subject must be either post-menopausal, permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) or a woman of childbearing potential (WOCBP) and must practice at least one of the following methods of birth control, throughout the study including 30 days after the last study drug dose is given.

- Contraceptives and/or hormonal replacement therapies containing only progestins (such as those containing norethindrone, desogestrel, or levonorgestrel) or those containing progestins with non-ethinyl estradiol estrogens (e.g., esterified or conjugated) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline Day 1.
- Bilateral tubal occlusion/ligation.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Vasectomized sexual partner(s) (the vasectomized partner(s) provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the trial participant).
- 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).
- True abstinence: 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).

For male study subjects no contraception is required.

5.3 Prohibited Medications and Therapy

Subjects must be able to safely discontinue any prohibited medications or supplements listed in Section 5 at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of any study drug and not use these during the entire Treatment Period and for 14 days following discontinuation of study drug. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

Contraceptives and/or hormonal replacement therapies containing only progestins (such as those containing norethindrone, desogestrel, or levonorgestrel) or those containing progestins with non-ethinyl estradiol estrogens (e.g., esterified or conjugated) may be used with GLE/PIB at the discretion of the Investigator.

5.4 Prior and Concomitant Therapy

The investigator should confirm that a concomitant medication/supplement can be safely administered with study drug. Some medications may require dose adjustments due to the potential for DDIs.

Any medication/supplement or vaccine (including over-the-counter or prescription medicines, vitamins and/or supplements) that the subject is receiving from the time of signing the consent through the Treatment Period and 30 days after study drug is stopped, must be recorded in the electronic case report form (eCRF) along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency. The investigator should review all concomitant medications for any potential drug-drug interactions.

During the Post-Treatment Period, all medications taken will be recorded until 30 days following the last dose of study drug. After 30 days post-treatment, during the Post-Treatment Period, only antiviral therapies related to the treatment of HCV and medications prescribed in association with a SAE will be recorded in eCRF. The AbbVie Primary Therapeutic Area Medical Director should be contacted if there are any questions regarding concomitant or prior therapies.

During the Post-Treatment Period, investigators should reassess concomitant medications/supplements and subjects may resume previously prohibited medications/supplements or revert to pre-study doses, 14 days following discontinuation of study drug, if applicable.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie Emergency Medical Contact.

Prior and Concomitant HIV-1 Therapy

If a subject is on an HIV-1 ART regimen, it must include at least 1 of the ARV agents defined in eligibility criterion 10.

Subjects will maintain the same dose and dosing interval of their HIV-1 ART regimen upon initiating the study drug regimen.

Subjects must remain on the same HIV-1 ART regimen for the entire Treatment Period. Any change to an allowed HIV-1 ART regimen during the Treatment Period must be discussed with the AbbVie Therapeutic Area MD prior to the change, unless the change is being made to address an immediate safety concern.

Subjects receiving any other HIV-1 ART in addition to those listed in eligibility Criterion 10 would not be eligible for enrollment in the study.

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 AbbVie Therapeutic Area Medical Director.
- 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, when continuation of the study drug would place the subject at risk.

- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug and the investigator, after discussion with the subject, concludes that the benefit of continuing therapy does NOT outweigh the risk.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial.

The following criteria will be considered evidence of HCV virologic failure for the purposes of subject management:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurement of > 1 $\log_{10}$ IU/mL above nadir) at any time point during study drug treatment.

  or

- Confirmed HCV RNA ≥ 100 IU/mL (defined as 2 consecutive HCV RNA measurements ≥ 100 IU/mL) after HCV RNA < LLOQ during study drug treatment.

When confirmatory testing is required, it should be completed as soon as possible and the subject should remain on study drug treatment until the virologic failure criteria has been confirmed. Subjects meeting the virologic failure criteria will be discontinued from study drug and will continue to be followed in the Post-Treatment Period for the emergence and persistence of resistant viral variants until 12 weeks post-treatment.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum (unless otherwise required by local regulations), 2 phone 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 his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the Investigator.

Refer to Section 6.2 for additional discontinuation criteria relating to Toxicity Management.

5.6 Follow-Up for Subject Withdrawal from Study

In order 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 they 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, during the course of study drug administration, the subject prematurely discontinues (D/C), the procedures outlined for the applicable Premature D/C Visit should be completed. Ideally this should occur on the day of study drug discontinuation, but no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy. However, these procedures should not

interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment. All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The last dose of any study drug and reason for discontinuation will be recorded in the eCRF. The subject should then begin the Post Treatment Period where the subject will be monitored for 12 weeks for HCV RNA, and the emergence and persistence of resistant viral variants.

If a subject is discontinued from study drug or the Post-Treatment Period with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

5.7 Study Drug

Identity of Study Drug

Information about the study drug to be used in this study is presented in Table 1.

Table 1. Identity of Study Drug

Study Drug	Manufacturer	Mode of Administration	Dosage Form	Strength
Glecaprevir/pibrentasvir	AbbVie	Oral	Film-coated tablet	100 mg/40 mg

Three tablets of GLE/PIB combination will be taken QD, beginning on Day 1 (baseline), and should be taken at approximately the same time each day. The study drug must be taken with food.

Glecaprevir/pibrentasvir combination tablets will be packaged in bottles with quantities sufficient to accommodate the study design. Each kit label will contain a unique kit number. This kit number which is assigned to a subject identifies the appropriate study drug to be dispensed at the subject's corresponding study visit. Each kit will be labelled as required per country requirements. Labels must remain affixed to the kits. All blank spaces on the label will be completed by the site staff prior to dispensing to the subjects.

Subject will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

AbbVie will not supply drug other than GLE/PIB combination.

5.8 Randomization/Drug Assignment

This is not applicable as this study is non-randomized/open label.

5.9 Protocol Deviations

The Investigator is responsible for complying with all protocol requirements, written instructions and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the Investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable) and AbbVie.

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. Complaints associated with any component of this investigational product must be reported to the AbbVie.

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.

An AE can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. 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, meets protocol specific criteria (see Section 6.2 regarding toxicity management) and/or if the investigator considers them to be AEs.

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 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.

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.

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event within 24 hours of the site being made aware of the serious adverse event:

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 adverse events reported from the time of study drug administration until 30 days or 5 half-lives after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines.

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 Definition of Severity Grade

Investigators will rate the severity of each AE as according to Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 – 5.

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf[15]

Grading System for Adverse Events *(a semi-colon indicates 'or' within the description of the grade).*

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

ADL = Activities of Daily Living

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Adverse Event Relationship to Study Drug

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 deemed "clinically significant" based on the medical judgment of the Investigator will be managed and followed to a satisfactory clinical resolution.

The investigator will use the following definitions to assess the relationship of the adverse event 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.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Information regarding a pregnancy occurring up to 30 days after end of treatment in a study subject and the outcome of the pregnancy will be collected.

The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the Treatment Period, the administration of study drug may be continued at the Principal Investigator's discretion after discussion with the subject, if the benefit of continuing study

drug is felt to outweigh the potential risk. If a subject is discontinued, the subject will be monitored for SVR in the Post-Treatment Period.

6.2 Toxicity Management

The management of specific AEs and laboratory parameters is described below and in the **Operations Manual**. This includes the following laboratory abnormalities:

If a subject experiences a post-baseline increase in ALT to > 5 × ULN which is also > 2 × baseline value, the subject should have a confirmatory ALT measurement performed.

If, the ALT increase is confirmed to be > 5 × ULN which is also > 2 × baseline value, the recommendations below should be followed:

- Complete hepatic questionnaire.
- 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 immunoglobulin M (HAV IgM), Anti-hepatitis A virus total (HAV Total), Anti-HBc IgM, Anti-HBc Total, Anti-HBs, HBV DNA, HBsAg, Anti-hepatitis E virus immunoglobulin M (HEV IgM), Anti-hepatitis E virus immunoglobulin G (HEV IgG) and HEV RNA, and other additional tests, as appropriate.
- Manage the subject as medically appropriate.
- Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and international normalized ratio (INR) within 1 week. Repeat liver chemistries as indicated until resolution.

Discontinue study drug 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.

Alternate management of ALT increases is permitted with approval of the AbbVie Therapeutic Area Medical Director.

6.3 Product Complaint

A Product Complaint is any complaint related to the biologic or drug component of the product.

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 (example: printing illegible), missing components/product, or packaging issues.

Product Complaints concerning the investigational product must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product Complaints occurring during the study will be followed up to a satisfactory conclusion.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock. The statistical analyses will be performed using a statistical analysis system (SAS) (SAS Institute Inc., Cary, NC, USA).

7.2 Definition for Analysis Populations

The Intention-to-Treat (ITT) population includes all enrolled subjects who received at least 1 dose of study drug. The ITT population will be used for all secondary and exploratory efficacy analyses as well as for baseline analyses.

The mITT population includes all enrolled subjects who received at least 1 dose of study drug, excluding subjects who did not achieve SVR_{12} for reasons other than virologic failure. The mITT population will be used for the primary efficacy analysis.

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

7.3 Statistical Analyses

Primary Analysis

The primary efficacy endpoint is the percentage of subjects who achieve SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) across genotypes in adults with HCV GT1 – GT6. The primary endpoint will be analyzed based on mITT population.

The secondary efficacy endpoints of SVR_{12}, on-treatment virologic failure, and post-treatment relapse will be analyzed across genotypes in adults with HCV GT1 – GT6 based on ITT population.

For the analysis of post-treatment HCV virologic relapse, completion of treatment is defined as any subject with study drug duration of 52 days or greater.

The number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless the number of subjects who fail to achieve SVR_{12} is less than 5, where the Wilson's score method will be used for the confidence interval instead. A summary of reason for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse, other) will be provided.

The efficacy of 8-week treatment duration for subjects with APRI ≤ 1 based on mITT population will be established if the lower boundary of two-sided 95% confidence interval for the percentage of subjects achieving SVR_{12} is greater than 92.4% among HCV GT1 – GT6 subjects.

The efficacy of 8-week treatment duration for subjects with APRI ≤ 1 based on ITT population will be established if the lower boundary of two-sided 95% confidence interval for the percentage of subjects achieving SVR_{12} is greater than 91.4% among HCV GT1- GT6 subjects.

In order to control the Type I error rate, a fixed sequence testing procedure will be used for the SVR_{12} endpoints. Only if success has been demonstrated for the primary endpoint of SVR_{12} based on mITT population, will the testing proceed to the first secondary endpoint of SVR_{12} based on ITT population.

The multiplicity controlled efficacy endpoints will be tested sequentially in the following order:

1. Efficacy of the 8-week treatment duration based on mITT population: If this endpoint is statistically significant, then proceed to the following efficacy endpoint. If this endpoint is not statistically significant then stop the testing procedure and declare that no endpoints in the study met statistical significance.
2. Efficacy of the 8-week treatment duration based on ITT population: If this endpoint is statistically significant, then declare the SVR_{12} endpoint is statistically significant for both mITT and ITT populations. If not, then announce that SVR_{12} endpoint is statistically significant only for mITT population.

For on-treatment virologic failure and post-treatment relapse, the number and percentage of subjects will be summarized along with a two-sided 95% confidence interval using Wilson's score method.

Further details on the primary and other efficacy analyses are provided in the SAP.

Sample Size Estimation

It is planned to enroll approximately 230 adult subjects with chronic HCV GT1 – GT6 infection with APRI ≤ 1 who are HCV treatment-naïve in the study. The enrollment will be monitored to have approximately maximum 46 GT3-infected subjects (20% of total subjects).

With approximately 230 GT1 – GT6 infected subjects (with 46 GT3 subjects) in mITT analysis, this study has approximately 90% power to demonstrate efficacy of the 8-week treatment in terms of SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 92.4%), assuming that 98% of the GT1, GT2, GT4, GT5, and GT6-infected subjects with APRI ≤ 1 and 94% of the GT3-infected subjects with APRI ≤ 1 achieve SVR_{12}.

With 230 GT1 – GT6 infected subjects (with 46 GT3 subjects) in ITT analysis, this study has approximately 83% power to demonstrate efficacy of the 8-week treatment in terms of SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 91.4%), assuming that 97% of the GT1, GT2, GT4, GT5, and GT6-infected subjects with APRI ≤ 1 and 93% of the GT3-infected subjects with APRI ≤ 1 achieve SVR_{12}.

Efficacy for the 8-week regimen in this study is established by demonstrating similarity to the historical control regimen of GLE/PIB administered for 8 weeks in treatment-naïve subjects without cirrhosis. The SVR_{12} rate of the historical control regimen is calculated, and a threshold is determined by subtracting a non-inferiority margin of 6% from the historical SVR_{12} rate. Efficacy is established if the lower 95% confidence boundary of the SVR_{12} rate in the 8-week regimen is greater than the threshold. Efficacy for the 8-week regimen in this study is established by demonstrating the lower boundary of 95% CI for SVR_{12} rate is higher than a cut off value (92.4% and 91.4% for mITT and ITT population, respectively).

In the registrational studies, different SVR_{12} rates based on mITT population have been observed among GT3- and non-GT3-infected treatment-naïve subjects without cirrhosis assigned to 8 weeks of GLE/PIB treatment. In these studies, approximately 98.9% and 96.2% SVR_{12} has been observed among non-cirrhotic, treatment naïve chronic HCV GT1, GT2, GT4, GT5, and GT6-infected subjects and GT3 subjects, respectively.[11-13] Hence, for the non-cirrhotic GT1 – GT6-infected subjects, based on mITT population, the historical SVR_{12} rate of 98.4% is estimated based on a weighted average of 80% GT1, GT2, GT4, GT5, and GT6 historical rate and 20% GT3 historical rate. To establish cut off for efficacy based on mITT population, a margin of 6% is applied to the historical control rate of 98.4%, resulting in a threshold of 92.4%.

Historical SVR_{12} rate based on ITT population depends on the non-virologic failure in a study. Study-to-study variability has been observed in non-virologic failure rates, and is typically around 1%. The observed rate of non-virologic failure in the registrational program is 1.2% (29/2369).[11-13] For this reason, this study assumes that the historical SVR_{12} rate based on ITT population for treatment naïve non-cirrhotic subjects is 97.4% (with 1% non virologic failure). To establish cut off for efficacy based on ITT population, a margin of 6% is applied to the historical control rate of 97.4%, resulting in a threshold of 91.4%.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant 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 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 Conference for Harmonization (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).

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 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit.

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	Antibody
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
APRI	Aminotransferase/platelet ratio index
ART	Anti-retroviral treatment
ARV	Anti-retroviral
AST	Aspartate aminotransferase
BID	Twice daily
CRF	Case report form
CTCAE	Common Terminology Criteria For Adverse Events
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
FIB-4	Fibrosis-4
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GLE	Glecaprevir
GT	Genotype
HAV	Hepatitis A virus
HAV IgM	Hepatitis A virus immunoglobulin M
HBc	Hepatitis B core
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus

HEV	Hepatitis E virus
HEV IgG	Hepatitis E virus immunoglobulin G
HEV IgM	Hepatitis E virus immunoglobulin M
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
ICH	International Conference for Harmonization
IEC	Independent ethics committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medical Product
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention-to-Treat
IU	International units
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
kPa	kilopascal
L	Liter
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
mITT	Modified Intention-to-Treat
mL	Milliliter
mm	Millimeter
N(t)RTI	Nucleoside/nucleotide reverse transcriptase inhibitor
NS	Nonstructural
NS3	Nonstructural viral protein 3
NS4A	Nonstructural viral protein 4A
NS5A	Nonstructural viral protein 5A
PI	Protease inhibitor
PIB	Pibrentasvir
PO	By mouth
PRO	Patient Reported Outcomes
PT	Post-Treatment
QD	Once daily

RBV	Ribavirin
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR_{12}	Sustained virologic response 12 weeks post dosing
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
ULN	Upper limit of normal
WHO	World Health Organization
Wk	Week
WOCBP	Woman of childbearing potential

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-133: Chronic HCV Genotype 1 – 6: Glecaprevir/Pibrentasvir Once Daily Therapy in Subjects with APRI ≤ 1

Protocol Date: 31 July 2017

Clinical research studies sponsored by AbbVie are subject to the International Conference for Harmonisation (ICH) Good Clinical Practices (GCP) and local 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 Institutional Review Board (IRB)/Independent Ethics Committee (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, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
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]	Protocol Author, Medical Writing TA MD Medical Affairs Statistics Clinical Pharmacology Bioanalysis CPD

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APPENDIX D. ACTIVITY SCHEDULE

Treatment Period Activity Schedule

The following table shows the distribution of required activities across the screening and 8 week treatment period study visits. The individual activities are described in detail in the **Operations Manual**.

Activity	Screening Day –35 to Day –1	DAY 1 Day 1	WEEK 4 Day 28	WEEK 8 EOT or Premature Discontinuation Day 56 or Day of Discontinuation
INTERVIEWS & PATIENT REPORTED OUTCOMES				
Informed consent	✓			
Evaluation of eligibility criteria	✓	✓		
Medical history	✓	✓		
Adverse event assessment	✓	✓	✓	✓
Prior and concomitant medications assessment	✓	✓	✓	✓
Dispense (d)/Review (r) Study Drug Dosing Card		✓(d)	✓(d), (r)	✓(r)
Patient Reported Outcomes (PROs) Instrument		✓	✓	✓
LABS & EXAMS				
Fibrotest (blinded to site and subject)	✓			
HCV genotype and subtype	✓			
APRI	✓			
12-lead ECG	✓			
Height	✓			
Weight	✓	✓	✓	✓
Vital signs (determinations of systolic and diastolic blood pressure, pulse rate, and body temperature)	✓	✓	✓	✓
Physical examination	✓	✓		✓
Drug/alcohol screen	✓			
FSH (all females)	✓			
Serum pregnancy test (women of childbearing potential only)	✓			
Urine pregnancy test (women of childbearing potential only)		✓	✓	✓
Hematology/chemistry/urinalysis/coagulation panel	✓	✓	✓	✓
Anti-HCV Ab, Anti-HIV Ab	✓			
Hepatitis B panel	✓			
Biomarker pharmacogenetic sample (optional)		✓		

Activity	Screening Day –35 to Day –1	DAY 1 Day 1	WEEK 4 Day 28	WEEK 8 EOT or Premature Discontinuation Day 56 or Day of Discontinuation
HCV RNA samples	✓	✓	✓	✓
HCV resistance sample		✓	✓	✓
HIV-1 RNA (HCV/HIV-1 co-infected subjects only)	✓			
Flow cytometry sample (HCV /HIV-1 co-infected subjects only)	✓			
Biomarker plasma sample	✓	✓	✓	✓
Pharmacokinetic sample			✓	✓
℞ TREATMENT				
Dispense study drug		✓	✓	
Study drug accountability and review of study drug adherence			✓	✓

Post-Treatment Period Follow-Up Activity Schedule

The following table shows the distribution of required activities across the 12 week post-treatment period subject encounters. The individual activities are described in detail in the **Operations Manual**.

Activity	Post-Treatment WEEK 4 Day 84	Post-Treatment WEEK 12 or Premature Discontinuation Day 140 or Day of Discontinuation
INTERVIEWS & PATIENT REPORTED OUTCOMES		
Adverse event assessment	✓	✓
Concomitant medications (all)	✓	
Concomitant medications (for SAEs and HCV)	✓	✓
PRO Instrument		✓
LABS & EXAMS		
Weight	✓	✓
Vital signs (determinations of systolic and diastolic blood pressure, pulse rate, and body temperature)	✓	✓
Urine pregnancy test (women of childbearing potential only)	✓	✓
Hematology/chemistry/urinalysis/coagulation panel	✓	✓
HCV RNA samples	✓	✓
HCV resistance sample	✓	✓
HIV-1 RNA (HCV/HIV-1 co-infected subjects only)	✓	
Flow cytometry sample (HCV /HIV-1 co-infected subjects only)	✓	
Biomarker plasma sample	✓	✓

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	25 May 2017

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

1. Provide clarification as to what dose of rosuvastatin can be taken with GLE/PIB.
    - Updated Section 5, Study Activities to change the allowed concomitant rosuvastatin dose from 10 mg to 5 mg based upon the anticipated European Union Summary of Product Characteristics label recommendation under Subsection 5.1, Eligibility Criteria, Concomitant Medications.
2. Provide clarification and additional information regarding contraception use during the study.
    - Updated Section 5, Study Activities to add Subsection 5.2, Contraception Recommendations.
3. Provide definition of serious adverse event, adverse event severity grade, and assessments for relationship of adverse event to study drug.
    - Updated Section 6, Safety Considerations to add regulatory definition of serious adverse events under subsection Medical Complaints/Adverse Events and Serious Adverse Events.
    - Updated Section 6, Safety Considerations to add definition of adverse event severity grade under subsection Adverse Event Definition of Severity Grade.
    - Updated Section 6, Safety Considerations to add the definition of reasonable possibility and no reasonable possibility under the subsection Adverse Event Severity and Relationship to Study Drug.
4. Provided clarification on the timing to report a serious adverse event
    - Updated Section 6, Safety Considerations, under subsection Medical Complaints/Adverse Events and Serious Adverse Events, to add the requirement by the Investigator to report a serious adverse event to the Sponsor within 24 hours of becoming aware of a serious adverse event.
5. Provide clarification around the risk-based monitoring approach
    - Updated Section 6, Safety Considerations, under subsection Medical Complaints/Adverse Events and Serious Adverse Events, to add the statement that adverse events will be monitored throughout the study to identify any which may indicate a risk to subjects.

- Updated Section 10, Data Quality Assurance, to add statement regarding the use of a quality management system to define quality tolerance limits.

6. Provide clarification on what vital sign measurements will be measured during each Treatment and Post-Treatment Follow-up Visit.

   - Updated Appendix D, Activity Schedule to include a list of what vital signs will be measured: systolic and diastolic blood pressure, pulse, and body temperature.

7. Provide clarification that HIV-1 RNA and flow cytometry will be performed at Post-treatment Week 4 Visit as well as the Screening Visit.

   - Updated Appendix D, Activity Schedule to add HIV-1 RNA and flow cytometry to the Post-Treatment Week 4 Visit study activities.

Document Approval

Study M16133 - A Single Arm, Open Label, Multicenter Study to Evaluate the Efficacy and Safety of Glecaprevir(GLE)/Pibrentasvir(PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotypes 1 – 6 Infection and Aspartate aminotransferase to Platelet Ratio Index (APRI) ≤ 1 - Version 2-0 - EudraCT 2016-004876-23 - 31Jul2017

Version: 2.0 **Date:** 31-Jul-2017 07:41:48 PM **Company ID:** 07312017-00F9F6839B3CDF-00002-en

Signed by:	Date:	Meaning Of Signature:
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	31-Jul-2017 06:47:25 PM	Approver
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	31-Jul-2017 07:01:04 PM	Author
	31-Jul-2017 07:10:16 PM	Study Director
	31-Jul-2017 07:11:45 PM	Approver
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