16.0 Appendices

16.1 Study Information

16.1__1 Protocol and Protocol Amendments

1.0 Title Page

Clinical Study Protocol M16-156

A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection

Incorporating Amendments 1 and 2

AbbVie Investigational Product:	Glecaprevir/Pibrentasvir
Date:	02 August 2018
Development Phase:	3b
Study Design:	This is an open-label, multicenter study
Investigators:	Multicenter Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc. (AbbVie)*
Sponsor/Emergency Contact:	[redacted] 1 North Waukegan Road North Chicago, IL 60064 Phone: [redacted] Mobile: eFax: Emergency 24 hour Number: [redacted]

* 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.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	17 February 2017
Amendment 1	08 November 2017

The purpose of this amendment is to:

- Update Section 1.0, Title Page and Section 6.1.5, Adverse Event Reporting

  Rationale: *Updated contact information to reflect changes on study team.*
- Update Section 1.2, Synopsis

  Rationale: *Updated the synopsis to be consistent with the text in the protocol.*
- Update Section 4.1, Primary Objectives and Section 8.1.6, Safety

  Rationale: *Updates were made to safety endpoints to combine results across durations as these durations are the approved durations for glecaprevir/pibrentasvir.*
- Update Section 5.1, Overall Study Design and Plan: Description

  Rationale: *Updated the enrollment criteria for GT3 subjects.*
- Update Section 5.2.1, Inclusion Criteria, Inclusion Criterion 7

  Rationale: *Clarified the criterion by specifying the METAVIR equivalent fibrosis stage and the Child-Pugh score for F4 subjects.*
- Update Section 5.2.2, Exclusion Criteria, Exclusion Criterion 8

  Rationale: *Clarified the exclusion criterion by removing language that applied to subjects with CKD Stage 4 or 5 as this was a typographical error.*
- Update Section 5.2.2, Exclusion Criteria, Exclusion Criterion 10

  Rationale: *Updated the list to reflect the recent approval of glecaprevir/pibrentasvir in Brazil and also to correct the generic name of paritaprevir to veruprevir, the denomination approved in Brazil.*
- Update Section 5.2.3.4, Prohibited Therapy and Section 5.6.4.1.1, GLE and PIB Dose and Treatment Duration

Rationale: *Updated the investigational product ABT-493/ABT-530 with generic names.*

- Update Section 5.3.1.1, Study Procedures, Hepatitis B, Hepatitis C Virus and HIV Screen

  Rationale: *Updated to allow HBV DNA testing at Screening, as needed, to exclude occult HCV infection.*

- Update Section 5.3.1.1, Study Procedures, Liver Diagnostic Testing

  Rationale: *Updated to include Child-Pugh classification score for subjects with compensated cirrhosis.*

- Update Section 5.3.1.1, Study Procedures, Child-Pugh Score and Category

  Rationale: *Clarified the language to state that all subjects with cirrhosis will undergo Child-Pugh score assessment at Screening.*

- Update Section 5.3.1.1, Study Procedures, Flow Cytometry, HIV RNA and HIV Resistance Testing Samples

  Rationale: *Removed language regarding HIV treatment failure after the use of highly active antiretroviral therapy (HAART), as it was a typographical error. HIV treatment failure is defined in Section 5.4.1.2.*

- Update Section 6.1.6, Pregnancy

  Rationale: *Updated the pregnancy language according to align with current company standards for Pregnancy follow-up.*

- Update Section 8.1.4, HCV Resistance Analyses

  Rationale: *Updated the section to include additional analyses being performed.*

- Update Appendix B, List of Protocol Signatories

  Rationale: *Updated to reflect changes in signatories.*

- Update Appendix C, Study Activities.

  Rationale: *Updated the tables and footnotes to be consistent with the changes made in the body of the protocol text.*

- Minor clerical updates/typographical correction made throughout the protocol.

  Rationale: *Revised text to correct typographical errors, improve consistency and readability throughout the protocol.*

An itemized list of all changes made to this protocol under this amendment can be found in Appendix F.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-156
Name of Study Drug: Glecaprevir, Pibrentasvir	**Phase of Development:** 3b
Name of Active Ingredient: Glecaprevir, Pibrentasvir	**Date of Protocol Synopsis:** 02 August 2018
Protocol Title: A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection	
Objectives: • The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving SVR_{12} (HCV RNA < LLOQ 12 weeks following therapy) and safety of GLE/PIB combination in treatment-naïve adults in Brazil with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis. The efficacy and safety endpoints will be analyzed on the overall population (i.e., across treatment durations and genotypes). • The secondary objectives are to assess efficacy of GLE/PIB by hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis by evaluating the percentages of subjects with HCV on-treatment virologic failure (OTVF) and HCV virologic relapse across treatment durations and genotypes.	
Investigators: Multicenter, single country (Brazil)	
Study Sites: Approximately 14	
Study Population: Chronic HCV GT 1 – 6-infected male and female adults with Metavir equivalent fibrosis stage of F2 – F4, at least 18 years of age, without cirrhosis or with compensated cirrhosis, who are HCV treatment-naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication).	
Number of Subjects to be Enrolled: Approximately 100 subjects	
Methodology: This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of GLE/PIB combination for an 8 or 12-week treatment duration in adults in Brazil with chronic HCV GT1 – 6 infection, without cirrhosis (F2 – F3) or with compensated cirrhosis (F4), who are HCV treatment-naïve. Approximately 100 subjects meeting the eligibility criteria will be enrolled. The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of 35 GT1 and approximately 25 GT3 subjects and 2) approximately 80 F2 – F3 and a maximum of approximately 20 F4 subjects.	

Methodology (Continued):

Approximately 100 eligible subjects will be enrolled into one of the following treatment arms:

- Arm A: HCV GT 1 – 6 without cirrhosis (F2 and F3) subjects will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks.
- Arm B: HCV GT 1 – 6 subjects with compensated cirrhosis (F4) will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 12 weeks.

The study will consist of a Screening Period, Treatment Period and Post Treatment Period:

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

Treatment Period: Eligible subjects will be enrolled to receive GLE/PIB 300 mg/120 mg once daily (QD) for an 8 (Arm A) or 12 (Arm B) week treatment duration based on their cirrhosis status.

Scheduled visits for subjects in the Treatment Period consist of Day 1 and Weeks 4 and 8 for all subjects and an additional Week 12 visit for subjects in Arm B. Study procedures, including assessment of adverse events, vital signs, study medication adherence, concomitant medications, HCV RNA, HCV resistance, and clinical laboratory tests, will be conducted at each visit.

Post-Treatment (PT) Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 12 weeks to monitor safety, HCV RNA levels and the emergence and persistence of resistance-associated substitutions.

During the Post-Treatment Period, all subjects will have visits at PT Weeks 4 and 12, following completion of the Treatment Period. Study procedures to monitor safety, HCV RNA, and the emergence and persistence of resistant viral variants will be conducted during these visits.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject has positive plasma HCV antibody and HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.
2. Subject must be documented as without cirrhosis (METAVIR equivalent fibrosis stage of F2 – F3), or with compensated cirrhosis (METAVIR equivalent fibrosis stage of F4 with a Child-Pugh score ≤ 6). See Section 5.3.1.1 for Liver Diagnostic Testing and Child-Pugh score and Category.
3. Subjects who are known to be HCV/HIV co-infected may enroll if they have a positive test result for anti-Human Immunodeficiency Virus antibody at Screening and are:

   Naïve to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study), or

   On a stable, qualifying HIV ART regimen for at least 8 weeks prior to Baseline.

   Subjects on stable HIV ART must have Plasma HIVRNA below 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once during the 12 months prior to Screening (by an approved plasma HIVRNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTi*m*e HIV-1 assay).
4. Subjects requiring dialysis should have been receiving dialysis for at least 1 month prior to enrollment, and may be on hemodialysis or peritoneal dialysis.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

5. Subjects With Compensated Cirrhosis Only: Absence of hepatocellular carcinoma (HCC) 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. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.

Main Exclusion:

1. Female subject who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Current HBV infection on screening tests, defined as:
   - A positive HBsAg, or;
   - HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., with negative HBsAg and Anti-HBs)
3. History of severe, life-threatening, or other significant sensitivity to any excipients of the study drug.
4. Any current or past clinical evidence of Child-Pugh B or C classification (score of > 6) or any current or past clinical history of liver decompensation including ascites on physical exam, hepatic encephalopathy or variceal bleeding. Prophylactic use of beta blockers is not exclusionary (see Section 5.3.1.1).
5. Laboratory parameters exclusions:
   - ALT > 10 × ULN; AST > 10 × ULN
   - Total Bilirubin > 3.0 mg/dL
   - Albumin < LLN (without cirrhosis); < 2.8 mg/dL (with compensated cirrhosis)
   - Platelets < 90,000 10^3/μL (without cirrhosis); < 60,000 10^3/μL (with compensated cirrhosis)
6. Receipt of any investigational or commercially available anti-HCV agents including, but not limited to: interferon, pegylated interferon, ribavirin, sofosbuvir, telaprevir, boceprevir, simeprevir, asunaprevir, veruprevir, glecaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, voxilaprevir, velpatasvir, pibrentasvir, or dasabuvir.

Investigational Products:	Glecaprevir/Pibrentasvir 100 mg/40 mg Film-coated tablet
Doses:	Glecaprevir/Pibrentasvir 300 mg/120 mg QD (3 tablets)
Mode of Administration:	Oral with food.
Reference Therapy:	N/A
Doses:	N/A
Mode of Administration:	N/A

Duration of Treatment: Subjects without cirrhosis will receive GLE/PIB for 8 weeks, while subjects with compensated cirrhosis will receive GLE/PIB for 12 weeks.

Criteria for Evaluation:

Efficacy:

Plasma HCV RNA (IU/mL) will be assessed at each Treatment and Post-Treatment Visit.

Criteria for Evaluation (Continued):

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests, and vital signs.

Patient Reported Outcomes (PROs):

The Short Form 36 Version 2 Health Status Survey (SF-36v2) will be used to assess the functional health and well-being of subjects. The Treatment Satisfaction Questionnaire (TSQM) will be used to assess treatment satisfaction with the GLE/PIB combined regime. EuroQol-5 Dimensions-3 Level (EQ-5D-3L) is a health state utility instrument that evaluates preference for health status (utility); subjects also rate their perception of their overall health on a separate visual analogue scale (VAS).

Resistance:

The following information will be tabulated and summarized: 1) for all subjects with available samples, baseline polymorphisms at signature resistance-associated amino acid positions relative to the appropriate prototypic reference sequences; and 2) for subjects who do not achieve SVR_{12}, post-baseline substitutions relative to the corresponding baseline sequence in available samples.

Pharmacokinetic:

Individual plasma concentrations of GLE, PIB, and their possible metabolites will be tabulated and summarized.

Statistical Methods:

Efficacy:

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 all genotypes (GT1 – 6 subjects) and treatment groups. The primary endpoint will be analyzed based on intention to treat (ITT) population. The number and percentage of subjects achieving SVR_{12} will be summarized with a two-sided 95% confidence interval based on the normal approximation of the binomial distribution unless the number of SVR_{12} non-responders is less than 5, in which case the Wilson's score method will be used to calculate the confidence interval.

The secondary efficacy endpoints are:

- The percentage of subjects with OTVF.
- The percentage of subjects with post-treatment HCV virologic relapse.

Subgroup analysis based on the treatment arm (i.e., without cirrhosis/with compensated cirrhosis) will be performed. For the secondary efficacy endpoints and subgroup analysis, the two-sided 95% confidence interval will be calculated using Wilson's score method.

PROs:

Change from baseline to each applicable visit in the patient reported outcome summary measures for SF-36 and EQ-5D-3L will be summarized. Summary measures at each applicable visit will be summarized for the TSQM.

Statistical Methods (Continued):

Safety:

Safety summaries will be provided overall. All subjects who receive at least one dose of study drug will be included in the safety analyses. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by MedDRA System Organ Class (SOC) and preferred term. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by grade and relationship to study drug.

Resistance:

For all subjects receiving study drug, baseline polymorphisms at signature resistance-associated amino acid positions identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the baseline sequences, 2) the amino acid substitutions in available post baseline samples at signature resistance-associated positions identified by NGS, and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral substitutions by NGS.

Pharmacokinetic:

Individual plasma concentrations of GLE, PIB, and their possible metabolites will be tabulated and summarized.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADC	AIDS-Defining Conditions
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Anti-HBc	Anti-Hepatitis B core antibody
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ART	Antiretroviral therapy
AUC	Area under the plasma concentration-time curve
BMI	Body mass index
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
CL/F	Apparent oral plasma clearance
CR/CL	Creatinine clearance
CRF	Case report form
CT	Computed tomography
C_{trough}	Pre-dose trough plasma concentration
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EQ-5D-3L	EuroQol-5 Dimensions-3 Level
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GT	Genotype
HBsAg	Hepatitis B surface antigen
HAART	Highly active antiretroviral therapy

HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention To Treat
IU	International units
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NGS	Next generation sequence
NONMEM	Non-linear mixed-effect modeling
NS5A	Nonstructural viral protein 5A
OTVF	On-treatment virologic failure
PegIFN	Pegylated-interferon alfa-2a or alfa-2b
PegIFN/RBV	Combination of pegylated-interferon alfa-2a or alfa-2b and ribavirin
PI	Protease Inhibitor
PK	Pharmacokinetic
POR	Proof of receipt
P/R	pegIFN/RBV
PRO	Patient reported outcome
PT	Post-Treatment

QD	Once daily
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Standard Deviation
SF-36v2	Short Form 36 – Version 2 Health Survey
SOC	System Organ Class/Standard of Care
SOF	Sofosbuvir
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
SVR_4	Sustained virologic response 4 weeks post dosing
SVR_{12}	Sustained virologic response 12 weeks post dosing
TE	Treatment Experienced
TN	Treatment-naïve
TSQM	Treatment Satisfaction Questionnaire-Medicine
ULN	Upper limit of normal
VAS	Visual Analog Scale
V/F	Apparent Volume of distribution
WBC	White blood cells
WOCBP	Women of child bearing potential

Definition of Terms

Study Drug	glecaprevir/pibrentasvir
Study Day 1	First day of study drug dosing
Treatment Period	Day 1 through last dose of study drug
Post-Treatment Period	Day after the last dose of study drug through Post-Treatment Week 12 or Post-Treatment Discontinuation

2.0 Table of Contents

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3.0 Introduction

Hepatitis C virus (HCV) infection is a global health problem, with over 184 million individuals infected worldwide.[1] There are 7 identified HCV genotypes, with genotype 1 (GT1) being the most prevalent worldwide. HCV genotypes 2 (GT2) and 3 (GT3) infections are more common in Latin America (5% to 30%), Europe (20% to 40%) and Asia (30% to 45%).[2-4] HCV GT4 is commonly found in parts of Africa and the Middle East, particularly in Egypt, GT5 is primarily found in South Africa, and GT6 is primarily found in south-east Asia, and GT7 has recently been described in Central Africa.[5] Genotype 1 (GT1) is the most frequent in all regions in Brazil (65%), followed by genotype 3 (30%) and GT2 (5%). Genotypes 4 to 6 are rarely reported (0.3%) in Brazil.[6]

Depending on various risk factors, between 10% and 40% of all patients with chronic HCV infection will develop cirrhosis. Death related to the complications of cirrhosis may occur at an incidence of approximately 4% per year; hepatocellular carcinoma (HCC) occurs in this population at an estimated incidence of 1% to 5% per year. Patients diagnosed with hepatocellular carcinoma have a 33% probability of death during the first year.[7] Successful treatment of HCV has been shown to significantly reduce the risk of disease progression and related mortality as well as the development of hepatocellular carcinoma.[8,9]

At the time of initiation of this study, therapy for HCV had improved considerably with the approval of several interferon (IFN)-free direct-acting antiviral agent (DAA) regimens (ledipasvir [LDV]/sofosbuvir [SOF], SOF plus simeprevir [SMV], SOF plus daclatasvir [DCV], ombitasvir [OBV]/veruprevir/ritonavir [r] ± dasabuvir [DSV], elbasvir [EBR]/grazoprevir [GZR], and SOF/velpatasvir [VEL]).[10,11] In Brazil, the National HCV Program provides specific regimens to a subset of subjects with confirmed HCV and specific GT infection. The mono HCV infected subjects must have confirmed Metavir F3 and F4 fibrosis stage, and the HCV/HIV co-infected should be treated regardless of liver fibrosis staging. A treatment guideline recommends SOF + DCV or SOF + SMV for

GT1; SOF + RBV for GT2; SOF + pegIFN or SOF + DCV for GT3; and SOF + pegIFN + RBV or SOF + DCV for GT4. Duration of treatment is based on history of monoinfection with HCV, or co-infection with HIV, GT subtype and fibrosis staging. These regimens are available across the country and prescribed free of charge within the country's universal health care system.

However, these approved and recommended regimens are not equally potent across all HCV genotypes and subpopulations. Additional limitations of several current regimens include the requirement of ribavirin (RBV) for certain populations, significant drug to drug interactions, limited options for subjects with renal insufficiency, reduced efficacy in patients with baseline amino acid polymorphisms associated with reduced susceptibility to the HCV nonstructural 5A (NS5A) inhibitors or NS3/4A protease inhibitors (PI), and limited options for patients who have failed regimens containing an NS5A inhibitor and/or PI. Efficacy in GT3-infected patients, particularly those who are treatment-experienced (TE) and/or cirrhotic, is also substantially lower than what is observed for other genotypes.[12]

AbbVie has developed two "next generation" DAAs, glecaprevir (GLE, formerly known as ABT-493), an HCV NS3/4A PI, and pibrentasvir (PIB, formerly known as ABT-530), an NS5A inhibitor, for use in combination for the treatment of HCV. GLE and PIB each has potent in vitro antiviral activity against genotypes 1 through 6[13] and a high genetic barrier to resistance, with no or little loss of potency against common resistant-associated substitutions. Additive or synergistic in vitro anti-HCV activity has been demonstrated with the combination of GLE and PIB. GLE 100 mg and PIB 40 mg are co-formulated into a fixed-dose combination tablet (hereafter referred to as GLE/PIB), which provides patients with a convenient once-daily (QD), fixed-dose combination treatment regimen of three tablets QD to maximize treatment compliance.

A detailed discussion of the preclinical pharmacology and toxicology, in vitro virology and metabolism, and clinical data can be found in the Investigator's Brochure.[14]

GLE/PIB

Overview of GLE/PIB Registrational Program and Supportive Phase 2 Studies

The GLE/PIB registrational program included a broad subject population including subjects with compensated liver disease and subjects with severe renal insufficiency across GT1 – 6 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 (TN) and TE subjects to any combination of pegylated IFN (pegIFN), RBV, SOF, NS5A inhibitors, or PIs were allowed in the program. In addition, the program included subjects with human immunodeficiency virus (HIV) coinfection (Study M13-590), subjects with chronic kidney disease [CKD] 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 (Table 1).

Table 1. Overview of Clinical Studies by Subject Population

Genotype	Clinical Study	Summary of Study Design
TN and TE Subjects Without Cirrhosis		
GT1	M13-590	GLE/PIB 300 mg/120 mg QD for 8 (n = 351) or 12 weeks (n = 352)
	M14-867	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 34)
GT2	M15-464	GLE/PIB 300 mg/120 mg QD (n = 202) or placebo (n = 100) for 12 weeks
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 199) or 12 weeks (n = 25)
GT3	M13-594	GLE/PIB 300 mg/120 mg QD for 8 (n = 157) or 12 weeks (n = 233) or SOF 400 mg + DCV 60 mg QD for 12 weeks (n = 115) (all subjects in study were TN)
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 29; TN only), 12 weeks (n = 76), or 16 weeks (n = 22; TE only)
GT4, 5, 6	M13-583	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 121)
	M14-867	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 32)
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 58)
TN and TE Subjects with Cirrhosis		
GT1, 2, 4, 5, 6	M14-172	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 146)
GT3	M14-868	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 64; TN only) or 16 weeks (n = 51; TE only)
Subjects with CKD Stages 4 – 5 With or Without Cirrhosis		
GT1 – 6	M15-462	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 104)
NS5A Inhibitor and/or PI-Experienced Subjects With or Without Cirrhosis		
GT1, 4	M15-410	GLE/PIB 300 mg/120 mg QD for 12 (n = 66) or 16 weeks (n = 47)

CKD = chronic kidney disease; DCV = daclatasvir; GLE = glecaprevir; GT = genotype; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; PIB = pibrentasvir; QD = once daily; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naïve

Efficacy

In treatment-naïve (TN) or IFN, pegIFN, RBV, and/or SOF treatment experienced (TE-PRS) subjects, the pooled overall SVR_{12} rates with GLE/PIB were > 97% across GT1, 2, 4, 5 and 6 regardless of treatment experience, treatment duration, including any degree of renal impairment, presence of compensated cirrhosis, or HIV coinfection (Table 2).

Among subjects with GT3 infection, the pooled SVR_{12} rates across durations were 95.2% among all subjects, 96.6% among cirrhotic subjects, and 100% among subjects with CKD Stages 4 – 5. The SVR_{12} rates among subjects previously treated with a PI and/or NS5A inhibitor were ≥ 89.0% for GT1 and GT4.

Table 2. SVR_{12} Rates by Treatment Experience and HCV Genotype – GT1 – 6 (ITT Population, Phase 2 and 3 Analysis Set)

Genotype	TN n/N (%) 95% CI[a]	TE-PRS n/N (%) 95% CI[a]	TN + TE-PRS All[a]	TN + TE-PRS Cirrhotic n/N (%) 95% CI[b]	TN + TE-PRS CKD 4 – 5 n/N (%) 95% CI[b]	TE-NS5A and/or PIs n/N (%) 95% CI[a]	Overall n/N (%) 95% CI[a]
Phase 2 and 3 Analysis Set	1604/1640 (**97.8**) 97.1, 98.5	602/616 (**97.7**) 96.6, 98.9	2206/2256 (**97.8**) 97.2, 98.4	274/281 (**97.5**) 95.7, 99.3	102/104 (**98.1**) 95.4, 100.0	101/113 (**89.4**) 83.7, 95.1	2307/2369 (**97.4**) 96.7, 98.0
GT1	555/561 (**98.9**) 98.1, 99.8	326/328 (**99.4**) 98.5, 100.0	881/889 (**99.1**) 98.5, 99.7	98/101 (**97.0**) 93.7, 100.0	53/55 (**96.4**) 91.4, 100.0	97/109 (**89.0**) 83.1, 94.9	978/998[c] (**98.0**) 97.1, 98.8
GT2	365/369 (**98.9**) 97.9, 100.0	95/97 (**97.9**) 95.1, 100.0	460/466 (**98.7**) 97.7, 99.7	35/35 (**100**) 100.0, 100.0	16/16 (**100**) 100.0, 100.0	N/A	460/466 (**98.7**) 97.7, 99.7
GT3	499/521 (**95.8**) 94.0, 97.5	113/122 (**92.6**) 88.0, 97.3	612/643 (**95.2**) 93.5, 96.8	112/116 (**96.6**) 93.2, 99.9	11/11 (**100**) 100.0, 100.0	N/A	612/643 (**95.2**) 93.5, 96.8
GT4	119/122 (**97.5**) 94.8, 100.0	55/56 (**98.2**) 94.7, 100.0	174/178 (**97.8**) 95.6, 99.9	20/20 (**100**) 100.0, 100.0	20/20 (**100**) 100.0, 100.0	4/4 (**100**) 100.0, 100.0	178/182 (**97.8**) 95.7, 99.9
GT5	26/26 (**100**) 100.0, 100.0	6/6 (**100**) 100.0, 100.0	32/32 (**100**) 100.0, 100.0	2/2 (**100**) 100.0, 100.0	1/1 (**100**) 100.0, 100.0	N/A	32/32 (**100**) 100.0, 100.0
GT6	40/41 (**97.6**) 92.8, 100.0	7/7 (**100**) 100.0, 100.0	47/48 (**97.9**) 93.8, 100.0	7/7 (**100**) 100.0, 100.0	1/1 (**100**) 100.0, 100.0	N/A	47/48 (**97.9**) 93.8, 100.0

CI = confidence interval; CKD = chronic kidney disease; GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat; N/A = not applicable; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SVR_{12} = sustained virologic response 12 weeks postdosing; TE = treatment-experienced; TN = treatment-naïve; TE-NS5A and/or PI = TE with NS5A inhibitor and/or PI

a. CI was calculated using a stratum-weighted proportion and variance.

b. CI was calculated using the normal approximation to the binomial distribution.

c. Eleven subjects were classified by the central laboratory and treated as GT2 but included here as GT1 due to being identified as such by phylogenetic analysis; all 11 subjects achieved SVR_{12}.

Cross reference: Summary of Clinical Efficacy R&D/16/0146: Table 1.2__2.2

Impact of Baseline Polymorphisms on Treatment Outcome

The association between baseline polymorphisms in NS3 and NS5A and treatment outcome in subjects who received GLE 300 mg QD with PIB 120 mg QD in the registrational or supportive Phase 2 studies was evaluated by conducting an integrated analysis of baseline sequence data. Next-generation sequencing (NGS) was conducted on all baseline samples, data was analyzed at the 15% detection threshold, and baseline polymorphisms at amino acid positions 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A were examined for impact on SVR_{12}.

In subjects who were TN or TE-PRS, baseline polymorphisms in NS3 were detected in 1.1% (9/845), 0.8% (3/398), 1.6% (10/613), 1.2% (2/164), 41.9% (13/31), and 2.9% (1/34) of subjects with HCV genotype 1, 2, 3, 4, 5 and 6 infection, respectively. Baseline polymorphisms in NS5A were detected in 26.8% (225/841), 79.8% (331/415), 22.1% (136/615), 49.7% (80/161), 12.9% (4/31), and 54.1% (20/37) of subjects with HCV genotype 1, 2, 3, 4, 5, and 6 infection, respectively.

The presence of baseline polymorphisms in NS3 and/or NS5A did not have an impact on SVR_{12} rates for GT1-, 2-, 4-, 5-, or 6-infected subjects.

Within GT3-infected subjects, baseline polymorphisms in NS3 did not have an impact on treatment outcome. The NS5A polymorphisms at positions 24, 28, 31, 58, 92, or 93 (including Y93H) did not have an impact on treatment outcome, whereas the A30K polymorphism was associated with a slightly decreased SVR_{12} rate. Given the low prevalence of A30K (6.3%; 39/615) and that the majority of subjects with A30K achieved SVR_{12}, its impact on overall SVR is expected to be minimal.

Amino Acid Substitutions in Subjects Experiencing Virologic Failure

Among TN and TE-PRS subjects without cirrhosis or with compensated cirrhosis treated for 8, 12, or 16 weeks, 23 subjects experienced virologic failure (2 with GT1, 2 with GT2, and 19 with GT3). A GT3-infected subject experiencing virologic failure was determined to have been reinfected with GT3a virus distinct from the one present at baseline.

Therefore, baseline polymorphisms and treatment-emergent substitutions were analyzed for 22 subjects experiencing virologic failure.

Among the 2 GT1-infected subjects, 1 had treatment-emergent substitutions A156V in NS3 and Q30R/L31M/H58D in NS5A, and 1 had treatment-emergent Q30R/H58D (while Y93N was present at baseline and post-treatment) in NS5A.

Among the 2 GT2-infected subjects, no treatment-emergent substitutions were observed in NS3 or NS5A; the prevalent M31 polymorphism in NS5A was present at baseline and post-treatment in both subjects.

Among the 18 GT3-infected subjects, the majority of subjects had treatment-emergent substitutions at the time of failure in NS3 (61.1%, 11/18) and NS5A (88.9%, 16/18). Treatment emergent NS3 substitutions Y56H/N, Q80K/R, A156G, and Q168L/R were observed in 11 subjects, and A166S or Q168R was present at both baseline and post-treatment in 5 subjects. Treatment-emergent NS5A substitutions M28G, A30G/K, L31F, P58T, or Y93H were observed in 16 subjects, and 13 subjects had A30K (n = 9) or Y93H (n = 5) at both baseline and post-treatment.

Integrated Safety Results

A summary of treatment-emergent adverse events (AEs) from pooled analyses of the registrational studies and supportive Phase 2 studies are presented in Table 3. Given the severity of the underlying renal disease and its associated comorbidities in patients with CKD Stages 4 and 5, the frequency and severity of the AEs in subjects enrolled Study M15-462 were expected to be higher than in subjects enrolled in the other registrational studies. Therefore, the summary of adverse events reported in Table 3 does not include the results of Study M15-462.

As shown in Table 3, AEs occurring with a frequency > 5% are headache, fatigue, nausea and diarrhea. The majority of subjects experienced an AE, which were mostly considered to be mild in severity by the investigator (Grade 1). Rates of AEs that were serious, led to premature study drug discontinuation or had a severity Grade ≥ 3 were low. Including

data from Study M15-462, there were 7 deaths, none of which were related to study drug, and the majority occurred several months after the last dose of study drug.

Table 3. Adverse Events Reported for ≥ 5.0% of Subjects (Phase 2 and 3 Analysis Set)

	Phase 2 and 3 Analysis Set[a] (N = 2,265) n (%)	
	All Adverse Events	DAA-Related Adverse Events[b]
Any AE	1,529 (67.5)	929 (41.0)
An AE Grade ≥ 3	65 (2.9)	4 (0.2)
Any SAE	48 (2.1)	1 (< 0.1)
Discontinuation of study drug due to any AE	8 (0.4)	3 (0.1)
All deaths[c]	6 (0.3)	0
Preferred Term		
Headache	410 (18.1)	298 (13.2)
Fatigue	330 (14.6)	259 (11.4)
Nausea	208 (9.2)	172 (7.6)
Diarrhea	146 (6.4)	86 (3.8)

AE = adverse event; DAA = direct-acting antiviral agent; GLE = glecaprevir; PIB = pibrentasvir; SAE = serious adverse event

a. Excludes Study M15-462.

b. DAAs = GLE, PIB, or GLE/PIB.

c. Includes nontreatment-emergent deaths. One additional death occurred in Study M15-462.

Cross reference: Summary of Clinical Safety R&D/16/0147: Table 2.2__2.2, Table 2.2__3.2

Adverse events in subjects without cirrhosis (n = 1,977) were similar in type, frequency, and severity compared with subjects with compensated cirrhosis (n = 288). The safety profile in subjects with HCV/HIV-1 coinfection (n = 33) was similar to that in HCV monoinfected subjects. Overall, the safety profile of GLE/PIB in the elderly population (≥ 65 years old, n = 328) was comparable to the safety profile in the non-elderly population (n = 2,041).

In Study M15-462, GLE/PIB was generally well-tolerated in subjects with CKD Stage 4 and 5 as evidenced by a treatment discontinuation rate of 1.9% (2/104) due to AEs that were considered DAA-related. No subject experienced a serious AE that was assessed as DAA-related. The safety profile in subjects (n = 104) in Study M15-462 was consistent with underlying severe renal impairment and its associated comorbidities. Pruritus was the most common AE among subjects (20.2%) in this study followed by fatigue (14.4%) and nausea (11.5%). Pruritus was not an unexpected finding, as it is commonly observed in patients with severe renal impairment.[15] Laboratory abnormalities were infrequent with no subject experiencing a Grade 3 or higher elevation in ALT or AST and 1 subject experiencing a Grade 3 elevation in total bilirubin. No safety signal or toxicity related to GLE/PIB specific to subjects with CKD Stage 4 and 5 has been identified.

The frequency and severity of hepatic-related AEs as well as liver chemistry abnormalities evaluating potential hepatotoxicity were low across the Phase 2 and 3 studies (excluding Study M15-462). Liver-related safety results indicated that:

- Four subjects had post-nadir Grade 3 ALT abnormalities or Grade 2 ALT with total bilirubin $\geq 2 \times$ ULN. None of these subjects prematurely discontinued study drug due to an ALT or bilirubin increase.
  - ALT abnormalities in 3 of these 4 subjects were not clinically significant
  - One subject experienced concurrent ALT $> 3 \times$ ULN (increased from nadir grade) and total bilirubin $\geq 2 \times$ ULN in the context of multiple gallstones that was not consistent with drug-induced liver injury
- Based on exposure-response analyses, no GLE/PIB exposure-dependent ALT increases were observed in subjects with ALT abnormalities
- Grade 3 increases in bilirubin were infrequent (0.4%) and without bilirubin-related AEs; none were associated with liver disease progression
- No subjects experienced drug-related hepatic decompensation. One subject with cirrhosis (Study M14-172) who had known esophageal varices experienced an episode of esophageal varices hemorrhage that was considered not related to study drug. Treatment was continued without clinical or laboratory signs of liver disease progression.

- A total of 6 (0.3%) subjects experienced a de novo event of HCC. In all 6 subjects, the events were considered related to subject's medical history of underlying liver disease and not to GLE/PIB.
- There were no cases consistent with drug-induced liver injury.

In summary, GLE/PIB demonstrated a favorable safety profile that was similar across durations of 8, 12, and 16 weeks. The regimen was well tolerated across a broad and diverse population of subjects, including subjects with compensated cirrhosis, HIV co-infection, and CKD Stage 4 or 5.

Common GLE/PIB-related AEs (ADRs) occurring in ≥ 5% of subjects were headache, fatigue, nausea. Adverse drug reactions were mostly Grade 1 (mild) in severity. Serious AEs and AEs leading to premature study drug discontinuation were rare.

There were no hematological or blood chemistry findings of concern or considered likely to be related to treatment. Unlike other protease inhibitors, no liver-related toxicities and no cases consistent with drug-induced liver injury were identified.

3.1 Differences Statement

The GLE/PIB fixed dose combination for 8 and 12 weeks was explored in treatment-naïve and -experienced HCV GT1 – 6 infected subjects, without cirrhosis or with compensated cirrhosis including subjects with HIV/HCV co-infection and subjects with CKD Stage 4 or 5 in several Phase 3 studies conducted in a randomized, controlled, double-blind or open-label fashion.

This is the first Phase 3b study designed to evaluate HCV GT1 – 6 treatment-naïve subjects without cirrhosis (Metavir F2 – F3) and with compensated cirrhosis (Metavir F4) treated with GLE/PIB for 8 or 12 weeks, respectively, in Brazil. This country did not participate in the Global GLE/PIB program.

3.2 Benefits and Risks

Benefits of treatment with GLE/PIB include: potent and pangenotypic antiviral activity in vitro, higher genetic barrier to development of drug resistance across genotypes compared to first generation DAA protease and NS5A inhibitors, no need for RBV, 8 or 12 weeks of treatment for NS5A inhibitor and PI naive, and the convenience of a once daily regimen. The combination of GLE/PIB has been evaluated in six Phase 3 registration studies and three Phase 2b supportive studies. The results of these studies show high SVR_{12} rates among subjects with HCV GT 1 – 6 infection who receive treatment with GLE/PIB.

Adverse events that are known, and those not previously identified, may occur with GLE/PIB as detailed in the informed consent of this study. In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures. Additional safety data for each DAA alone and the combination of PIB/GLE are detailed in Section 3.0 and in the Investigator's Brochure.[14]

Risks associated with GLE/PIB, including the risks of adverse reactions, virologic failure, and development of resistance-associated substitutions (Section 5.3.4), appear to be limited and manageable based upon the available data. Given the potential for high SVR_{12} rates in populations of HCV-infected subjects, including HIV/HCV co-infected, and with CKD 4 – 5, the risk-benefit profile for GLE/PIB is favorable.

4.0 Study Objective

4.1 Primary Objectives

The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving SVR_{12} (HCV RNA < LLOQ 12 weeks following therapy) and safety of GLE/PIB combination in treatment-naïve adults in Brazil with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis. The efficacy and safety endpoints will be analyzed on the overall population (i.e., across treatment durations and genotypes).

4.2 Secondary Objectives

The secondary objectives are to assess efficacy of GLE/PIB based on overall population (i.e., across treatment durations and genotypes) by evaluating the following:

- The percentages of subjects with HCV on-treatment virologic failure (OTVF);
- The percentages of subjects with HCV virologic relapse.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of GLE/PIB for an 8- or 12-week treatment duration in adults in Brazil with chronic HCV GT1 – 6 infection, without cirrhosis or with compensated cirrhosis with a METAVIR System Fibrosis Score of F2, F3 or F4 (F2-F4) or equivalent,[16] who are HCV treatment-naïve. Approximately 100 subjects meeting the eligibility criteria will be enrolled. The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of 35 GT1 and approximately 25 GT3 subjects and 2) approximately 80 F2 – 3 and a maximum of approximately 20 F4 subjects.

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

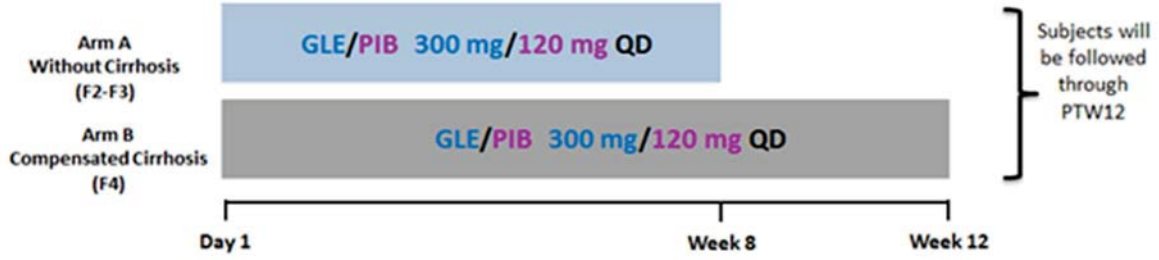
Screening Period: Subjects will have up to 35 days following the Screening Visit to confirm eligibility and enroll in the study.

Treatment Period: Eligible subjects will be enrolled to receive GLE/PIB 300 mg/120 mg once daily (QD) for an 8 (Arm A) or 12 (Arm B) week treatment duration based on cirrhosis status.

Post-Treatment Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 12 weeks to monitor HCV RNA levels to evaluate efficacy and the emergence and persistence of resistance-associated substitutions.

A study schematic is shown below in Figure 1.

Figure 1. Study Design



* **The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of approximately 35 GT1 and 25 GT3 subjects and 2) approximately 80 F2 – F3 and a maximum of approximately 20 F4 subjects.**

Approximately 100 eligible subjects will be enrolled into one of the following treatment arms:

- Arm A: HCV GT 1 – 6 without cirrhosis (F2 – F3) subjects will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks.
- Arm B: HCV GT 1 – 6 subjects with compensated cirrhosis (F4) will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 12 weeks.

The study was designed to enroll approximately 100 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening may not be enrolled.

5.1.1 Screening Period

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study-specific procedures will receive a unique subject number via the Interactive Response Technology (IRT) system. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through Study Day 1 prior to dosing, and will

record the results of this assessment and the details of the informed consent process in the subject's medical records. Eligible subjects have up to 35 days following the Screening Visit to enroll into the study.

5.1.1.1 Rescreening

Subjects who at Screening have any of the following are not eligible to rescreen or retest:

- A positive Hepatitis B surface antigen (HBsAg);
- HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti-HBs); or
- If Woman of Childbearing Potential (WOCBP), a positive serum pregnancy test;
- Development of decompensated liver disease during the screening period, as defined by the Exclusion Criterion 6.

Otherwise subjects may be retested or rescreened only once unless approved by the Primary Therapeutic Area Medical Director.

Subjects who have exclusionary laboratory parameter(s) are allowed to retest on the related panel(s) (e.g., exclusionary ALT requires a repeat chemistry panel) within the same screening period and must meet all eligibility laboratory criteria on any panel that is repeated. If any of the retest result(s) are exclusionary, the subject may not be rescreened again.

Subjects that exceed the initial 35 day screening period should be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary during the first screening attempt (with the exception of HIV, HBV, HCV genotype and subtype, follicle stimulating hormone (FSH), which do not need to be repeated). The FibroScan and liver biopsy do not need to be repeated for rescreened subjects provided that the date of the liver biopsy is within 24 months of the rescreening date and the FibroScan is within 6 months of the rescreening date (Section 5.1.1).

Subjects who rescreen or subjects not meeting the study eligibility criteria must be identified by site personnel as a screen failure in both IRT and EDC systems.

5.1.2 Treatment Period

After meeting the eligibility criteria, subjects will be enrolled via IRT on Study Day 1. Subjects will be administered study drug at the site on Study Day 1, and provided dosing instructions.

Study visits and procedures during the Treatment Period are detailed in Appendix C. Safety and tolerability will be assessed throughout the study. Laboratory testing will include chemistry and hematology as specified in Table 5. Plasma samples for pharmacokinetic analysis and HCV RNA analysis will be collected as detailed in Section 5.3 and Section 5.3.1.1.

All subjects will continue to return to the site on an outpatient basis as outlined in Appendix C. Sites should ensure that subjects adhere to all study visits. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

HCV virologic failure criteria will be evaluated and applied by the investigator as detailed in Section 5.4.1.1.

Subjects who prematurely discontinue from the Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined in Appendix C and as described in Section 5.4.1. Subjects who prematurely discontinue from study treatment will continue to be followed in the Post-Treatment Period (see Section 5.1.3).

5.1.3 Post-Treatment Period

All subjects who received at least one dose of study drug will be monitored in the Post-Treatment Period for 12 weeks following the last dose of study drug for safety, HCV RNA, and the emergence and persistence of HCV resistance-associated substitutions.

The Post-Treatment Period will begin the day following the last dose of study drug. Study visits during the Post-Treatment period are detailed in Appendix D and Section 5.3.1.1.

Subjects who prematurely discontinue during the Post-Treatment Period should return to the site for a Post-Treatment discontinuation visit as outlined in Appendix D.

5.2 Selection of Study Population

The study population consists of male and female adults aged 18 years or older with chronic HCV GT1 – 6 infection with METAVIR equivalent fibrosis stage of F2 – F4 (without cirrhosis or with compensated cirrhosis) who are HCV treatment naïve (i.e., subject has never received a single dose of any approved or investigational anti-HCV medication). Subjects with HIV/HCV co-infection and subjects at all CKD stages (CKD Stages 1 – 5) are allowed to participate.[17] Subjects who meet all inclusion criteria and none of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

1. Male or female, at least 18 years of age at time of Screening.
2. If female, subject must be either

   Postmenopausal defined as:

   - Age > 55 years with no menses for 12 or more months without an alternative medical cause; or
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L; or

- Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

OR

- A WOCBP practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.

3. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.

   Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing.

4. Screening laboratory result indicating HCV GT1-, 2-, 3-, 4-, 5- and/or 6-infection. Mixed and indeterminate genotypes are acceptable.

5. Subject has positive plasma HCV antibody and HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.

6. Subjects who are known to be HCV/HIV co-infected may enroll if they have a positive test result for anti-Human Immunodeficiency Virus antibody at Screening and are:

   Naïve to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study), or on a stable, qualifying HIVART regimen for at least 8 weeks prior to Baseline. (Substituting TDF for TAF as part of the combination regimen is allowed at any time.)

   The HIVART regimen must include at least one of the following ARV agents:

   - Raltegravir (RAL)
   - Dolutegravir (DTG)
   - Rilpivirine (RPV)
   - Elvitegravir/cobicistat (EVG/COBI)

In addition to the above medications, HIV Ab positive subjects (both without cirrhosis or with compensated cirrhosis) may take a nucleoside/nucleotide reverse transcriptase inhibitor (N(t)RTI) backbone containing any of the following:

- Tenofovir disoproxil fumarate (TDF)
- Tenofovir alafenamide (TAF)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Lamivudine (3TC)

Subjects receiving any other HIV ART in addition to those noted above are not eligible for enrollment in the study.

Subjects on stable HIV ART must have Plasma HIVRNA below 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once during the 12 months prior to Screening (by an approved plasma HIVRNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTi*m*e HIV-1 assay).

7. Subject must be documented as without cirrhosis (METAVIR equivalent fibrosis stage of F2 – 3), or with compensated cirrhosis (METAVIR equivalent fibrosis stage of F4 with a Child-Pugh score of ≤ 6). See Section 5.3.1.1 for Liver Diagnostic Testing and Child-Pugh Score and Category.
8. Subjects with compensated cirrhosis only: Absence of hepatocellular carcinoma (HCC) 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. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.
9. Subject must voluntarily sign and date an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to the initiation of any Screening or study specific procedures.

10. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.
11. Subjects requiring dialysis should have been receiving dialysis for at least 1 month prior to enrollment, and may be on hemodialysis or peritoneal dialysis.

Rationale for Inclusion Criteria

1, 4 – 11	In order to select the appropriate subject population with appropriate disease characteristics for evaluation
2, 3	The impact of GLE and PIB on human pregnancies has not been established. However, assessment of the completed nonclinical reproductive toxicology studies indicates that there is no drug-related effect on teratogenicity/fetotoxicity. In addition, the compounds are non-genotoxic
10	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Current HBV infection on screening tests, defined as:
   - A positive HBsAg, or;
   - HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., with negative HBsAg and Anti-HBs)
3. Requirement for and inability or unwillingness to safely discontinue the medications or supplements listed in Table 4 at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of any study drug.

4. Requirement for 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).
5. 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.
6. Any current or past clinical evidence of Child-Pugh B or C classification (score of > 6) or any current or past clinical history of liver decompensation including ascites on physical exam, hepatic encephalopathy or variceal bleeding. Prophylactic use of beta blockers is not exclusionary (see Section 5.3.1.1).
7. Laboratory parameters exclusions:
   - ALT > 10 × ULN; AST > 10 × ULN
   - Total Bilirubin > 3.0 mg/dL
   - Albumin < LLN (without cirrhosis); < 2.8 mg/dL (with compensated cirrhosis)
   - Platelets < 90,000 10^3/μL (without cirrhosis); < 60,000 10^3/μL (with compensated cirrhosis)
8. History of solid organ transplantation, unless the implanted organ has since been removed, or is non-functional, and subject is no longer on immunosuppressive medication. If the organ is non-functional, the subject must be clinically stable off of immunosuppressive medication for a minimum of 6 months prior to screening.
9. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks (whichever is longer) prior to study drug administration.
10. Receipt of any investigational or commercially available anti-HCV agents, including, but not limited to: interferon, pegylated interferon ribavirin, sofosbuvir, telaprevir, boceprevir, simeprevir, asunaprevir, veruprevir, glecaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, voxilaprevir, velpatasvir, pibrentasvir, or dasabuvir.

11. History of severe, life-threatening or other significant sensitivity to any excipients of the study drug.
12. Treatment for an AIDS-Defining Conditions (ADC) (Appendix E) within 6 months of Screening.
13. Subjects who cannot participate in the study per local law.

Rationale for Exclusion Criteria

1, 3, 4, 6 – 13	In order to ensure safety of the subjects throughout the study
2, 5	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal 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 drugs. 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 serious adverse event (SAE) will be recorded in EDC. The AbbVie Primary Therapeutic Area Medical Director should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior HCV Therapy

Subjects must be HCV treatment-naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication).

5.2.3.2 Prior and Concomitant HIV Therapy

Subject on an HIV ART regimen must include ARV agents as defined in Inclusion Criterion 6 (Section 5.2.1).

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

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

Subjects receiving any other HIV ART in addition to those listed in Inclusion Criterion 6 (Section 5.2.1) would not be eligible for enrollment in the study.

5.2.3.3 Concomitant Therapy

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

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 drugs, if applicable.

Flu shots and other vaccinations are allowed during Screening through the Post-Treatment Period for all subjects. Flu shots and vaccinations may affect plasma HIV RNA levels.

5.2.3.4 Prohibited Therapy

Medications or supplements prohibited to be administered with GLE/PIB (glecapravir/pibrentasvir) are listed in Table 4. Since GLE/PIB has received marketing authorization in Brazil, any medications in the local label that are contraindicated to be administered with GLE/PIB are also considered to be prohibited medications. Subjects must be able to safely discontinue any prohibited medications or supplements 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 drugs.

Table 4. Prohibited Medications and Supplements

Medication or Supplement Name
Red yeast rice (monacolin K), St. John's Wort
Carbamazepine, efavirenz, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin*
Astemizole, cisapride, terfenadine
Ethinyl estradiol

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drug. After signing the informed consent form, 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) 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 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 either 1) reduce or limit the pravastatin or rosuvastatin dose in accordance with the GLE/PIB (glecapravir/pibrentasvir) product label (if approved in the country); or 2) reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drug if GLE/PIB is not yet approved in the country.

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

The chronic use of systemic immunosuppressants is prohibited from 2 weeks prior to the first dose of study drug and until 30 days after the last dose of study drug including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab).

For HCV/HIV coinfected subjects, the investigator must refer to the current package insert(s) or product label(s) of a subject's ART regimen for a complete list of medications prohibited to be used with those drugs, which should not be used at least 2 weeks prior to the first dose of any study drug and not use these during the entire Treatment Period and for 30 days following discontinuation of study drugs.

5.2.4 Contraception Recommendations

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a Woman of Childbearing Potential, practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 30 days after the last dose of study drug:

- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- 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, symptom-thermal, post-ovulation methods] and withdrawal are not acceptable).

For male study subjects, no contraception is required.

5.3 Efficacy, Pharmacokinetic, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C (Treatment Period) and Appendix D (Post-Treatment Period).

5.3.1.1 Study Procedures

Informed Consent

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Medical History

A complete medical history, including history of tobacco, alcohol and drug use, will be taken from each subject at Screening Visit. The subject's medical history will be updated at the Study Day 1 Visit. This updated medical history will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will be performed at visits specified in Appendix C, or upon subject discontinuation. A symptom-directed physical examination may be performed at any other visit, when necessary.

The physical examination performed on Study Day 1 will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after the first dose will be recorded as adverse events.

Height will be measured only at Screening.

Vital Signs and Weight

Body temperature, blood pressure, pulse, and body weight will be measured at each study visit as specified in Appendix C and Appendix D. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes. The subject should wear lightweight clothing and no shoes during weighing. The vital signs performed on Day 1 of the Treatment Period will serve as the baseline for clinical assessment.

12-Lead Electrocardiogram

A 12-lead resting ECG will be obtained at the visits indicated in Appendix C. The ECG should be performed prior to blood collection.

The ECG will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign, and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 5 at the visits indicated in Appendix C and Appendix D.

Blood samples for serum chemistry tests should be collected following a minimum 8-hour fast prior to study drug intake (with the exception of the Screening Visit, which may be non-fasting). Subjects whose visits occur prior to the morning dose of study drug should be instructed to fast after midnight until the blood sample is collected in the morning and thereafter take their study medications with food. Subjects whose visits occur following the morning dose of study drug should be instructed to fast after breakfast until the study visit occurs. At the Study Day 1 visit, a fasting blood sample should be collected prior to the first dose of study drug. Blood samples should still be drawn if the subject did not fast for at least 8 hours. Fasting or non-fasting status will be recorded in the source documents and on the laboratory requisition. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

A central laboratory will be utilized to process and provide results for the clinical laboratory tests.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study. The certified laboratory chosen for this study is Covance. Samples will be sent to the following address:

Covance
8211 SciCor Drive
Indianapolis, IN 46214 USA

Table 5. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Additional Tests
Hematocrit	Blood Urea Nitrogen (BUN)	Anti-HCV Ab[a]
Hemoglobin	Creatinine	HCV RNA
Red Blood Cell (RBC) count	Total bilirubin	HCV genotype and subtype[a]
White Blood Cell (WBC) count	Direct and indirect bilirubin	HIV Ab[a]
Neutrophils	Alanine transaminase (ALT)	HIV RNA[b]
Bands, if detected	Aspartate transaminase (AST)	Hepatitis B Panel (Anti-HB[c]
Lymphocytes	Alkaline phosphatase	Total, Anti-HBs and HBsAg)[c]
Monocytes	Sodium	Anti-HBc IgM[c]
Basophils	Potassium	Anti-HBc Total[c]
Eosinophils	Calcium	Anti-HBs[c]
Platelet count (estimate not acceptable)	Inorganic phosphorus	Anti-HAV
	Total protein	IgM[d]
Prothrombin Time/INR[a]	Glucose	Anti_HAV Total[d]
Activated partial thromboplastin time (aPTT)	Albumin	Anti-HEV IgG[d]
	Chloride	Anti-HEV IgM[d]
	Bicarbonate	HEV RNA[d]
	Magnesium	HBV DNA[e]
	Gamma-glutamyl transferase (GGT)	Follicle Stimulating Hormone (FSH)[f]
		Urine and Serum Human Chorionic Gonadotropin (hCG) for females[g]
		Alpha2-macroglobulin[h]
		Haptoglobin[h]
		Apolipoprotein A1[h]
		CD4, CD4%[b]
		CD8, CD8%[b]
		CD4:CD8[b]

a. Performed only at Screening.

b. Only for known HCV/HIV co-infected subjects.

c. Performed at Screening for all subjects and also performed for management of transaminase elevations (Section 6.1.7.1).

d. Performed for management of transaminase elevation (Section 6.1.7.1).

e. Performed at Screening for subjects who have occult HBV infection (positive Anti-HBc Total with negative HBsAg and Anti-HBs) and also performed for management of transaminase elevation (Section 6.1.7.1).

f. Only performed if requested during screening for post-menopausal women < 55 to verify FSH level if site does not have a previous result available.

g. Required only for females of child bearing potential.

h. Component of FibroTest and collected only if required for FibroTest calculation during the Screening Period.

For any laboratory test value outside the reference range that the investigator considers to be clinically significant:

- The investigator will repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.
- A laboratory test value that requires a subject to be discontinued from the study or study drug or requires a subject to receive treatment will be recorded as an adverse event.

The management of laboratory abnormalities that may occur during the study is described in Section 6.1.7.

Pregnancy Testing

- WOCBP must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.
- Monthly pregnancy testing should be performed during treatment, including at the last dose and until 30 days of last study drug dose, as indicated in Appendix C and Appendix D.
- Subjects with borderline pregnancy tests at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
- Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in inclusion criterion #2) at Screening do not require pregnancy testing.

Concomitant Medication Assessment

Please refer to Section 5.2.3.2.

Hepatitis B, Hepatitis C Virus and HIV Screen

HBsAg, anti-HBc and anti-HBs, anti-HCV Ab and anti-HIV Ab testing will be performed at Screening. HBV DNA testing may be performed to exclude occult HBV infection.

The investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report these results per local regulations, if necessary. The HIV results will not be reported by the central laboratory to the clinical database.

Liver Diagnostic Testing

Subjects will be considered to be without cirrhosis or with cirrhosis based on the definitions below:

Without Cirrhosis (F2 and F3)

- A liver biopsy within 24 months prior to or during Screening demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of 2 – 3, Ishak fibrosis score of 3 or 4; or
- A FibroScan® score of 8.8 to < 12.5 kPa within ≤ 6 months of Screening or during Screening period (FibroScan® must be approved by the local regulatory agency to qualify for entrance criteria); or
- A Screening FibroTest score of 0.49 to 0.72 (inclusive).[18]

With Cirrhosis (F4)

- 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 or on a liver biopsy conducted during Screening; or
- A FibroScan® score of ≥ 12.5 kPa within ≤ 6 months of Screening or during Screening period (FibroScan® must be approved by the local regulatory agency to qualify for entrance criteria); or
- A Screening FibroTest result that is ≥ 0.73.

The result of the liver biopsy supersedes the results of FibroScan and FibroTest and result of FibroScan supersedes the results of FibroTest. At Screening, it is recommended that subjects should otherwise meet all other inclusion criteria and none of the exclusion criteria before undergoing a liver biopsy.

Subjects with cirrhosis will be defined as having compensated cirrhosis if the Child-Pugh Score at screening is ≤ 6.

Child-Pugh Score and Category

All subjects with cirrhosis will have Child-Pugh scores assessed at screening. The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments) as shown in Table 6. Child-Pugh score will be determined at the visits indicated in Appendix C and Appendix D.

Table 6. Child-Pugh Classification of Severity of Cirrhosis

	Points Assigned for Observed Findings		
Parameter	**1**	**2**	**3**
Total bilirubin, µmol/L (mg/dL)	< 34.2 (< 2)	34.2 – 51.3 (2 – 3)	> 51.3 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28 – 35 (2.8 – 3.5)	< 28 (< 2.8)
INR	< 1.7	1.7 – 2.3	> 2.3
Ascites**	None	Slight	Moderate to severe
Hepatic encephalopathy*	None	Grade 1 or 2 (or suppressed with medication)	Grade 3 or 4 (or refractory)

Child-Pugh category A: 5 – 6 points; Child-Pugh category B: 7 – 9 points; Child-Pugh category C: 10 – 15 points.

* None: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.
Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

** None.
Slight ascites = Ascites detectable only by ultrasound examination.
Moderate ascites = Ascites manifested by moderate symmetrical distension of the abdomen.
Severe ascites = Large or gross ascites with marked abdominal distension.

Clinical Assessment of Hepatic Decompensation

A clinical assessment of hepatic encephalopathy and ascites, as defined in Exclusion Criterion #6, will be performed at Study Day 1 prior to dosing to confirm the subject has not progressed to hepatic decompensation since Screening for all subjects who have

compensated cirrhosis. Subjects who present symptoms and signs of hepatic decompensation, including assessment at Day 1 prior to receiving study drug, will neither be dosed nor enrolled into the trial.

Hepatocellular Carcinoma Screening: Liver Ultrasound

HCC screening will be required as a protocol-specified study procedure only at the Screening Visit and at the last Post-Treatment Study Visit, as indicated in Appendix C and Appendix D, for subjects with compensated cirrhosis only. In-between those visits, HCC screening should be performed according to standard of care.

At the Screening Visit and at the last Post-Treatment Study Visit, subjects with compensated cirrhosis will be required to undergo a liver ultrasound to screen for HCC, unless the subject has a historical liver ultrasound, CT scan or MRI performed for HCC screening within 3 months prior to those visits, in which case the result of the historical ultrasound, CT scan or MRI will be used as the result for the Study Visit assessment. A positive ultrasound result suspicious of HCC will be confirmed with CT scan or MRI. Alternate methods of screening for HCC (i.e., CT scan or MRI) at a study visit should be discussed with the study designated physician.

Patient Reported Outcomes (PRO) Instruments (Questionnaires)

Subjects will complete the self-administered PRO instruments on the study visits specified in Appendix C and Appendix D. Subjects should be instructed to follow the instructions provided with each instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaires to them. Site personnel should encourage completion of each instrument at all specified visits and should ensure that a response is entered for all items.

Short Form 36 – Version 2 Health Survey (SF-36v2)

The SF-36v2 is a general Health Related Quality of Life (HRQoL) instrument with extensive use broad variety of health conditions and is the standard in literature for HCV. The SF-36v2 instrument comprises 36 total items (questions) targeting a subject's functional health and well-being in 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). Domain scores are also aggregated into a Physical Component Summary score and a Mental Component Summary score. Higher SF-36v2 scores indicate a better state of health. The SF-36v2 should require approximately 10 minutes to complete.

Treatment Satisfaction Questionnaire-Medicine (TSQM)

The TSQM is a 14-item instrument and includes assessments of satisfaction with a medication's effectiveness (Effectiveness, three items), lack of side effects (Side Effects; five items), convenience (three items) and the subject's global satisfaction (Global Satisfaction; three items).

The subject should complete the questionnaire before site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response. TSQM scores range from 0 – 100 with higher scores indicating better satisfaction. The TSQM should require approximately 5 minutes to complete.

EuroQol-5 Dimensions-3 Level (EQ-5D-3L)

The EQ-5D-3L is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-3L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on 3 levels of severity. Responses to the 5 items encode a discrete health state which is mapped to a preference (utility) specific for different societies. Subjects also rate their perception of their overall health on a separate visual analogue scale (VAS). The EQ-5D-3L should require approximately 5 minutes to complete.

PRO instruments should be consistently presented so that subjects complete the questionnaires in the following order: the SF-36v2, TSQM, and EQ-5D-3L. PRO instruments should be completed prior to drug administration on Day 1 and prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels, at all study specified visits listed in Appendix C and Appendix D. The TSQM is the only PRO assessment that will not be performed at Day 1.

Enrollment and Assignment of Subject Numbers

All Screening activities must be completed and reviewed prior to enrollment. Subjects who meet all the Inclusion Criteria and none of the Exclusion Criteria at Screening will proceed to enrollment via the IRT system on Study Day 1.

Subject numbers will be unique 4 digit numbers and will begin with 1001 with the first two digits representing the investigative site, and the last two digits representing the subjects at that site. Enrolled subjects will keep their subject number throughout the study. Subjects will be enrolled on Study Day 1 as described in Section 5.5.4.

Study Drug Compliance for Kits

Individual bottles of GLE/PIB will be provided for subject dosing to the site. Each subject will have compliance documented by the site in the subject's source notes for GLE/PIB. At each Study Drug Accountability Visit in Appendix C, the overall number of tablets of GLE/PIB remaining in each bottle will be recorded and entered in the IRT system along with the date of reconciliation.

Additional information regarding treatment compliance can be found in Section 5.5.6.

HCV Genotype and Subgenotype

Plasma samples for HCV genotype and subtype determination will be collected at Screening. Genotype and subtype will be assessed using the Versant® HCV Genotype Inno LiPA Assay, Version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY) by the central laboratory. If the LiPA assay is unable to genotype a

sample, its genotype and subtype will be evaluated by a Sanger sequencing assay of a region of the NS5B gene by the central laboratory.

HCV RNA Levels

Plasma samples for HCV RNA levels will be collected as indicated in Appendix C and Appendix D. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan HCV Quantitative Test, v2.0. The lower limit of detection (LLOD) and lower limit of quantification (LLOQ) for this assay (regardless of genotype) are both 15 IU/mL.

HCV Resistance Testing Sample

A plasma sample for HCV resistance testing will be collected prior to dosing on Day 1 and at the study visits indicated in Appendix C and Appendix D. Specific instructions for preparation and storage of HCV RNA and HCV resistance samples will be provided by the central laboratory, AbbVie, or its designee.

Study Drug Dosing Card

Subjects will be provided with self-administration instructions and study drug dosing cards to record the exact date, time (record to the nearest minute) and number of tablets of study drug administration (GLE/PIB) for the last 2 doses of study drug taken prior to the scheduled pharmacokinetic sample collection visits during the Treatment Period as detailed in Appendix C.

The site staff will record the information about the last 2 doses taken prior to the scheduled pharmacokinetic sample collection from the study drug dosing card into the eCRF. In the event that the dosing card is not available, the site may obtain dosing information via patient interview and record this information in the source notes and the eCRF.

To facilitate proper dosing of study drug before pharmacokinetic evaluation blood samples are taken, the following procedures should be performed:

- The Investigator or designee should make sure the subject is given the dosing card at the visits listed in Appendix C.
- The Investigator or designee will contact the subject approximately 2 days before the scheduled visit date to review the importance of proper study drug administration relative to the pharmacokinetic blood collection and documentation of dosing times on the dosing card. The date and time of the contact will be entered into the subject's source documents.
- The completed dosing card will be collected by the Investigator or designee on the day of the visit and be kept as a source record of dosage administration times documented in the eCRF.

Flow Cytometry, HIV RNA and HIV Resistance Testing Samples

For subjects with HCV/HIV coinfection, samples for plasma HIV RNA levels and flow cytometry (including but not limited to CD4+ T-cell and CD8+ T-cell counts [absolute and percent]) will be obtained at the times specified in Appendix C and Appendix D. Plasma HIV-1 RNA will be measured by the central laboratory using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, version 2.0 HIV-1 Assay. Results below the LLOD are reported as: "Not Detected."

If a HIV RNA level result of subject on stable HIV ART is ≥ 200 copies/mL, the subject's HIV RNA is to be repeated as noted in Section 5.4.1.2. At the time the repeat plasma HIV RNA is drawn, a sample should be obtained for HIV genotypic resistance testing. If the subject's repeat HIV RNA is ≥ 500 copies/mL, the sample obtained for HIV genotypic resistance testing will be analyzed.

HIV protease (PR), reverse transcriptase (RT) and integrase (IN) sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assay.

If the subject's repeat HIV RNA is < 200 copies/mL, then the subject will resume routine plasma HIV RNA assessments as shown in Appendix C and Appendix D, and described in Section 5.4.1.2.

Specific instructions for preparation and storage of flow cytometry, plasma HIV RNA, and HIV resistance samples will be provided by the central laboratory, AbbVie, or its designee.

5.3.1.2 Meals and Dietary Requirements

Study drug (GLE/PIB) tablets should be dosed together and taken with food.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic assay of GLE, PIB, and their possible metabolites will be collected by venipuncture at each study visit indicated below and in Appendix C.

- At all Treatment-Period visits, except Day 1, a single blood sample for pharmacokinetic analysis will be collected without regard to the time of dosing. The date and time of blood sample collection and the two previous doses of the study drug will be recorded to the nearest minute in the source documents. Additionally, the date and time of the two previous doses of the study drug will be recorded to the nearest minute on the eCRF.

5.3.2.2 Handling/Processing of Samples

Specific instructions for collection of blood samples and subsequent preparation and storage of plasma samples for the pharmacokinetic assays of GLE, PIB, and their possible metabolites will be provided by the central laboratory, AbbVie, or its designee.

5.3.2.3 Disposition of Samples

The frozen plasma samples for the pharmacokinetic assays of GLE, PIB, and their possible metabolites will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory.

The central laboratory will then ship the GLE and PIB samples to AbbVie or the reference laboratories following separately provided instructions.

5.3.2.4 Measurement Methods

Plasma concentrations of GLE and PIB will be determined using validated assay methods in the Drug Analysis Department at AbbVie. Plasma concentrations of any possible GLE and PIB metabolites may also be determined using either validated or non-validated methods.

5.3.3 Efficacy Variables

Virologic response will be assessed by plasma HCV RNA levels in IU/mL at various time points from Day 1 through 12 weeks after completion or discontinuation of study drug.

5.3.3.1 Primary Variable

The primary efficacy variable is the percentage of subjects who achieve SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

5.3.3.2 Secondary Variables

The secondary efficacy variables are:

- The percentage of subjects with HCV OTVF.
- The percentage of subjects with HCV virologic relapse.

5.3.3.3 HCV Resistance Variables

For all subjects receiving GLE/PIB and with available samples, baseline polymorphisms at signature resistance-associated amino acid positions identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA ≥ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples at signature resistance-associated positions identified by NGS and comparison to the baseline sequence, 2) the amino acid substitutions in available post-baseline samples at signature resistance-associated positions identified by NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of resistance-associated substitutions by NGS.

5.3.4 Safety Variables

The following safety evaluations will be performed during the study: adverse events, vital signs, physical examination, ECG, and laboratory tests assessments.

5.3.5 Pharmacokinetic Variables

Individual plasma concentrations of GLE, PIB, and their potential metabolites, if measured, will be tabulated and summarized.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.

If, during the course of study drug administration, the subject prematurely discontinues, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Appendix C and Appendix D. 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. The last dose of any study drug and reason for discontinuation will be recorded in the EDC (electronic data capture) system. 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 substitutions.

If a subject is discontinued from study drug or in 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.

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. Specific instructions regarding subject pregnancy can be found in Section 6.1.6. If a subject is discontinued, subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

5.4.1.1 HCV Virologic Failure Criteria

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.
- 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 resistance-associated viral substitutions until 12 weeks post-treatment. Alternative management will only be considered with the approval of TA MD.

5.4.1.2 Failure to Maintain HIV Virologic Suppression

HIV RNA will be assessed at each scheduled study visit during the Treatment and Post Treatment Period, as detailed in Appendix C and Appendix D.

The criteria for failure to maintain HIV virologic suppression among subjects on stable ARTs is as follows:

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

Subjects should remain on HCV study drug treatment and his/her current ART regimen while the failure to maintain HIV virologic suppression is being confirmed. A confirmatory HIV RNA and HIV genotypic resistance blood draw can be done as an unscheduled visit. However, if this blood draw falls on the date of a scheduled study visit (Appendix C and Appendix D), only a single HIV RNA and HIV genotypic resistance blood draw needs to be performed at this visit.

At the time a confirmatory HIV RNA is drawn, a sample for HIV genotypic resistance testing should also be obtained; this sample will be analyzed if the subject's repeat plasma HIV RNA is ≥ 500 copies/mL. Subjects should remain on HCV study drug treatment and his/her current ART regimen while the failure to maintain HIV virologic suppression is being confirmed. A confirmatory HIV RNA and HIV genotypic resistance blood draw can be done as an unscheduled visit. However, if this blood draw falls on the date of a scheduled study visit (Appendix C and Appendix D), only a single HIV RNA and HIV genotypic resistance blood draw needs to be performed at this visit.

During the Treatment Period, subjects with confirmed failure to maintain HIV RNA suppression should continue HCV study drug treatment unless there is a requirement for prohibited concomitant medications (Section 5.2.3.2) to construct a new HIV ART regimen.

Clinical management of failure to maintain HIV virologic suppression during the study (Treatment and Post-Treatment Period) will be handled by the Investigator according to current HIV treatment guidelines and local standard of care. Subject's change of HIV ART regimen must be discussed with the AbbVie TA MD prior to the change being made, unless the change is being made to address an immediate safety concern.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Each dose of GLE/PIB will be dispensed in the form of film-coated co-formulated tablets at the visits listed in Appendix C. Subjects will be instructed to take study drug at the same time every day with food. Please refer to Section 5.3.1.1 and Section 5.3.2.1 for more details.

GLE/PIB will be provided by AbbVie as 100 mg/40 mg film-coated tablets. GLE/PIB will be taken orally at GLE 300 mg/PIB 120 mg (three × GLE 100 mg/PIB 40 mg tablets) QD and with food.

Beginning with Study Day 1, the site will use the IRT system to obtain the study drug kit numbers to dispense at the study visits specified in Appendix C. Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. The site will also contact the IRT system to provide study drug return information for each kit at the visits specified in Appendix C. At the end of the Treatment Period or at the Premature D/C Visit from the Treatment Period, the site will contact the IRT system to provide the discontinuation visit date information and study drug return information for each kit (Section 5.5.7).

All subjects who receive at least one dose of study drug and meet the HCV virologic failure criteria defined in Section 5.4.1.1 will be discontinued from treatment.

5.5.2 Identity of Investigational Products

Information about the study drug to be used in this study is presented in Table 7.

Table 7. Identity of Investigational Products

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
Glecaprevir/Pibrentasvir	AbbVie	Oral	Film-coated tablet	100 mg/ 40 mg

5.5.2.1 Packaging and Labeling

Study drug will be supplied in bottles. Each bottle will be labeled as required per country requirements. Labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to subject.

5.5.2.2 Storage and Disposition of Study Drug

Study Drug	Storage Conditions
Glecaprevir/Pibrentasvir bottles	15° to 25°C (59° to 77°F)

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be

maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to AbbVie (or designee).

5.5.3 Method of Assigning Subjects to Treatment Groups

At the Screening Visit, all subjects will be assigned a unique subject number through the use of IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number, assigned at the Screening Visit, throughout the study. For enrollment of eligible subjects into the study, the site will utilize the IRT system in order to receive the treatment assignment. Enrolled subjects will be assigned to either Arm A (8 weeks of treatment) or Arm B (12 weeks of treatment) based on cirrhosis status. The study drug kit numbers will be assigned according to schedules computer-generated before the start of the study by the AbbVie Statistics Department.

Contact information and user guidelines for IRT use will be provided to each site. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Subjects meeting the eligibility criteria will be enrolled as described in Section 8.3.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.6.4. Study drug dosing will be initiated at the Study Day 1 Visit.

All tablets of GLE/PIB will be dosed together (three tablets once daily). All subjects should take all doses of study medications with food.

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

At the start of the study, each subject should receive counseling regarding the importance of dosing compliance with the treatment regimen with regard to HCV virologic response and potential development of resistance due to poor compliance.

At each study visit after Day 1 during the Treatment Period, subjects will be instructed to bring all bottles of study drug (full, partial, or empty) for assessment of treatment compliance. At Study Drug Accountability visits denoted in Appendix C, study site personnel will assess subject compliance by inspecting the contents of the bottles and record the status of each one, as well as the exact number of remaining tablets of GLE/PIB in IRT. Treatment compliance will be based on the number of tablets dispensed, as recorded in IRT, and the number of remaining tablets. If poor compliance is noted, the subject should be counseled and this should be documented in the subject's source.

5.5.7 Drug Accountability

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt (POR) or similar document and via recording in the IRT system. A current (running) and accurate inventory of study drug will be kept by the investigator and will include lot number, kit number, number of tablets dispensed, subject number, initials of person who dispensed study drug, and date dispensed for each subject. An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the Treatment Period. The monitor will review study drug accountability on an ongoing basis. Final accountability will be verified by the monitor at the end of study drug treatment at the site.

During the study, should an enrolled subject misplace or damage a study drug bottle of GLE/PIB the IRT system must be contacted and informed of the misplaced or damaged study drug. If the bottle is damaged, the subject will be requested to return the remaining study drug to the site. Replacement study drug may only be dispensed to the subject by contacting the IRT system. Study drug replacement(s) and an explanation of the reason for the misplaced or damaged study drug(s) will be documented within the IRT system. The study drug start date and the last dose of the regimen will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each bottle, number of tablets remaining in each one returned, and the date of reconciliation will be documented in the IRT system. The monitor will review study drug accountability on an ongoing basis.

Upon completion of or discontinuation from the Treatment Period, all original study drug bottles (containing unused study drug) will be returned to AbbVie (or designee) or destroyed on site. All destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of drug accountability procedures. Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The GLE/PIB combination regimen for 8- and 12-weeks in HCV treatment-naïve subjects without cirrhosis and with compensated cirrhosis respectively, was evaluated in HCV GT1 – 6 infected subjects in the Phase 3 studies discussed in detail in Section 3.0. A high (> 97%) efficacy and positive safety profile was demonstrated in these studies. AbbVie plans to evaluate the same combination regimen at the proposed label durations in a similar HCV GT1 – 6 infected population in Brazil. The study is designed to include subpopulations of HCV-infected patients (e.g., GT1 and GT3; severe renal disorder and HIV/HCV co-infected population) that represents the unmet clinical treatment need in Brazil. The selection of a two arm study design is appropriate so that treatment naïve

GT1 – 6 Brazilian subjects receive the proposed label treatment duration based on their cirrhosis status.

In view of the expected high SVR rate in this study and the established safety profile of GLE/PIB in patients with advanced fibrosis, a control arm would be of limited value for efficacy comparison. In this context, an open-label study is appropriate to adequately describe the efficacy and safety of this regimen administered for the proposed global label recommended durations for treatment naïve subjects.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study. HCV RNA assays are standard and validated. Next generation sequencing (NGS) methods are experimental.

5.6.3 Suitability of Subject Population

This study is intended to enroll HCV treatment-naïve adults in Brazil with chronic HCV genotype 1 – 6 without cirrhosis and with compensated cirrhosis with METAVIR equivalent fibrosis stage F2-F4. Patients with HCV/HIV co-infection and CKD Stages 1 – 5 may participate in the study. The study population includes subpopulations of HCV-infected patients (e.g., GT1 and GT3; severe CKD and HIV/HCV co-infected populations) with high unmet clinical treatment need currently in Brazil.

5.6.4 Selection of Doses in the Study

5.6.4.1 Rationale for Dose Selections

The dose GLE/PIB 300 mg/120 mg 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.

5.6.4.1.1 GLE and PIB Dose and Treatment Duration

GLE/PIB is proposed to be indicated for the treatment of chronic HCV infection in adults. In DAA-treatment naïve adults, the recommended oral dose of GLE/PIB is three 100 mg/40 mg tablets QD with food (total daily dose of 300 mg/120 mg) for 8 weeks in subjects without cirrhosis and for 12 weeks in subjects with compensated cirrhosis based on the ITT SVR_{12} rates in the registrational studies. Only HCV treatment naïve subjects will be enrolled in this study. The efficacy in subjects with CKD4 – 5 did not differ from those without CKD. Similar efficacy result was observed on HCV/HIV co-infected subjects and HCV monoinfected subjects. The recommended durations for all HCV treatment naive patients of all HCV genotypes are summarized in Table 8, and SVR_{12} is summarized by GT in Table 9. These are recommendations for all HCV-infected patients, including those co-infected with HIV and patients with any degree of renal impairment.

A favorable safety profile has been observed in HCV-infected subjects without cirrhosis or with compensated cirrhosis who received the GLE + PIB 300 mg + 120 mg dose combination. No dose response relationship was observed for adverse events, or for treatment-emergent post-nadir alanine aminotransferase elevations.

The maximum dose of GLE/PIB will not exceed 300 mg/120 mg per day for 12 weeks.

Table 8. Recommended GLE/PIB Duration for TN Patients

	Recommended Treatment Duration	
Patient Population	**No Cirrhosis**	**Cirrhosis**
Genotype 1 – 6	8 weeks	12 weeks

GLE = glecaprevir; PIB = pibrentasvir; TN = treatment-naïve

Table 9. Summary of SVR_{12} Rates for TN and TE-PR, SOF/R or PI by Subject Population (Phase 2 and 3 Analysis Set)

	SVR_{12}%										
	GT1		GT2		GT3		GT4 – 6		GT1 – 6		
	No Cirr	Cirr	No Cirr	Cirr	No Cirr	Cirr	No Cirr	Cirr	No Cirr	Cirr	All
TN[a] + TE-P/R, SOF/R or PI[b]	99.0	97.2	98.0	100	95.2	96.6	93.1	100	97.4	97.6	97.5

cirr = cirrhosis; GT = genotype; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; P/R = regimens containing interferon, pegylated interferon, and/or ribavirin; SOF/R = regimens containing sofosbuvir and ribavirin; SVR_{12} = sustained virologic response 12 weeks postdosing; TE = treatment-experienced; TN = treatment-naive

a. Recommended treatment duration for subjects without cirrhosis is 8 weeks and with cirrhosis is 12 weeks.

b. Recommended treatment duration for GT1, 2, 4 – 6 subjects without cirrhosis is 8 weeks and with cirrhosis is 12 weeks. Recommended treatment duration for GT3 subjects is 16 weeks.

Cross reference: AbbVie. R&D16/0146. Summary of Clinical Efficacy for Glecaprevir/Pibrentasvir in HCV. 2016.

6.0 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 after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.7.1. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other" cause of the event. For adverse events to be

considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (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 accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (see Section 6.1.7 regarding toxicity management) and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during the study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been 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 adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) 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.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4).

The table of clinical toxicity grades "National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4" is available from the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf and is to be used in the grading of adverse events. Below are the general grading categories. However, the investigator should always search NCI CTC AE for a given diagnostic/symptomatic AE term to identify and apply specific grading details for that AE entity.

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.

6.1.3 Relationship to Study Drug

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

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

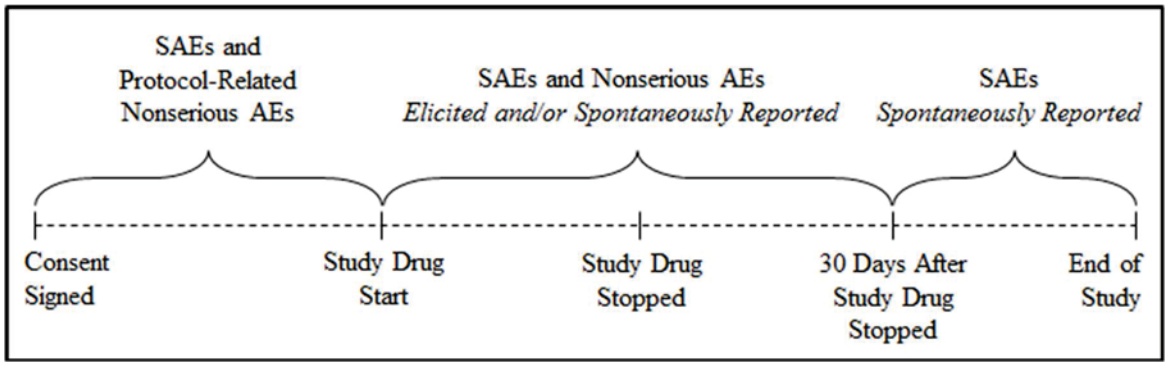
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All serious adverse events as well as protocol-related nonserious adverse events (e.g., infection at liver biopsy site) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days following discontinuation of study treatment has elapsed, all adverse events will be collected, whether solicited or spontaneously reported by the subject. After 30 days following completion of study treatment and throughout the Post-Treatment Period, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected).

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the

electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Antiviral Safety Team at:

Antiviral Safety Team
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Email: [redacted]

For any subject safety concerns, please contact the physician listed below:

Therapeutic Area Medical Director:

[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:
Office: [redacted]
Mobile: [redacted]
eFAX: [redacted]
Email: [redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie

Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: [redacted]

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

6.1.6 Pregnancy

While not an adverse event, pregnancy in a study subject must be reported to AbbVie within 1 working day after the site becomes aware of the pregnancy. If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Information regarding pregnancy in a subject or a subject's partners will be collected for pregnancies occurring from the date of the first dose through 30 days following the last dose of study drug.

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

Please refer to Section 5.4.1 for management of study drug in case of pregnancy.

6.1.7 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the investigator. All adverse events 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 "National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4" is to be used in the grading of adverse events and laboratory abnormalities, which is available on the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Specific toxicity management guidelines apply to the instances of increases in ALT (Section 6.1.7.1).

6.1.7.1 Management of Increases in ALT

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 the hepatic questionnaire.
- Evaluate for an alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain Anti-HAV IgM, Anti-HAV Total, Anti-HBc IgM, Anti-HBc Total, Anti-HBs, HBV DNA, HBsAg, Anti-HEV IgM, Anti-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 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 liver failure.
- At the discretion of the investigator.

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

6.1.8 Collection of Data Regarding Known AIDS-Defining Conditions

HIV infected subjects participating in clinical trials may develop infections typically associated with AIDS. A list of these known AIDS-Defining Conditions (ADC) is presented in Appendix E. The events listed in Appendix E will be summarized as HIV-related events, not as adverse events. These ADCs will be collected from the time of study drug administration until 30 days following discontinuation of study drug.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) 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.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 1 business day of the study site's knowledge of the event via the Product

Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. 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 adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitors:

Primary Contact:

[redacted]
AbbVie
[redacted]
North Chicago, IL 60064
USA

Office: [redacted]

Alternate Contact:

[redacted]
AbbVie
[redacted]
North Chicago, IL 60064
USA

Office: [redacted]
Cell:

Email: [redacted] Email: [redacted]

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

An interim data lock may occur in the study if interim study results are needed for regulatory interaction purposes. No changes to the study design or treatment of subjects would result from this interim analysis; therefore, no adjustment for multiplicity is needed.

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

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

Safety and demographic analyses will be performed on all subjects who receive at least one dose of study drug.

Efficacy analyses will be performed on the intention-to-treat (ITT) population defined as all enrolled subjects who receive at least one dose of study drug, unless otherwise specified.

Sensitivity analyses of the primary efficacy endpoint, when applicable, will be performed on the intention-to-treat population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-VF).

No data will be imputed for any efficacy or safety analysis except for analyses of SVR endpoints (HCV RNA data). HCV RNA values will be selected for the analyses of all SVR endpoints (e.g., SVR_4 and SVR_{12}) based on defined visit windows. A backward imputation method will be used to impute missing responses for SVR analyses.

8.1.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all treated subjects by Arm (A and B), and overall. Demographics include age, weight, height, body mass index (BMI), gender, race, and ethnicity. Baseline characteristics include HCV genotype subtype, CKD stage, baseline HCV RNA level, fibrosis stage (F2, F3, F4), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no), use of stable opiate substitution, history of diabetes, baseline metabolic syndrome, history of bleeding disorders, history of depression or bipolar disorder, history of cardiovascular disease, and HIV coinfection status.

All the demographics and baseline characteristics will be summarized as continuous or categorical variables where appropriate. Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and BMI), and the number and percentage of subjects will be presented for categorical variables (e.g., sex and race).

Treatment compliance to study drug will be calculated based on the percentage of tablets taken relative to the total tablets expected to be taken. A subject is considered to be compliant if the percentage is between 80% and 120%. Compliance will be calculated for each subject and summarized with the mean, median, standard deviation, minimum, and maximum. The percentage of compliant subjects will be summarized.

8.1.2 Efficacy

All efficacy analyses will be performed on the ITT population, unless otherwise specified.

The efficacy analyses will be performed across all treatment durations and genotypes.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. The notation "HCV RNA < LLOQ" is used to represent all HCV RNA values < 15 IU/mL, regardless of whether the HCV RNA is detectable or not. HCV RNA ≥ LLOQ are all quantifiable values.

8.1.2.1 Primary Efficacy Endpoints

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 all genotypes (GT1 – 6 subjects) will be analyzed on combined treatment groups. The primary endpoint will be analyzed based on intention to treat (ITT) population. The number and percentage of subjects achieving SVR_{12} will be summarized with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless the number of SVR_{12} non-responders is less than 5, in which case the Wilson's score method will be used for the confidence interval instead.

A summary of reason for SVR_{12} non-response (e.g., OTVF, relapse, other) will be provided.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The percentage of subjects with HCV OTVF (defined as confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and
- The percentage of subjects with post-treatment HCV virologic relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment; excluding subjects who have been shown to be reinfected)

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 and 77 days or greater for subjects allocated to treatment durations of 8 weeks and 12 weeks, respectively.

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

8.1.2.3 Sensitivity Analysis

As sensitivity analyses, the number and percentage of subjects in the mITT-VF population achieving SVR_{12}, as applicable, will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution and a two-sided 95% confidence interval using the Wilson's score method.

The two-sided 95% confidence interval using Wilson's score method will also be calculated as a sensitivity analysis for the primary endpoint of SVR_{12} based on ITT population.

8.1.2.4 Subgroup Analysis

The subgroup analyses will be performed based on the combined treatment groups. The percentage of subjects with SVR_{12} will be calculated, as will the corresponding two sided 95% Wilson score intervals, for the following subgroups:

- HCV genotype and available subtype
- Sex
- Age
- Race
- Baseline HCV RNA level
- Baseline fibrosis stage
- Baseline cirrhosis status
- Baseline platelet count

- Baseline albumin
- Chronic Kidney Disease Stage
- HIV co-infection
- HIV ART regimen (for HIV coinfected)
- Baseline CD4+ count (for HIV coinfected)

Further details about subgroup analysis will be described in the statistical analysis plan.

8.1.2.5 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized by genotype:

- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of subjects who achieve SVR 4 weeks after the last actual dose of study drug (SVR_4);

The number and percentage of subjects meeting each additional efficacy endpoint will be summarized along with a two-sided 95% confidence interval using the Wilson's score interval.

8.1.3 Patient Reported Outcomes

The handling of missing data for patient reported outcomes (PROs) will be as follows. If a respondent answers at least 50% of the items in a multi-item scale of the SF-36v2, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing. The Mental and Physical Component Summary measures will not be computed if any domain is missing. For TSQM, if a respondent answers at least 2 items in the 3 item scales of Side Effects or Effectiveness, the missing items will be imputed with the average score of the answered items in the same scale. For EQ-5D-3L, health state index and VAS scores no imputation will be performed for missing items.

The mean change from baseline to each applicable post-baseline timepoint in the SF-36v2 Mental Component Summary (SF-36-MCS) and Physical Component Summary (SF-36-PCS) scores; EQ5D-3L health state index and VAS score will be summarized descriptively at each applicable visit and for change from baseline to each applicable visit.

For each of these scores, mean change from Baseline to Final Treatment Visit and from Baseline to Post-Treatment Week 12 will be summarized using an analysis of covariance (ANCOVA) model with baseline score as a covariate.

The following analyses of patient reported outcomes (PROs) also will be performed:

- Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable timepoint of greater than or equal to 3 points in the SF-36 MCS and PCS;
- Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable timepoint of greater than or equal to 5 points in the SF-36 MCS and PCS;
- Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable timepoint of greater than or equal to 5 points in the SF-36 domain scores;

TSQM Effectiveness, Side Effects, Convenience, and Global Satisfaction scores will be summarized descriptively at each applicable visit.

Additional analyses of PROs will be performed as useful and appropriate.

8.1.4 HCV Resistance Analyses

For all subjects with an available sample, full length NS3/4A and NS5A genes from baseline samples will be sequenced by NGS. For subjects who experience virologic failure (OTVF or post-treatment relapse), full length NS3/4A and NS5A genes from the first available sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS. An appropriate subtype specific prototypic reference sequence will be used for comparison with sequences from samples. Subjects treated with study drug

who do not achieve SVR_{12} due to reasons other than virologic failure but have a time point with HCV RNA ≥ 1000 IU/mL after treatment discontinuation, will have the sample at that time point sequenced.

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore, if the HCV RNA level at the time of HCV virologic failure or treatment discontinuation is < 1000 IU/mL, the sample closest in time after HCV virologic failure/treatment discontinuation with an HCV RNA level ≥ 1000 IU/mL will be used.

For each DAA target, signature amino acid positions and a key subset of amino acid positions for the respective inhibitor class are identified. An appropriate subtype-specific prototypic reference sequence will be used for comparison with sequences from each sample.

The following definitions will be used in the resistance analyses:

- Baseline polymorphism: a polymorphism by NGS in a baseline sample (≥ 2% or ≥ 15% prevalence within a subject's viral population depending on polymorphism frequency threshold utilized) that was not present in the appropriate prototypic reference amino acid sequence for a given DAA target (NS3/4A or NS5A).
- Polymorphism/substitution at a signature amino acid position: polymorphism (relative to reference) present in a baseline sample or substitution (relative to baseline) present in a post-baseline sample at a signature amino acid position.
- Post-baseline substitution: an amino acid substitution in a post-baseline time point sample that was not detected at baseline (< 2%) in the subject and is detectable in ≥ 2% of the sequences from the post-baseline sample.
- Enriched polymorphism: polymorphism present in both the baseline and a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post-baseline % – baseline %) ≥ 20].

- Treatment-emergent substitution by NGS: A post-baseline substitution or an enriched polymorphism detected by NGS.

Analysis 1: The following analyses will be provided for all subjects, separated by HCV subtype:

- By-subject listings of all baseline polymorphisms at signature amino acid positions for each DAA target (NS3/4A and NS5A) at detection thresholds of 2% and 15%.
- The number and percentage of subjects with baseline polymorphisms at signature amino acid positions at detection thresholds of 2% and 15%.
- Total number and percentage of subjects with baseline polymorphisms at a key subset of amino acid positions in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A, by subtype, and total (include all subtypes).

Analysis 2: The impact of baseline polymorphisms on treatment outcome will be assessed as follows: for each polymorphism, the SVR_{12} rate will be calculated for subjects with and without the polymorphism and the 2 rates will be compared. Analysis will be grouped by HCV subtype and DAA target (NS3/4A or NS5A).

The following will be included in the analyses of impact of baseline polymorphisms on treatment outcome:

- For each signature amino acid position, presence of any polymorphism at that position (vs no polymorphism at that position), using detection thresholds of both 2% and 15%.
- Each individual polymorphism at each signature amino acid position (vs not that polymorphism) using detection thresholds of 2% and 15%.

Analysis 3: In subjects with or without polymorphisms in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A at the key subset of amino acid positions at 15% detection threshold, the SVR_{12} rate will be calculated, and

the rates with or without polymorphisms will be compared using Fisher's exact test. Analysis will be separated by HCV subtype.

Analysis 4: The following analyses will be performed for subjects who do not achieve SVR_{12} and who have post-baseline resistance data available:

- Listings by subject of all treatment-emergent substitutions relative to the baseline amino acid sequence will be provided for each DAA target (NS3/4A and NS5A).
- Listings by subject and time point of all post-baseline substitutions at signature amino acid position relative to the baseline amino acid sequence will be provided for each DAA target (NS3/4A and NS5A).

HCV Genotype/Subtype

Phylogenetic analysis will be conducted on HCV NS3/4A and/or NS5A sequence from baseline samples from all subjects in order to accurately determine genotype/subtype. If the phylogenetic analysis is not available, then the result from Sanger sequencing of a region of NS5B by AbbVie or by the Central laboratory will be used to determine the subject's HCV genotype/subtype, if available. Finally, if neither the phylogenetic analysis result nor the Sanger sequencing assay results is available, then the Inno-LIPA assay results from the Central laboratory will be used to categorize the subject. This final HCV genotype subtype will be used in efficacy subgroup analyses.

8.1.5 HIV Resistance Analyses

In a subject being evaluated for failure to maintain HIV virologic suppression, if the confirmatory plasma HIV RNA level is ≥ 500 copies/mL, the subject's HIV PR, RT, and/or IN sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assays. The number of subjects who demonstrate HIV genotypic resistance and the genotypic resistance mutations detected in the samples obtained from these subjects will be tabulated and summarized. Resistance will be defined as described by the IAS-USA Panel.[19]

8.1.6 Safety

Safety summaries will be provided overall (i.e., across study drug durations). All subjects who receive at least one dose of study drug will be included in the safety analyses.

8.1.6.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term. The tabulation of the number of subjects with treatment-emergent adverse events by severity grade (Grades 1 – 5) and relationship to each study drug will also be provided. Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe grade for the severity grade table and the most related for the relationship to study drug tables. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC.

Additional analyses will be described in the statistical analysis plan.

8.1.6.2 Clinical Laboratory Data

Clinical laboratory tests will be summarized at each visit. The baseline value will be the last non-missing measurement prior to the initial dose of study drug. Mean changes from baseline to each post-baseline visit, including Final Treatment Visit, will be summarized descriptively. Changes from baseline to maximum post-baseline CTCAE grade of laboratory values will also be summarized.

8.1.6.3 Vital Signs Data

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each post-baseline visit, including Final Treatment Visit, will be summarized descriptively. The number and percentage of subjects with post-baseline

values meeting pre-defined criteria for Potentially Clinically Significant (PCS) vital signs values will be summarized.

8.1.6.4 HCV/HIV Co-Infection

The following additional safety data will be summarized and analyzed for subjects with HCV/HIV co-infection overall:

- The percentage of subjects with plasma HIV RNA suppression at the end of treatment and at Post-Treatment Week 12 using the FDA Snapshot Algorithm;
- The number and percentage of subjects with plasma HIV RNA < 20 copies/mL at each applicable time point;
- Change from baseline in CD4+ T-cell count (absolute and percent) to each applicable post-baseline time point;
- Change from baseline in lymphocytes (count and percentage) and CD8+ T-cell counts (absolute and percent) to each applicable post-baseline time point;
- The listing of subjects with a plasma HIV RNA value ≥ 200 copies/mL at any baseline or post-baseline visit during the study.

The analysis of change from baseline in CD4+ T-cell count (absolute and percent), lymphocytes (count and percentage) and CD8+ T-cell counts (absolute and percent) will report the mean and median values at baseline and at each applicable post-baseline visit, as well as N, mean, median, standard deviation (SD), minimum and maximum values for the change from baseline overall.

8.1.7 Pharmacokinetic and Exposure-Response Analyses

Plasma concentrations of GLE, PIB, and their possible metabolites, if measured, will be tabulated for each subject and group. Summary statistics will be computed for each time and visit.

Plasma concentration data from this study may be combined with data from other studies and analyzed using the following general methodology:

Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (version VII, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. Apparent oral clearance (CL/F) and apparent volume of distribution (V/F) of the PK analytes will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis. Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM.

Relationship between exposure (noncompartmental or population pharmacokinetic model based values of concentrations over time, AUC, C_{trough} or some other appropriate measure of exposure) and clinical observations (antiviral activity or virologic end points, such as SVR_{12} response) may be explored, if appropriate.

Exposure-response relationships for primary and secondary efficacy variables and/or some safety measures of interest may also be explored. Exposure response relationships will utilize a logistic regression analysis and/or a semi-mechanistic viral dynamic model. Additionally, relationship between exposure and safety endpoints of interest may also be explored. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

It is anticipated that a total of approximately 100 HCV infected treatment naïve GT1 – 6 subjects will be enrolled in this study. No formal hypothesis is being tested. If the observed SVR_{12} rate in this study is 97% among 100 HCV GT1 – 6 treatment naive subjects, then the half-width of 2-sided 95% normal approximation interval is 3.3%.

8.3 Randomization Methods

This study is not randomized. Eligible subjects will be allocated to a treatment arm according to their cirrhosis status (presence/absence).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific, and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information, and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain, and archive study essential documents according to ICH GCP and all other applicable regulatory requirements.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on 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 clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. The Investigator Awareness Date (SAE CRF) may serve

as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

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

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

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

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

Any research that may be done using optional exploratory research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from optional exploratory research may be provided to investigators and used in scientific publications or presented at medical conventions. Optional exploratory research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

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

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for GLE/PIB Fixed-Dose Combination.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection

Protocol Date: 02 August 2018

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
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., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
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 investigation and all 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. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Pharmacokinetics
		Clinical
		Clinical
		Clinical
		Statistics
		Bioanalysis
		Clinical

Appendix C. Study Activities – Treatment Period

Activity	Screening	Day 1[a]	Wk 4	Wk 8 (Arm B Only)	EOT (Arm A and Arm B) or Premature D/C from Treatment[b]
Informed Consent[c]	X				
Dispense/Review Study Drug Dosing Card		X (Dispense only)	X	X	X (Review only)
Medical History[d]	X	X			
Physical Exam[e]	X	X			X
Vital Signs, Weight, Height[f]	X	X	X	X	X
ECG	X				
Hematology/Chemistry[g]/Coagulation Panel	X	X	X	X	X
Pregnancy Test (serum [s] urine [u])[h]	X (s)	X (u)	X (u)	X (u)	X (u)
Anti-HCV Ab, Anti-HIV Ab	X				
Hepatitis B Panel	X				
HCV Genotype and Subgenotype	X				
FibroTest or FibroScan® or Liver Biopsy[i]	X				
Concomitant Medication Assessment	X	X	X	X	X
Adverse Event Assessment[k]	X	X	X	X	X
Study Drug Dispensed		X	X	X[k]	
HCV RNA Samples	X	X	X	X	X
Study Drug Accountability and Review of Study Drug Adherence			X	X	X[l]
HCV Resistance Sample		X	X	X	X

Activity	Screening	Day 1[a]	Wk 4	Wk 8 (Arm B Only)	EOT (Arm A and Arm B) or Premature D/C from Treatment[b]
Pharmacokinetic Samples[m]			X	X	X
Child-Pugh Score (cirrhotic subjects only)[n]	X				X
Clinical Assessment of Hepatic Decompensation (cirrhotic subjects only)[n]		X			
HCC Screening Liver ultrasound (cirrhotic subjects only)[n]	X				
Patient Reported Outcomes Instruments (PROs)[o]		X			X
Flow cytometry sample[p]	X	X			X
HIV RNA[p]	X	X	X	X	X

Wk = Week; EOT = End of treatment; D/C = Discontinuation

* The EOT visit can be at Week 8 or 12 in accordance with treatment duration as described in Section 5.1.

a. All procedures to be performed prior to first dose.

b. Subjects who prematurely discontinue during the Treatment Period should return to the site to complete the Premature D/C Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy).

c. Subjects need to sign an IRB/IEC approved informed consent for the study (prior to performing any Screening or study-specific procedures).

d. A complete medical history will be taken at Screening and will be updated at the Study Day 1 Visit.

e. A symptom-directed physical examination may be performed at any other visit, when necessary. Any significant physical examination findings after the first dose will be recorded as adverse events.

f. Height will be measured at the Screening Visit only.

g. Blood samples for serum chemistry tests should be collected following a minimum 8-hour fast prior to study drug intake (with the exception of the Screening Visit, which may be non-fasting).

h. Pregnancy testing is not required for women not of childbearing potential as defined in Section 5.2.4.

i. For subjects who have not had a qualifying liver biopsy within the previous 24 months for subjects without cirrhosis or at any time for subjects with compensated cirrhosis) or a qualifying FibroScan® within the previous 6 months for subjects without cirrhosis or at any time prior to Screening for subjects with compensated cirrhosis).

j. Subjects with a historical negative Liver Ultrasound, CT or MRI (within 3 months prior to screening) are not required to have a screening Liver Ultrasound performed. If additional Liver Ultrasound testing is required it should be completed as an unscheduled visit. A positive ultrasound result suspicious of HCC will be confirmed with CT scan or MRI. A liver ultrasound should be performed at the end of treatment visit if it has been 6 months or more since the historical evaluation.

k. See specific information regarding adverse event collection in Section 6.1.1.1.

l. Dispensation at Week 8 and Study Drug Accountability at Week 12 are only applicable to Arm B. Subjects should bring all study drug to every visit for the site to review adherence. However, the site will record the number of tablets returned only at the Study Drug Accountability Visits at Weeks 4, 8, 12 (if applicable) or Premature D/C.

m. PK samples will be collected at each scheduled study visit. Detail regarding timing of samples is provided in Section 5.3.2.1.

n. Child-Pugh Score, Clinical Assessment of Hepatic Decompensation, and Liver Ultrasound are only performed for subjects in Arm B as described in Section 5.3.1.1.

o. PROs should be administered before any study procedures in the order listed in Section 5.3.1.1. TSQM will be the only PRO not administered at Day 1.

p. For HCV/HIV co-infected subjects.

Appendix D. Study Activities – Post-Treatment (PT) Period

Activity	PT Wk 4	PT Wk 12	PT D/C[a]
Vital Signs and Weight	X	X	X
Hematology/Chemistry/Coagulation Panel	X	X[b]	X[c]
Pregnancy Test (urine)[d]	X (u)		X (u)[c]
Concomitant Medication Assessment[e]	X	X[e]	X[e]
Child-Pugh Score (cirrhotic subjects only)		X	X
Adverse Event Assessment[f]	X[f]	X[g]	X[g]
HCV RNA Samples	X	X	X
HCV Resistance Sample	X	X	X
Patient Reported Outcomes Instruments (PROs)[h]		X	X
Flow cytometry sample[h]	X	X	
HIV RNA[i]	X	X	
HCC Screening: Liver Ultrasound[j]		X	X

Wk = Week; PT D/C = Post-Treatment Discontinuation

a. Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C Visit procedures.

b. Chemistry/Coagulation panel will only be collected at PT Wk 12 for subjects in Arm B (compensated cirrhosis).

c. Hematology/Chemistry/Coagulation Panel and Pregnancy Test are not required at PT Wk 12, but only at PT D/C if subject discontinues prior to PT Wk 4.

d. Women of childbearing potential do not require pregnancy testing beyond PTW4. Pregnancy testing will be performed at PT D/C visit only if the subject discontinues prior to PTW4. Pregnancy testing in PT Period is not required for females of non-childbearing potential as defined in Section 5.2.4.

e. Only medications taken for SAEs and treatment of HCV will be collected after 30 days post-dosing.

f. Nonserious AEs and all SAEs will be collected until 30 days post dosing. All spontaneously reported SAEs will be collected thereafter. See specific information regarding adverse event collection in Section 6.1.4.

g. Only SAEs will be collected thereafter as described in Section 6.1.4.

h. PROs should be administered before any study procedures in the order listed in Section 5.3.1.1.

i. For HCV/HIV co-infected subjects.

j. HCC Screening Liver Ultrasound performed only subjects in Arm B as described in Section 5.3.1.1.

Note: Day 1 of the Post-Treatment Period will be defined as the day after the last dose of study drug.

Appendix E. List of AIDS-Defining Conditions

Collection of data regarding known AIDS-Defining Conditions is covered in Section 6.1.8.

AIDS-Defining Conditions:

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus†
- Cervical cancer, invasive§
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age > 1 month
- Cytomegalovirus retinitis (with loss of vision)†
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (> 1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi sarcoma†
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*,†
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary†

- Mycobacterium tuberculosis of any site, pulmonary,[†,§] disseminated,[†] or extrapulmonary[†]
- Mycobacterium, other species or unidentified species, disseminated[†] or extrapulmonary[†]
- Pneumocystis jirovecii pneumonia[†]
- Pneumonia, recurrent[†,§]
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age > 1 month[†]
- Wasting syndrome attributed to HIV

* Only among children aged < 13 years. (CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43[No. RR-12].)

† Condition that might be diagnosed presumptively.

§ Only among adults and adolescents aged > 13 years. (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41[No. RR-17].)

Cross reference: Morbidity and Mortality Weekly Report (MMWR). AIDS Defining Conditions. 2008. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2 htm.

Appendix F. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Global Protocol Change

"ABT-493/ABT-530" and "ABT-493/ABT-530 (glecapravir/pibrentasvir)" has been changed to read "GLE/PIB" or "GLE/PIB (glecapravir/pibrentasvir)" throughout the protocol.

Specific Protocol Changes

Section 1.0 Title Page
"Sponsor/Emergency Contact:"
Previously read:

Sponsor/Emergency Contact:	[redacted] Infectious Disease Development 1500 Seaport Blvd, Suite 289H Redwood City, CA 94063	Phone: [redacted] Mobile: Fax: Emergency 24 hour Number: [redacted]

Has been changed to read:

Sponsor/Emergency Contact:	[redacted] 1 North Waukegan Road North Chicago, IL 60064	Phone: [redacted] Mobile: eFax: Emergency 24 hour Number: [redacted]

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M16-156
Name of Study Drug: Glecaprevir, Pibrentasvir	**Phase of Development:** 3b
Name of Active Ingredient: Glecaprevir, Pibrentasvir	**Date of Protocol Synopsis:** 08 November 2017
Protocol Title: A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection	
Objectives: • The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving SVR_{12} (HCV RNA < LLOQ 12 weeks following therapy) and safety of GLE/PIB combination in treatment-naïve adults in Brazil with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis. The efficacy endpoints will be analyzed based on combined treatment duration and genotypes and safety analysis will be done by individual treatment groups. • The secondary objectives are to assess efficacy of GLE/PIB by hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis by evaluating the percentages of subjects with HCV on-treatment virologic failure (OTVF) and HCV virologic relapse across treatment durations and genotypes.	
Investigators: Multicenter, single country (Brazil)	
Study Sites: Approximately 14	
Study Population: Chronic HCV GT 1 – 6-infected male and female adults with Metavir equivalent fibrosis stage of F2 – F4, at least 18 years of age, without cirrhosis or with compensated cirrhosis, who are HCV treatment-naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication).	
Number of Subjects to be Enrolled: Approximately 100 subjects	
Methodology: This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of GLE/PIB combination for an 8 or 12-week treatment duration in adults in Brazil with chronic HCV GT1 – 6 infection, without cirrhosis (F2 – F3) or with compensated cirrhosis (F4), who are HCV treatment-naïve. Approximately 100 subjects meeting the eligibility criteria will be enrolled. The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of 35 GT1 and 35 GT3 subjects and 2) approximately 80 F2 – F3 and a maximum of approximately 20 F4 subjects.	

Methodology (Continued):

Approximately 100 eligible subjects will be enrolled into one of the following treatment arms:

- Arm A: HCV GT 1 – 6 without cirrhosis (F2 and F3) subjects will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks.
- Arm B: HCV GT 1 – 6 subjects with compensated cirrhosis (F4) will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 12 weeks.

The study will consist of a Screening Period, Treatment Period and Post Treatment Period:

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

Treatment Period: Eligible subjects will be enrolled to receive GLE/PIB 300 mg/120 mg once daily (QD) for an 8 (Arm A) or 12 (Arm B) week treatment duration based on their cirrhosis status.

Scheduled visits for subjects in the Treatment Period consist of Day 1 and Weeks 4 and 8 for all subjects and an additional Week 12 visit for subjects in Arm B. Study procedures, including assessment of adverse events, vital signs, study medication adherence, concomitant medications, HCV RNA, HCV resistance, and clinical laboratory tests, will be conducted at each visit.

Post-Treatment (PT) Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 12 weeks to monitor safety, HCV RNA levels and the emergence and persistence of resistance-associated substitutions.

During the Post-Treatment Period, all subjects will have visits at PT Weeks 4 and 12, following completion of the Treatment Period. Study procedures to monitor safety, HCV RNA, and the emergence and persistence of resistant viral variants will be conducted during these visits.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject has positive plasma HCV antibody and HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.
2. Subject must be documented as without cirrhosis with METAVIR equivalent fibrosis stage of F2 – F3 or with compensated cirrhosis (F4) based on results of a liver biopsy, or FibroScan, or FibroTest score (as described in Section 5.3.1.1).
3. Subjects who are known to be HCV/HIV co-infected may enroll if they have a positive test result for anti-Human Immunodeficiency Virus antibody at Screening and are:

   Naïve to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study), or

   On a stable, qualifying HIV ART regimen for at least 8 weeks prior to Baseline.

   Subjects on stable HIV ART must have Plasma HIVRNA below 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once during the 12 months prior to Screening (by an approved plasma HIVRNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTi*m*e HIV-1 assay).
4. Subjects requiring dialysis should have been receiving dialysis for at least 1 month prior to enrollment, and may be on hemodialysis or peritoneal dialysis.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

5. Subjects With Compensated Cirrhosis Only: Absence of hepatocellular carcinoma (HCC) 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. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.

Main Exclusion:

1. Female subject who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Current HBV infection on screening tests, defined as:
   - A positive HBsAg, or;
   - HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti-HBs)
3. History of severe, life-threatening, or other significant sensitivity to any excipients of the study drug.
4. Any current or past clinical evidence of Child-Pugh B or C classification or clinical history, including on Day 1 prior to dose, of liver decompensation including hepatic encephalopathy or variceal bleeding, radiographic evidence of small ascites, or empiric use of lactulose/rifaximin. Prophylactic use of beta blockers is not exclusionary (see Section 5.3.1.1).
5. Laboratory parameters exclusions:
   - ALT > 10 × ULN; AST > 10 × ULN
   - Total Bilirubin > 3.0 mg/dL
   - Albumin < LLN (without cirrhosis); < 2.8 mg/dL (with compensated cirrhosis)
   - Platelets < 90,000 10^3/μL (without cirrhosis); < 60,000 10^3/μL (with compensated cirrhosis)
6. Receipt of any investigational or commercially available anti-HCV agents examples include, but are not limited to: interferon, pegylated interferon, ribavirin, sofosbuvir, telaprevir, boceprevir, simeprevir, asunaprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, voxilaprevir, velpatasvir or dasabuvir.

Investigational Products:	Glecaprevir/Pibrentasvir 100 mg/40 mg Film-coated tablet
Doses:	Glecaprevir/Pibrentasvir 300 mg/120 mg QD (3 tablets)
Mode of Administration:	Oral with food.
Reference Therapy:	N/A
Doses:	N/A
Mode of Administration:	N/A

Duration of Treatment: Subjects without cirrhosis will receive GLE/PIB for 8 weeks, while subjects with compensated cirrhosis will receive GLE/PIB for 12 weeks.

Criteria for Evaluation:

Efficacy:

Plasma HCV RNA (IU/mL) will be assessed at each Treatment and Post-Treatment Visit.

Criteria for Evaluation (Continued):

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests, and vital signs.

Patient Reported Outcomes (PROs):

The Short Form 36 Version 2 Health Status Survey (SF-36v2) will be used to assess the functional health and well-being of subjects. The Treatment Satisfaction Questionnaire (TSQM) will be used to assess treatment satisfaction with the GLE/PIB combined regime. EuroQol-5 Dimensions-3 Level (EQ-5D-3L) is a health state utility instrument that evaluates preference for health status (utility); subjects also rate their perception of their overall health on a separate visual analogue scale (VAS).

Resistance:

The following information will be tabulated and summarized: 1) for all subjects with available samples, baseline polymorphisms at signature resistance-associated amino acid positions relative to the appropriate prototypic reference sequences; and 2) for subjects who do not achieve SVR_{12}, post-baseline substitutions relative to the corresponding baseline sequence in available samples.

Pharmacokinetic:

Individual plasma concentrations of GLE, PIB, and their possible metabolites will be tabulated and summarized.

Statistical Methods:

Efficacy:

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 all genotypes (GT1 – 6 subjects) and treatment groups. The primary endpoint will be analyzed based on intention to treat (ITT) population. The number and percentage of subjects achieving SVR_{12} will be summarized with a two-sided 95% confidence interval based on the normal approximation of the binomial distribution unless the number of SVR_{12} non-responders is less than 5, in which case the Wilson's score method will be used to calculate the confidence interval.

The secondary efficacy endpoints are:

- The percentage of subjects with OTVF.
- The percentage of subjects with post-treatment HCV virologic relapse.

Subgroup analysis based on the treatment arm (i.e., without cirrhosis/with compensated cirrhosis) will be performed. For the secondary efficacy endpoints and subgroup analysis, the two-sided 95% confidence interval will be calculated using Wilson's score method.

PROs:

Change from baseline to each applicable visit in the patient reported outcome summary measures for SF-36 and EQ-5D-3L will be summarized. Summary measures at each applicable visit will be summarized for the TSQM.

Statistical Methods (Continued):

Safety:

Safety summaries will be provided by the treatment arm (i.e., cirrhosis status/study drug duration) and overall. All subjects who receive at least one dose of study drug will be included in the safety analyses. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by MedDRA System Organ Class (SOC) and preferred term. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by grade and relationship to study drug.

Resistance:

For all subjects receiving study drug, baseline polymorphisms at signature resistance-associated amino acid positions identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the baseline sequences, 2) the amino acid substitutions in available post baseline samples at signature resistance-associated positions identified by NGS, and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral substitutions by NGS.

Pharmacokinetic:

Individual plasma concentrations of GLE, PIB, and their possible metabolites will be tabulated and summarized. Pharmacokinetic data from this study may be combined with data from other studies for the population pharmacokinetic analyses using a non-linear mixed-effect modeling approach with the NONMEM software. Relationships between exposure and clinical observations (antiviral activity) may be explored.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M16-156
Name of Study Drug: Glecaprevir, Pibrentasvir	**Phase of Development:** 3b
Name of Active Ingredient: Glecaprevir, Pibrentasvir	**Date of Protocol Synopsis:** 02 August 2018
Protocol Title: A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection	

Objectives:

- The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving SVR_{12} (HCV RNA < LLOQ 12 weeks following therapy) and safety of GLE/PIB combination in treatment-naïve adults in Brazil with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis. The efficacy and safety endpoints will be analyzed on the overall population (i.e., across treatment durations and genotypes).
- The secondary objectives are to assess efficacy of GLE/PIB by hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis by evaluating the percentages of subjects with HCV on-treatment virologic failure (OTVF) and HCV virologic relapse across treatment durations and genotypes.

Investigators: Multicenter, single country (Brazil)

Study Sites: Approximately 14

Study Population: Chronic HCV GT 1 – 6-infected male and female adults with Metavir equivalent fibrosis stage of F2 – F4, at least 18 years of age, without cirrhosis or with compensated cirrhosis, who are HCV treatment-naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication).

Number of Subjects to be Enrolled: Approximately 100 subjects

Methodology:

This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of GLE/PIB combination for an 8 or 12-week treatment duration in adults in Brazil with chronic HCV GT1 – 6 infection, without cirrhosis (F2 – F3) or with compensated cirrhosis (F4), who are HCV treatment-naïve. Approximately 100 subjects meeting the eligibility criteria will be enrolled. The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of 35 GT1 and approximately 25 GT3 subjects and 2) approximately 80 F2 – F3 and a maximum of approximately 20 F4 subjects.

Methodology (Continued):

Approximately 100 eligible subjects will be enrolled into one of the following treatment arms:

- Arm A: HCV GT 1 – 6 without cirrhosis (F2 and F3) subjects will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks.
- Arm B: HCV GT 1 – 6 subjects with compensated cirrhosis (F4) will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 12 weeks.

The study will consist of a Screening Period, Treatment Period and Post Treatment Period:

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

Treatment Period: Eligible subjects will be enrolled to receive GLE/PIB 300 mg/120 mg once daily (QD) for an 8 (Arm A) or 12 (Arm B) week treatment duration based on their cirrhosis status.

Scheduled visits for subjects in the Treatment Period consist of Day 1 and Weeks 4 and 8 for all subjects and an additional Week 12 visit for subjects in Arm B. Study procedures, including assessment of adverse events, vital signs, study medication adherence, concomitant medications, HCV RNA, HCV resistance, and clinical laboratory tests, will be conducted at each visit.

Post-Treatment (PT) Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 12 weeks to monitor safety, HCV RNA levels and the emergence and persistence of resistance-associated substitutions.

During the Post-Treatment Period, all subjects will have visits at PT Weeks 4 and 12, following completion of the Treatment Period. Study procedures to monitor safety, HCV RNA, and the emergence and persistence of resistant viral variants will be conducted during these visits.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject has positive plasma HCV antibody and HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.
2. Subject must be documented as without cirrhosis (METAVIR equivalent fibrosis stage of F2 – F3), or with compensated cirrhosis (METAVIR equivalent fibrosis stage of F4 with a Child-Pugh score ≤ 6). See Section 5.3.1.1 for Liver Diagnostic Testing and Child-Pugh score and Category.
3. Subjects who are known to be HCV/HIV co-infected may enroll if they have a positive test result for anti-Human Immunodeficiency Virus antibody at Screening and are:

   Naïve to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study), or

   On a stable, qualifying HIV ART regimen for at least 8 weeks prior to Baseline.

   Subjects on stable HIV ART must have Plasma HIVRNA below 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once during the 12 months prior to Screening (by an approved plasma HIVRNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTi*m*e HIV-1 assay).
4. Subjects requiring dialysis should have been receiving dialysis for at least 1 month prior to enrollment, and may be on hemodialysis or peritoneal dialysis.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

5. Subjects With Compensated Cirrhosis Only: Absence of hepatocellular carcinoma (HCC) 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. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.

Main Exclusion:

1. Female subject who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Current HBV infection on screening tests, defined as:
   - A positive HBsAg, or;
   - HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., with negative HBsAg and Anti-HBs)
3. History of severe, life-threatening, or other significant sensitivity to any excipients of the study drug.
4. Any current or past clinical evidence of Child-Pugh B or C classification (score of > 6) or any current or past clinical history of liver decompensation including ascites on physical exam, hepatic encephalopathy or variceal bleeding. Prophylactic use of beta blockers is not exclusionary (see Section 5.3.1.1).
5. Laboratory parameters exclusions:
   - ALT > 10 × ULN; AST > 10 × ULN
   - Total Bilirubin > 3.0 mg/dL
   - Albumin < LLN (without cirrhosis); < 2.8 mg/dL (with compensated cirrhosis)
   - Platelets < 90,000 10^3/μL (without cirrhosis); < 60,000 10^3/μL (with compensated cirrhosis)
6. Receipt of any investigational or commercially available anti-HCV agents including, but not limited to: interferon, pegylated interferon, ribavirin, sofosbuvir, telaprevir, boceprevir, simeprevir, asunaprevir, veruprevir, glecaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, voxilaprevir, velpatasvir, pibrentasvir, or dasabuvir.

Investigational Products:	Glecaprevir/Pibrentasvir 100 mg/40 mg Film-coated tablet
Doses:	Glecaprevir/Pibrentasvir 300 mg/120 mg QD (3 tablets)
Mode of Administration:	Oral with food.
Reference Therapy:	N/A
Doses:	N/A
Mode of Administration:	N/A

Duration of Treatment: Subjects without cirrhosis will receive GLE/PIB for 8 weeks, while subjects with compensated cirrhosis will receive GLE/PIB for 12 weeks.

Criteria for Evaluation:

Efficacy:

Plasma HCV RNA (IU/mL) will be assessed at each Treatment and Post-Treatment Visit.

Criteria for Evaluation (Continued):

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests, and vital signs.

Patient Reported Outcomes (PROs):

The Short Form 36 Version 2 Health Status Survey (SF-36v2) will be used to assess the functional health and well-being of subjects. The Treatment Satisfaction Questionnaire (TSQM) will be used to assess treatment satisfaction with the GLE/PIB combined regime. EuroQol-5 Dimensions-3 Level (EQ-5D-3L) is a health state utility instrument that evaluates preference for health status (utility); subjects also rate their perception of their overall health on a separate visual analogue scale (VAS).

Resistance:

The following information will be tabulated and summarized: 1) for all subjects with available samples, baseline polymorphisms at signature resistance-associated amino acid positions relative to the appropriate prototypic reference sequences; and 2) for subjects who do not achieve SVR_{12}, post-baseline substitutions relative to the corresponding baseline sequence in available samples.

Pharmacokinetic:

Individual plasma concentrations of GLE, PIB, and their possible metabolites will be tabulated and summarized.

Statistical Methods:

Efficacy:

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 all genotypes (GT1 – 6 subjects) and treatment groups. The primary endpoint will be analyzed based on intention to treat (ITT) population. The number and percentage of subjects achieving SVR_{12} will be summarized with a two-sided 95% confidence interval based on the normal approximation of the binomial distribution unless the number of SVR_{12} non-responders is less than 5, in which case the Wilson's score method will be used to calculate the confidence interval.

The secondary efficacy endpoints are:

- The percentage of subjects with OTVF.
- The percentage of subjects with post-treatment HCV virologic relapse.

Subgroup analysis based on the treatment arm (i.e., without cirrhosis/with compensated cirrhosis) will be performed. For the secondary efficacy endpoints and subgroup analysis, the two-sided 95% confidence interval will be calculated using Wilson's score method.

PROs:

Change from baseline to each applicable visit in the patient reported outcome summary measures for SF-36 and EQ-5D-3L will be summarized. Summary measures at each applicable visit will be summarized for the TSQM.

Statistical Methods (Continued):

Safety:

Safety summaries will be provided overall. All subjects who receive at least one dose of study drug will be included in the safety analyses. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by MedDRA System Organ Class (SOC) and preferred term. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by grade and relationship to study drug.

Resistance:

For all subjects receiving study drug, baseline polymorphisms at signature resistance-associated amino acid positions identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the baseline sequences, 2) the amino acid substitutions in available post baseline samples at signature resistance-associated positions identified by NGS, and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral substitutions by NGS.

Pharmacokinetic:

Individual plasma concentrations of GLE, PIB, and their possible metabolites will be tabulated and summarized.

Section 3.0 Introduction
First paragraph, last sentence previously read:

Genotypes 4 to 6 are rarely reported (0.3%) in the country.[6]

Has been changed to read:

Genotypes 4 to 6 are rarely reported (0.3%) in Brazil.[6]

Section 3.0 Introduction
Third paragraph, first sentence previously read:

At the time of initiation of this study, therapy for HCV had improved considerably with the approval of several interferon (IFN)-free direct-acting antiviral agent (DAA) regimens (ledipasvir [LDV]/sofosbuvir [SOF], SOF plus simeprevir [SMV], SOF plus daclatasvir [DCV], ombitasvir [OBV]/paritaprevir [PTV]/ritonavir [r] ± dasabuvir [DSV], elbasvir [EBR]/grazoprevir [GZR], and SOF/velpatasvir [VEL]).[10,11]

Has been changed to read:

At the time of initiation of this study, therapy for HCV had improved considerably with the approval of several interferon (IFN)-free direct-acting antiviral agent (DAA) regimens (ledipasvir [LDV]/sofosbuvir [SOF], SOF plus simeprevir [SMV], SOF plus daclatasvir [DCV], ombitasvir [OBV]/veruprevir/ritonavir [r] ± dasabuvir [DSV], elbasvir [EBR]/grazoprevir [GZR], and SOF/velpatasvir [VEL]).[10,11]

Section 3.0 Introduction
Fourth paragraph, second sentence previously read:

Additional limitations of several current regimens include the requirement of ribavirin (RBV) for certain populations, significant drug to drug interactions, limited options for subjects with renal insufficiency, reduced efficacy in patients with baseline amino acid polymorphisms associated with reduced susceptibility to the HCV nonstructural 5A (NS5A) inhibitors (NS5AI) or NS3/4A protease inhibitors (PI), and limited options for patients who have failed regimens containing an NS5AI and/or PI.

Has been changed to read:

Additional limitations of several current regimens include the requirement of ribavirin (RBV) for certain populations, significant drug to drug interactions, limited options for subjects with renal insufficiency, reduced efficacy in patients with baseline amino acid polymorphisms associated with reduced susceptibility to the HCV nonstructural 5A (NS5A) inhibitors or NS3/4A protease inhibitors (PI), and limited options for patients who have failed regimens containing an NS5A inhibitor and/or PI.

Section 3.0 Introduction
Fifth paragraph, first sentence previously read:

AbbVie has developed two "next generation" DAAs, glecaprevir (GLE, formerly known as ABT-493), an HCV NS3/4A PI, and pibrentasvir (PIB, formerly known as ABT-530), an NS5AI, for use in combination for the treatment of HCV. GLE and PIB each has potent in vitro antiviral activity against genotypes 1 through 6[13] and a high genetic barrier

to resistance, with no or little loss of potency against common resistant-associated substitutions.

Has been changed to read:

AbbVie has developed two "next generation" DAAs, glecaprevir (GLE, formerly known as ABT-493), an HCV NS3/4A PI, and pibrentasvir (PIB, formerly known as ABT-530), an NS5A inhibitor, for use in combination for the treatment of HCV. GLE and PIB each has potent in vitro antiviral activity against genotypes 1 through 6[13] and a high genetic barrier to resistance, with no or little loss of potency against common resistant-associated substitutions.

Section 3.2 Benefits and Risks
First paragraph, first sentence previously read:

Benefits of treatment with GLE/PIB include: potent and pangenotypic antiviral activity in vitro, higher genetic barrier to development of drug resistance across genotypes compared to first generation DAA protease and NS5A inhibitors, no need for RBV, 8 or 12 weeks of treatment for NS5AI and PI naive, and the convenience of a once daily regimen.

Has been changed to read:

Benefits of treatment with GLE/PIB include: potent and pangenotypic antiviral activity in vitro, higher genetic barrier to development of drug resistance across genotypes compared to first generation DAA protease and NS5A inhibitors, no need for RBV, 8 or 12 weeks of treatment for NS5A inhibitor and PI naive, and the convenience of a once daily regimen.

Section 4.1 Primary Objectives
Last sentence previously read:

The efficacy endpoints will be analyzed based on combined treatment duration and genotypes and safety analysis will be done by individual treatment groups.

Has been changed to read:

The efficacy and safety endpoints will be analyzed on the overall population (i.e., across treatment durations and genotypes).

Section 5.1 Overall Study Design and Plan: Description
First paragraph, last sentence previously read:

The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of approximately 35 GT1 and 35 GT3 subjects and 2) approximately 80 F2 – 3 and a maximum of approximately 20 F4 subjects.

Has been changed to read:

The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of 35 GT1 and approximately 25 GT3 subjects and 2) approximately 80 F2 – 3 and a maximum of approximately 20 F4 subjects.

Figure 1. Study Design
Table note "*" previously read:

The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of approximately 35 GT1 and 35 GT3 subjects and 2) approximately 80 F2 – F3 and a maximum of approximately 20 F4 subjects.

Has been changed to read:

The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of approximately 35 GT1 and 25 GT3 subjects and 2) approximately 80 F2 – F3 and a maximum of approximately 20 F4 subjects.

Section 5.2 Selection of Study Population
Second sentence previously read:

Subjects with HIV/HCV co-infection and subjects at all CKD stages (CKD Stages 1 – 5) are allowed to participate.

Has been changed to read:

Subjects with HIV/HCV co-infection and subjects at all CKD stages (CKD Stages 1 – 5) are allowed to participate.[17]

Section 5.2.1 Inclusion Criteria
Criterion 2, last bullet previously read:

A WOCBP practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 through at least 30 days after the last dose of study drug.

Has been changed to read:

A WOCBP practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.

Section 5.2.1 Inclusion Criteria
Criterion 3, last paragraph previously read:

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing.

Has been changed to read:

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing.

Section 5.2.1 Inclusion Criteria
Criterion 7 previously read:

Subject must be documented as without cirrhosis with METAVIR equivalent fibrosis stage of F2 – 3 or with compensated cirrhosis (F4) based on results of a liver biopsy, or FibroScan, or FibroTest score (as described in Section 5.3.1.1).

Has been changed to read:

Subject must be documented as without cirrhosis (METAVIR equivalent fibrosis stage of F2 – 3), or with compensated cirrhosis (METAVIR equivalent fibrosis stage of F4 with a Child-Pugh score of ≤ 6). See Section 5.3.1.1 for Liver Diagnostic Testing and Child-Pugh Score and Category.

Section 5.2.2 Exclusion Criteria
Criterion 2, last bullet previously read:

HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti-HBs)

Has been changed to read:

HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., with negative HBsAg and Anti-HBs)

Section 5.2.2 Exclusion Criteria
Criterion 6, first sentence previously read:

Any current or past clinical evidence of Child-Pugh B or C classification (score of > 6) or clinical history of liver decompensation including ascites on physical exam, including hepatic encephalopathy or variceal bleeding.

Has been changed to read:

Any current or past clinical evidence of Child-Pugh B or C classification (score of > 6) or any current or past clinical history of liver decompensation including ascites on physical exam, hepatic encephalopathy or variceal bleeding.

Section 5.2.2 Exclusion Criteria
Criterion 8
Delete: last sentence

This only applies to subjects with CKD Stage 4 or 5.

Section 5.2.2 Exclusion Criteria
Criterion 10 previously read:

Receipt of any investigational or commercially available anti-HCV agents examples include, but are not limited to: interferon, pegylated interferon ribavirin, sofosbuvir, telaprevir, boceprevir, simeprevir, asunaprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, voxilaprevir, velpatasvir or dasabuvir.

Has been changed to read:

Receipt of any investigational or commercially available anti-HCV agents, including, but not limited to: interferon, pegylated interferon ribavirin, sofosbuvir, telaprevir, boceprevir, simeprevir, asunaprevir, veruprevir, glecaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, voxilaprevir, velpatasvir, pibrentasvir, or dasabuvir.

Section 5.2.3.4 Prohibited Therapy
First paragraph, second sentence previously read:

For subjects in the study in countries where GLE/PIB has received marketing authorization, any medications in the local label that are contraindicated to be administered with GLE/PIB are also considered to be prohibited medications.

Has been changed to read:

Since GLE/PIB has received marketing authorization in Brazil, any medications in the local label that are contraindicated to be administered with GLE/PIB are also considered to be prohibited medications.

Section 5.3.1.1 Study Procedures
Subsection <u>Clinical Laboratory Tests</u>
Last bullet previously read:

Samples will be sent to the following addresses:

Has been changed to read:

Samples will be sent to the following address:

Section 5.3.1.1 Study Procedures
Subsection Pregnancy Testing
Last bullet previously read:

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in the inclusion criteria) at Screening do not require pregnancy testing.

Has been changed to read:

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in inclusion criterion #2) at Screening do not require pregnancy testing.

Section 5.3.1.1 Study Procedures
Subsection Hepatitis B, Hepatitis C Virus and HIV Screen
First sentence previously read:

HBsAg, anti-HBc and anti-HBs, anti-HCV Ab and anti-HIV Ab will be performed at Screening.

Has been changed to read:

HBsAg, anti-HBc and anti-HBs, anti-HCV Ab and anti-HIV Ab testing will be performed at Screening. HBV DNA testing may be performed to exclude occult HBV infection.

Section 5.3.1.1 Study Procedures
Subsection Liver Diagnostic Testing
First paragraph previously read:

Subjects will be considered to be without cirrhosis or with compensated cirrhosis based on the definitions below:

Has been changed to read:

Subjects will be considered to be without cirrhosis or with cirrhosis based on the definitions below:

Section 5.3.1.1 Study Procedures
Subsection Liver Diagnostic Testing
Heading "With Compensated Cirrhosis (F4)"
Heading previously read:

With Compensated Cirrhosis (F4)

Has been changed to read:

With Cirrhosis (F4)

Section 5.3.1.1 Study Procedures
Subsection Liver Diagnostic Testing
Subheading "With Compensated Cirrhosis (F4)"
Add: new last paragraph

Subjects with cirrhosis will be defined as having compensated cirrhosis if the Child-Pugh Score at screening is ≤ 6.

Section 5.3.1.1 Study Procedures
Subsection Child-Pugh Score and Category
First sentence previously read:

Subjects with compensated cirrhosis will have Child-Pugh scores assessed, except those who are on ongoing use of anticoagulants.

Has been changed to read:

All subjects with cirrhosis will have Child-Pugh scores assessed at screening.

Table 6. Child-Pugh Classification of Severity of Cirrhosis
Table note "*" previously read:

Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.

Has been changed to read:

None: normal consciousness, personality, neurological examination, electroencephalogram.

Section 5.3.1.1 Study Procedures
Subsection Clinical Assessment of Hepatic Decompensation
Previously read:

A clinical assessment of hepatic encephalopathy and ascites will be performed at Study Day 1 prior to dosing to confirm the subject has not progressed to hepatic decompensation since Screening for all subjects who have compensated cirrhosis. Grading system guidelines for ascites are listed above in Table 6. Subjects who present symptoms and signs of hepatic decompensation including assessment at Day 1 prior to receiving study drug, will not be enrolled into the trial.

Has been changed to read:

A clinical assessment of hepatic encephalopathy and ascites, as defined in Exclusion Criterion #6, will be performed at Study Day 1 prior to dosing to confirm the subject has not progressed to hepatic decompensation since Screening for all subjects who have compensated cirrhosis. Subjects who present symptoms and signs of hepatic decompensation, including assessment at Day 1 prior to receiving study drug, will neither be dosed nor enrolled into the trial.

Section 5.3.1.1 Study Procedures
Subsection Flow Cytometry, HIV RNA and HIV Resistance Testing Samples
Delete: last sentence

HIV treatment failure is defined as detectable HIV RNA after 6 months of highly active antiretroviral therapy (HAART) or HIV RNA detectable after a period of undetectable measurement following use of HAART.

Section 5.3.2.4 Measurement Methods
First sentence previously read:

Plasma concentrations of GLE and PIB will be determined using a validated assay methods in the Drug Analysis Department at AbbVie.

Has been changed to read:

Plasma concentrations of GLE and PIB will be determined using validated assay methods in the Drug Analysis Department at AbbVie.

Section 5.3.3.1 Primary Variable
Previously read:

The primary efficacy variable is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

Has been changed to read:

The primary efficacy variable is the percentage of subjects who achieve SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

Section 5.3.3.3 HCV Resistance Variables
Last paragraph previously read:

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA ≥ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the baseline sequence, 2) the amino acid substitutions in available post-baseline samples at signature resistance associated positions identified by NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of resistance-associated substitutions by NGS.

Has been changed to read:

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA ≥ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples at signature resistance-associated positions identified by NGS and comparison to the baseline sequence, 2) the amino acid substitutions in available post-baseline samples at signature resistance-associated positions identified by NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of resistance-associated substitutions by NGS.

Section 6.1.5 Adverse Event Reporting
"Primary Therapeutic Area Medical Director:" previously read:

Primary Therapeutic Area Medical Director:

[redacted]
Infectious Disease Development
1500 Seaport Blvd, Suite 289H
Redwood City, CA 94063

Telephone Contact Information:
Office:
Mobile:
Email:

Has been changed to read:

Therapeutic Area Medical Director:

[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:
Office: [redacted]
Mobile:
eFAX:
Email:

Section 6.1.6 Pregnancy
Previously read:

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming 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 5.4.1). If a subject is discontinued, the subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

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 end of treatment.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

Has been changed to read:

While not an adverse event, pregnancy in a study subject must be reported to AbbVie within 1 working day after the site becomes aware of the pregnancy. If a pregnancy

occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Information regarding pregnancy in a subject or a subject's partners will be collected for pregnancies occurring from the date of the first dose through 30 days following the last dose of study drug.

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

Please refer to Section 5.4.1 for management of study drug in case of pregnancy.

Section 8.1 Statistical and Analytical Plans
First paragraph, last sentence previously read:

No changes to the study design or treatment of subjects would result from this interim analysis, so adjustment for multiplicity is needed.

Has been changed to read:

No changes to the study design or treatment of subjects would result from this interim analysis; therefore, no adjustment for multiplicity is needed.

Section 8.1.1 Demographics and Baseline Characteristics
First paragraph, last sentence previously read:

Baseline characteristics include HCV genotype subtype, CKD stage, baseline HCV RNA level, fibrosis stage (F2, F3, F4), tobacco (user, ex user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no), use of stable opiate substitution, history of diabetes, baseline metabolic syndrome, history of bleeding disorders, history of

depression or bipolar disorder, history of cardiovascular disease, geographic region, and HIV coinfection status.

Has been changed to read:

Baseline characteristics include HCV genotype subtype, CKD stage, baseline HCV RNA level, fibrosis stage (F2, F3, F4), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no), use of stable opiate substitution, history of diabetes, baseline metabolic syndrome, history of bleeding disorders, history of depression or bipolar disorder, history of cardiovascular disease, and HIV coinfection status.

Section 8.1.2.1 Primary Efficacy Endpoints
First paragraph, first sentence previously read:

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) within all genotypes (GT1 – 6 subjects) will be analyzed on combined treatment groups.

Has been changed to read:

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 all genotypes (GT1 – 6 subjects) will be analyzed on combined treatment groups.

Section 8.1.2.2 Secondary Efficacy Endpoints
Second paragraph previously read:

For the analysis of post-treatment HCV virologic relapse, completion of treatment is defined as any subject with study drug duration of 52 days and 77 days or greater for subjects allocated to treatment durations of 8 weeks and 12 weeks, respectively.

Has been changed to read:

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 and 77 days or greater for subjects allocated to treatment durations of 8 weeks and 12 weeks, respectively.

Section 8.1.2.5 Additional Efficacy Endpoints
Last bullet previously read:

The percentage of subjects who achieve SVR_4 4 weeks after the last actual dose of study drug (SVR_4);

Has been changed to read:

The percentage of subjects who achieve SVR 4 weeks after the last actual dose of study drug (SVR_4);

Section 8.1.4 HCV Resistance Analyses
First paragraph, first sentence previously read:

For all subjects with an available sample, full length NS3/4A or NS5A from baseline samples will be sequenced by NGS.

Has been changed to read:

For all subjects with an available sample, full length NS3/4A and NS5A genes from baseline samples will be sequenced by NGS.

Section 8.1.4 HCV Resistance Analyses
Add: new third paragraph

For each DAA target, signature amino acid positions and a key subset of amino acid positions for the respective inhibitor class are identified. An appropriate subtype-specific prototypic reference sequence will be used for comparison with sequences from each sample.

Section 8.1.4 HCV Resistance Analyses
Fourth paragraph and bullet list previously read:

Analysis 1: The following analyses will be provided for all subjects, separated by HCV subtype:

- A listing of all baseline polymorphisms (2% detection threshold) at signature resistance-associated amino acid positions for each DAA target (NS3/4A and NS5A).
- A listing of all baseline polymorphisms (15% detection threshold) at non-signature resistance-associated amino acid positions for each DAA target (NS3/4A and NS5A) for subjects who experience virologic failure.
- The number and percentage of subjects with baseline polymorphisms at signature amino acid positions at detection thresholds of 2% and 15%.

Has been changed to read:

Analysis 1: The following analyses will be provided for all subjects, separated by HCV subtype:

- By-subject listings of all baseline polymorphisms at signature amino acid positions for each DAA target (NS3/4A and NS5A) at detection thresholds of 2% and 15%.
- The number and percentage of subjects with baseline polymorphisms at signature amino acid positions at detection thresholds of 2% and 15%.
- Total number and percentage of subjects with baseline polymorphisms at a key subset of amino acid positions in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A, by subtype, and total (include all subtypes).

Section 8.1.4 HCV Resistance Analyses
Sixth paragraph
Delete: last bullet

Polymorphisms at each non-signature amino acid position at a detection threshold of 15%.

Section 8.1.4 HCV Resistance Analyses
Add: new seventh paragraph

Analysis 3: In subjects with or without polymorphisms in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A at the key subset of amino acid positions at 15% detection threshold, the SVR_{12} rate will be calculated, and the rates with or without polymorphisms will be compared using Fisher's exact test. Analysis will be separated by HCV subtype.

Section 8.1.4 HCV Resistance Analyses
Seventh paragraph previously read:

Analysis 3: The following analyses will be performed for subjects who do not achieve SVR_{12} and who have post-baseline resistance data available:

Has been changed to read:

Analysis 4: The following analyses will be performed for subjects who do not achieve SVR_{12} and who have post-baseline resistance data available:

Section 8.1.5 HIV Resistance Analyses
First sentence previously read:

If a subject develops a confirmed, plasma HIV RNA level ≥ 500 copies/mL after starting the study, the subject's HIV PR, RT, and/or IN sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assays.

Has been changed to read:

In a subject being evaluated for failure to maintain HIV virologic suppression, if the confirmatory plasma HIV RNA level is ≥ 500 copies/mL, the subject's HIV PR, RT, and/or IN sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assays.

Section 8.1.6 Safety
First sentence previously read:

Safety summaries will be provided by the treatment arm (i.e., study drug duration assigned by cirrhosis status) and overall.

Has been changed to read:

Safety summaries will be provided overall (i.e., across study drug durations).

Section 8.1.6.4 HCV/HIV Co-Infection
First paragraph previously read:

The following additional safety data will be summarized and analyzed for subjects with HCV/HIV co-infection overall and in each treatment arm:

Has been changed to read:

The following additional safety data will be summarized and analyzed for subjects with HCV/HIV co-infection overall:

Section 8.1.6.4 HCV/HIV Co-Infection
Last paragraph previously read:

The analysis of change from baseline in CD4+ T-cell count (absolute and percent), lymphocytes (count and percentage) and CD8+ T-cell counts (absolute and percent) will report the mean and median values at baseline and at each applicable post-baseline visit, as well as N, mean, median, standard deviation (SD), minimum and maximum values for the change from baseline overall and within each treatment arm.

Has been changed to read:

The analysis of change from baseline in CD4+ T-cell count (absolute and percent), lymphocytes (count and percentage) and CD8+ T-cell counts (absolute and percent) will report the mean and median values at baseline and at each applicable post-baseline visit,

as well as N, mean, median, standard deviation (SD), minimum and maximum values for the change from baseline overall.

Section 15.0 Reference List
Add: new Reference 17

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Kidney Int. 2017;7 (Suppl):1-59.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Pharmacokinetics
		Clinical
		Clinical
		Clinical
		Statistics
		Bioanalysis
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]		Pharmacokinetics
		Clinical
		Clinical
		Clinical
		Statistics
		Bioanalysis
		Clinical

Appendix C. Study Activities – Treatment Period
Activity "Child-Pugh Score (subjects with compensated cirrhosis only)[n]," "Clinical Assessment of Hepatic Decompensation (subjects with compensated cirrhosis only)[n]," and "HCC Screening Liver ultrasound (subjects with compensated cirrhosis only)[n]," previously read:

Child-Pugh Score (subjects with compensated cirrhosis only)[n]

Clinical Assessment of Hepatic Decompensation (subjects with compensated cirrhosis only)[n]

HCC Screening Liver ultrasound (subjects with compensated cirrhosis only)[n]

Has been changed to read:

Child-Pugh Score (cirrhotic subjects only)[n]

Clinical Assessment of Hepatic Decompensation (cirrhotic subjects only)[n]

HCC Screening Liver ultrasound (cirrhotic subjects only)[n]

Appendix C. Study Activities – Treatment Period
Table note "n." previously read:

Child-Pugh Score, Clinical Assessment of Hepatic Decompensation, and Liver Ultrasound are only performed for subjects in Arm B (compensated cirrhotic) as described in Section 5.3.1.1.

Has been changed to read:

Child-Pugh Score, Clinical Assessment of Hepatic Decompensation, and Liver Ultrasound are only performed for subjects in Arm B as described in Section 5.3.1.1.

Appendix D. Study Activities – Post-Treatment (PT) Period
Activity "Child-Pugh Score (subjects with compensated cirrhosis only)" previously read:

Child-Pugh Score (subjects with compensated cirrhosis only)

Has been changed to read:

Child-Pugh Score (cirrhotic subjects only)

Appendix D. Study Activities – Post-Treatment (PT) Period
Table note "j." previously read:

HCC Screening Liver Ultrasound performed only subjects in Arm B (compensated cirrhosis) as described in Section 5.3.1.1.

Has been changed to read:

HCC Screening Liver Ultrasound performed only subjects in Arm B as described in Section 5.3.1.1.

Document Approval

Study M16156 - A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection - Amendment 2 - 02Aug2018

Version: 1.0 **Date:** 08-Aug-2018 07:04:57 AM **Company ID:** 08082018-00F9F683CD7884-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	02-Aug-2018 08:46:36 PM	Approver
	02-Aug-2018 08:56:27 PM	Approver
	03-Aug-2018 02:33:26 PM	Approver
	06-Aug-2018 02:10:35 P	Approver
	06-Aug-2018 07:26:05 PM	Approver
	07-Aug-2018 03:48:54 PM	Approver
	08-Aug-2018 07:04:57 A	Author

1.0 Title Page

Clinical Study Protocol M16-156

A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection

Incorporating Amendment 1

AbbVie Investigational Product:	Glecaprevir/Pibrentasvir
Date:	08 November 2017
Development Phase:	3b
Study Design:	This is an open-label, multicenter study
Investigators:	Multicenter Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc. (AbbVie)*
Sponsor/Emergency Contact:	[redacted] Infectious Disease Development 1500 Seaport Blvd, [redacted] Redwood City, CA 94063 Phone: Mobile: Fax: [redacted] Emergency 24 hour Number: [redacted]

* 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.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	17 February 2017

The purpose of this amendment is to:

- Update Section 1.0, Title Page

  Rationale: *A 24-hour emergency number was added in the event emergency calls need to be re-directed to a designated back-up AbbVie Therapeutic Area Medical Director (TA MD). Language was updated, per the latest protocol template.*
- Update Synopsis, Study Sites to 14

  Rationale: *Increased the number of sites per recommendation from Regulatory Authority.*
- Update Section 1.3, List of Abbreviations and Definition of Terms, Section 5.2.2, Exclusion Criteria, Section 6.1.8, Collection of Data Regarding Known AIDS-Defining Conditions, and Appendix E, List of AIDS-Defining Conditions

  Rationale: *Updated the abbreviation for AIDS-Defining Conditions throughout the protocol and the list of AIDS-Defining Conditions.*
- Update Section 5.2.1, Inclusion Criteria, Section 5.3.1.1, Study Procedures, and Appendix C, Study Activities – Treatment Period

  Rationale: *To remove the serum pregnancy test at Study Day 1 so that only a urine pregnancy test is required.*
- Update Section 5.2.2, Exclusion Criteria, and Appendix C, Study Activities – Treatment Period

  Rationale: *Exclusion Criterion 6 was updated to remove the calculation of Child-Pugh Score at Day 1 since only assessment of liver decompensation will be done prior to dose.*

- Update Section 5.2.3.4, Prohibited Therapy, Table 4, Prohibited Medications and Supplements

  Rationale: *To allow the investigator to reintroduce the medications prohibited by the protocol 14 or more days following the last dose of study drug instead of 30 days or more based on the half-lives of glecaprevir and pibrentasvir. Guidance for investigators for prohibited medications or supplements administered with ABT-493/ABT-530 was also provided. One additional prohibited medication was added to Table 4. Updated the table's footnote text to specify the discontinuation period for HMG-CoA reductase inhibitors prior to the first dose of study drug. Added progestogen in the section to be consistent with the language in the AbbVie protocol template.*

- Update Section 5.3.1.1, Study Procedures, Hepatocellular Carcinoma Screening: Liver Ultrasound, Appendix C, Study Activities – Treatment Period, and Appendix D, Study Activities – Post-Treatment (PT) Period

  Rationale: *The HCC Screening Liver Ultrasound at the last Post-Treatment Study Visit was added to ascertain the subject did not develop HCC during the course of the trial.*

- Update Section 1.2, Synopsis, Section 5.3.1.1, Study Procedures, Patient Reported Outcomes (PRO) Instruments (Questionnaires), Appendix C, Study Activities – Treatment Period

  Rationale: *Removed the administration of the Treatment Satisfaction Questionnaire from the Day 1 study visit.*

- Update Section 6.1.7.1, Management of Increases in ALT

  Rationale: *Updated the section by deleting anti-hepatitis A virus immunoglobulin test and replacing it with anti-hepatitis A virus total test as a result of an error in the original list of tests.*

- Update Section 7.0, Protocol Deviations

  Rationale: *Updated contact information*

- Update Section 8.1.1, Demographics and Baseline Characteristics

  Rationale: *To remove one of the baseline characteristics from the summary of subjects as it was not applicable for this study.*

- Update Synopsis and Section 8.1.2.1, Primary Efficacy Endpoints

  Rationale: *For high SVR_{12} rates, that are nonetheless less than 100%, the normal approximation to binomial distribution does not provide good coverage. Thus, the Wilson score test will be used for calculating the 95% confidence interval in the primary efficacy analysis, rather than using the normal approximation to the binomial distribution, if the number of SVR_{12} non-responders is less than 5; otherwise, the normal approximation to the binomial distribution will be used.*

- Update Synopsis and Section 8.1.3, Patient Reported Outcomes

  Rationale: *To remove mean change from baseline calculation for TSQM Effectiveness, Side Effects, Convenience, and Global Satisfaction scores. The Treatment Satisfaction Questionnaire (TSQM) is to measure the satisfaction of a treatment. At Day 1 prior to dosing, the subject has not received any study medication.*

- Update Synopsis and Section 8.1.2.5, Additional Efficacy Endpoints

  Rationale: *To remove the endpoint of the percentage of subjects with relapse after SVR_{12} as this information will not be collected.*

- Update Section 6.2.2, Reporting, Section 9.1, Independent Ethics Committee (IEC) or Institutional Review Board (IRB), Section 10.1, Source Documents, and Section 13.0, Completion of the Study.

  Rationale: *Language was updated, per the latest AbbVie protocol template.*

- Update Appendix B, List of Protocol Signatories

  Rationale: *Updated to reflect changes in signatories.*

- Update Appendix D, Study Activities – Post-Treatment (PT) Period

  Rationale: *Updated collection of chemistry/coagulation panel during PT WK12 visit for subjects with compensated cirrhosis.*

- Minor clerical updates/typographical correction made throughout the protocol.

  Rationale: *Revised text to correct typographical errors, improve consistency and readability throughout the protocol.*

An itemized list of all changes made to this protocol under this amendment can be found in Appendix F.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-156
Name of Study Drug: Glecaprevir, Pibrentasvir	**Phase of Development:** 3b
Name of Active Ingredient: Glecaprevir, Pibrentasvir	**Date of Protocol Synopsis:** 08 November 2017
Protocol Title: A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection	
Objectives: • The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving SVR_{12} (HCV RNA < LLOQ 12 weeks following therapy) and safety of GLE/PIB combination in treatment-naïve adults in Brazil with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis. The efficacy endpoints will be analyzed based on combined treatment duration and genotypes and safety analysis will be done by individual treatment groups. • The secondary objectives are to assess efficacy of GLE/PIB by hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis by evaluating the percentages of subjects with HCV on-treatment virologic failure (OTVF) and HCV virologic relapse across treatment durations and genotypes.	
Investigators: Multicenter, single country (Brazil)	
Study Sites: Approximately 14	
Study Population: Chronic HCV GT 1 – 6-infected male and female adults with Metavir equivalent fibrosis stage of F2 – F4, at least 18 years of age, without cirrhosis or with compensated cirrhosis, who are HCV treatment-naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication).	
Number of Subjects to be Enrolled: Approximately 100 subjects	
Methodology: This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of GLE/PIB combination for an 8 or 12-week treatment duration in adults in Brazil with chronic HCV GT1 – 6 infection, without cirrhosis (F2 – F3) or with compensated cirrhosis (F4), who are HCV treatment-naïve. Approximately 100 subjects meeting the eligibility criteria will be enrolled. The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of 35 GT1 and 35 GT3 subjects and 2) approximately 80 F2 – F3 and a maximum of approximately 20 F4 subjects.	

Methodology (Continued):

Approximately 100 eligible subjects will be enrolled into one of the following treatment arms:

- Arm A: HCV GT 1 – 6 without cirrhosis (F2 and F3) subjects will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks.
- Arm B: HCV GT 1 – 6 subjects with compensated cirrhosis (F4) will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 12 weeks.

The study will consist of a Screening Period, Treatment Period and Post Treatment Period:

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

Treatment Period: Eligible subjects will be enrolled to receive GLE/PIB 300 mg/120 mg once daily (QD) for an 8 (Arm A) or 12 (Arm B) week treatment duration based on their cirrhosis status.

Scheduled visits for subjects in the Treatment Period consist of Day 1 and Weeks 4 and 8 for all subjects and an additional Week 12 visit for subjects in Arm B. Study procedures, including assessment of adverse events, vital signs, study medication adherence, concomitant medications, HCV RNA, HCV resistance, and clinical laboratory tests, will be conducted at each visit.

Post-Treatment (PT) Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 12 weeks to monitor safety, HCV RNA levels and the emergence and persistence of resistance-associated substitutions.

During the Post-Treatment Period, all subjects will have visits at PT Weeks 4 and 12, following completion of the Treatment Period. Study procedures to monitor safety, HCV RNA, and the emergence and persistence of resistant viral variants will be conducted during these visits.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject has positive plasma HCV antibody and HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.
2. Subject must be documented as without cirrhosis with METAVIR equivalent fibrosis stage of F2 – F3 or with compensated cirrhosis (F4) based on results of a liver biopsy, or FibroScan, or FibroTest score (as described in Section 5.3.1.1).
3. Subjects who are known to be HCV/HIV co-infected may enroll if they have a positive test result for anti-Human Immunodeficiency Virus antibody at Screening and are:

   Naïve to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study), or

   On a stable, qualifying HIV ART regimen for at least 8 weeks prior to Baseline.

   Subjects on stable HIV ART must have Plasma HIVRNA below 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once during the 12 months prior to Screening (by an approved plasma HIVRNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTi*m*e HIV-1 assay).
4. Subjects requiring dialysis should have been receiving dialysis for at least 1 month prior to enrollment, and may be on hemodialysis or peritoneal dialysis.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

5. Subjects With Compensated Cirrhosis Only: Absence of hepatocellular carcinoma (HCC) 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. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.

Main Exclusion:

1. Female subject who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Current HBV infection on screening tests, defined as:
   - A positive HBsAg, or;
   - HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti-HBs)
3. History of severe, life-threatening, or other significant sensitivity to any excipients of the study drug.
4. Any current or past clinical evidence of Child-Pugh B or C classification or clinical history, including on Day 1 prior to dose, of liver decompensation including hepatic encephalopathy or variceal bleeding, radiographic evidence of small ascites, or empiric use of lactulose/rifaximin. Prophylactic use of beta blockers is not exclusionary (see Section 5.3.1.1).
5. Laboratory parameters exclusions:
   - ALT > 10 × ULN; AST > 10 × ULN
   - Total Bilirubin > 3.0 mg/dL
   - Albumin < LLN (without cirrhosis); < 2.8 mg/dL (with compensated cirrhosis)
   - Platelets < 90,000 10^3/μL (without cirrhosis); < 60,000 10^3/μL (with compensated cirrhosis)
6. Receipt of any investigational or commercially available anti-HCV agents examples include, but are not limited to: interferon, pegylated interferon, ribavirin, sofosbuvir, telaprevir, boceprevir, simeprevir, asunaprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, voxilaprevir, velpatasvir or dasabuvir.

Investigational Products:	Glecaprevir/Pibrentasvir 100 mg/40 mg Film-coated tablet
Doses:	Glecaprevir/Pibrentasvir 300 mg/120 mg QD (3 tablets)
Mode of Administration:	Oral with food.
Reference Therapy:	N/A
Doses:	N/A
Mode of Administration:	N/A

Duration of Treatment: Subjects without cirrhosis will receive GLE/PIB for 8 weeks, while subjects with compensated cirrhosis will receive GLE/PIB for 12 weeks.

Criteria for Evaluation:

Efficacy:

Plasma HCV RNA (IU/mL) will be assessed at each Treatment and Post-Treatment Visit.

Criteria for Evaluation (Continued):

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests, and vital signs.

Patient Reported Outcomes (PROs):

The Short Form 36 Version 2 Health Status Survey (SF-36v2) will be used to assess the functional health and well-being of subjects. The Treatment Satisfaction Questionnaire (TSQM) will be used to assess treatment satisfaction with the GLE/PIB combined regime. EuroQol-5 Dimensions-3 Level (EQ-5D-3L) is a health state utility instrument that evaluates preference for health status (utility); subjects also rate their perception of their overall health on a separate visual analogue scale (VAS).

Resistance:

The following information will be tabulated and summarized: 1) for all subjects with available samples, baseline polymorphisms at signature resistance-associated amino acid positions relative to the appropriate prototypic reference sequences; and 2) for subjects who do not achieve SVR_{12}, post-baseline substitutions relative to the corresponding baseline sequence in available samples.

Pharmacokinetic:

Individual plasma concentrations of GLE, PIB, and their possible metabolites will be tabulated and summarized.

Statistical Methods:

Efficacy:

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 all genotypes (GT1 – 6 subjects) and treatment groups. The primary endpoint will be analyzed based on intention to treat (ITT) population. The number and percentage of subjects achieving SVR_{12} will be summarized with a two-sided 95% confidence interval based on the normal approximation of the binomial distribution unless the number of SVR_{12} non-responders is less than 5, in which case the Wilson's score method will be used to calculate the confidence interval.

The secondary efficacy endpoints are:

- The percentage of subjects with OTVF.
- The percentage of subjects with post-treatment HCV virologic relapse.

Subgroup analysis based on the treatment arm (i.e., without cirrhosis/with compensated cirrhosis) will be performed. For the secondary efficacy endpoints and subgroup analysis, the two-sided 95% confidence interval will be calculated using Wilson's score method.

PROs:

Change from baseline to each applicable visit in the patient reported outcome summary measures for SF-36 and EQ-5D-3L will be summarized. Summary measures at each applicable visit will be summarized for the TSQM.

Statistical Methods (Continued):

Safety:

Safety summaries will be provided by the treatment arm (i.e., cirrhosis status/study drug duration) and overall. All subjects who receive at least one dose of study drug will be included in the safety analyses. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by MedDRA System Organ Class (SOC) and preferred term. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by grade and relationship to study drug.

Resistance:

For all subjects receiving study drug, baseline polymorphisms at signature resistance-associated amino acid positions identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the baseline sequences, 2) the amino acid substitutions in available post baseline samples at signature resistance-associated positions identified by NGS, and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral substitutions by NGS.

Pharmacokinetic:

Individual plasma concentrations of GLE, PIB, and their possible metabolites will be tabulated and summarized. Pharmacokinetic data from this study may be combined with data from other studies for the population pharmacokinetic analyses using a non-linear mixed-effect modeling approach with the NONMEM software. Relationships between exposure and clinical observations (antiviral activity) may be explored.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADC	AIDS-Defining Conditions
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Anti-HBc	Anti-Hepatitis B core antibody
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ART	Antiretroviral therapy
AUC	Area under the plasma concentration-time curve
BMI	Body mass index
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
CL/F	Apparent oral plasma clearance
CR/CL	Creatinine clearance
CRF	Case report form
CT	Computed tomography
C_{trough}	Pre-dose trough plasma concentration
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EQ-5D-3L	EuroQol-5 Dimensions-3 Level
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GT	Genotype
HBsAg	Hepatitis B surface antigen
HAART	Highly active antiretroviral therapy

HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention To Treat
IU	International units
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NGS	Next generation sequence
NONMEM	Non-linear mixed-effect modeling
NS5A	Nonstructural viral protein 5A
OTVF	On-treatment virologic failure
PegIFN	Pegylated-interferon alfa-2a or alfa-2b
PegIFN/RBV	Combination of pegylated-interferon alfa-2a or alfa-2b and ribavirin
PI	Protease Inhibitor
PK	Pharmacokinetic
POR	Proof of receipt
P/R	pegIFN/RBV
PRO	Patient reported outcome
PT	Post-Treatment

QD	Once daily
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Standard Deviation
SF-36v2	Short Form 36 – Version 2 Health Survey
SOC	System Organ Class/Standard of Care
SOF	Sofosbuvir
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
SVR_4	Sustained virologic response 4 weeks post dosing
SVR_{12}	Sustained virologic response 12 weeks post dosing
TE	Treatment Experienced
TN	Treatment-naïve
TSQM	Treatment Satisfaction Questionnaire-Medicine
ULN	Upper limit of normal
VAS	Visual Analog Scale
V/F	Apparent Volume of distribution
WBC	White blood cells
WOCBP	Women of child bearing potential

Definition of Terms

Study Drug	glecaprevir/pibrentasvir
Study Day 1	First day of study drug dosing
Treatment Period	Day 1 through last dose of study drug
Post-Treatment Period	Day after the last dose of study drug through Post-Treatment Week 12 or Post-Treatment Discontinuation

2.0 Table of Contents

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3.0 Introduction

Hepatitis C virus (HCV) infection is a global health problem, with over 184 million individuals infected worldwide.[1] There are 7 identified HCV genotypes, with genotype 1 (GT1) being the most prevalent worldwide. HCV genotypes 2 (GT2) and 3 (GT3) infections are more common in Latin America (5% to 30%), Europe (20% to 40%) and Asia (30% to 45%).[2-4] HCV GT4 is commonly found in parts of Africa and the Middle East, particularly in Egypt, GT5 is primarily found in South Africa, and GT6 is primarily found in south-east Asia, and GT7 has recently been described in Central Africa.[5] Genotype 1 (GT1) is the most frequent in all regions in Brazil (65%), followed by genotype 3 (30%) and GT2 (5%). Genotypes 4 to 6 are rarely reported (0.3%) in the country.[6]

Depending on various risk factors, between 10% and 40% of all patients with chronic HCV infection will develop cirrhosis. Death related to the complications of cirrhosis may occur at an incidence of approximately 4% per year; hepatocellular carcinoma (HCC) occurs in this population at an estimated incidence of 1% to 5% per year. Patients diagnosed with hepatocellular carcinoma have a 33% probability of death during the first year.[7] Successful treatment of HCV has been shown to significantly reduce the risk of disease progression and related mortality as well as the development of hepatocellular carcinoma.[8,9]

At the time of initiation of this study, therapy for HCV had improved considerably with the approval of several interferon (IFN)-free direct-acting antiviral agent (DAA) regimens (ledipasvir [LDV]/sofosbuvir [SOF], SOF plus simeprevir [SMV], SOF plus daclatasvir [DCV], ombitasvir [OBV]/paritaprevir [PTV]/ritonavir [r] ± dasabuvir [DSV], elbasvir [EBR]/grazoprevir [GZR], and SOF/velpatasvir [VEL]).[10,11] In Brazil, the National HCV Program provides specific regimens to a subset of subjects with confirmed HCV and specific GT infection. The mono HCV infected subjects must have confirmed Metavir F3 and F4 fibrosis stage, and the HCV/HIV co-infected should be treated regardless of liver fibrosis staging. A treatment guideline recommends SOF + DCV or SOF + SMV for

GT1; SOF + RBV for GT2; SOF + pegIFN or SOF + DCV for GT3; and SOF + pegIFN + RBV or SOF + DCV for GT4. Duration of treatment is based on history of monoinfection with HCV, or co-infection with HIV, GT subtype and fibrosis staging. These regimens are available across the country and prescribed free of charge within the country's universal health care system.

However, these approved and recommended regimens are not equally potent across all HCV genotypes and subpopulations. Additional limitations of several current regimens include the requirement of ribavirin (RBV) for certain populations, significant drug to drug interactions, limited options for subjects with renal insufficiency, reduced efficacy in patients with baseline amino acid polymorphisms associated with reduced susceptibility to the HCV nonstructural 5A (NS5A) inhibitors (NS5AI) or NS3/4A protease inhibitors (PI), and limited options for patients who have failed regimens containing an NS5AI and/or PI. Efficacy in GT3-infected patients, particularly those who are treatment-experienced (TE) and/or cirrhotic, is also substantially lower than what is observed for other genotypes.[12]

AbbVie has developed two "next generation" DAAs, glecaprevir (GLE, formerly known as ABT-493), an HCV NS3/4A PI, and pibrentasvir (PIB, formerly known as ABT-530), an NS5AI, for use in combination for the treatment of HCV. GLE and PIB each has potent in vitro antiviral activity against genotypes 1 through 6[13] and a high genetic barrier to resistance, with no or little loss of potency against common resistant-associated substitutions. Additive or synergistic in vitro anti-HCV activity has been demonstrated with the combination of GLE and PIB. GLE 100 mg and PIB 40 mg are co-formulated into a fixed-dose combination tablet (hereafter referred to as GLE/PIB), which provides patients with a convenient once-daily (QD), fixed-dose combination treatment regimen of three tablets QD to maximize treatment compliance.

A detailed discussion of the preclinical pharmacology and toxicology, in vitro virology and metabolism, and clinical data can be found in the Investigator's Brochure.[14]

GLE/PIB

Overview of GLE/PIB Registrational Program and Supportive Phase 2 Studies

The GLE/PIB registrational program included a broad subject population including subjects with compensated liver disease and subjects with severe renal insufficiency across GT1 – 6 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 (TN) and TE subjects to any combination of pegylated IFN (pegIFN), RBV, SOF, NS5A inhibitors, or PIs were allowed in the program. In addition, the program included subjects with human immunodeficiency virus (HIV) coinfection (Study M13-590), subjects with chronic kidney disease [CKD] 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 (Table 1).

Table 1. Overview of Clinical Studies by Subject Population

Genotype	Clinical Study	Summary of Study Design
TN and TE Subjects Without Cirrhosis		
GT1	M13-590	GLE/PIB 300 mg/120 mg QD for 8 (n = 351) or 12 weeks (n = 352)
	M14-867	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 34)
GT2	M15-464	GLE/PIB 300 mg/120 mg QD (n = 202) or placebo (n = 100) for 12 weeks
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 199) or 12 weeks (n = 25)
GT3	M13-594	GLE/PIB 300 mg/120 mg QD for 8 (n = 157) or 12 weeks (n = 233) or SOF 400 mg + DCV 60 mg QD for 12 weeks (n = 115) (all subjects in study were TN)
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 29; TN only), 12 weeks (n = 76), or 16 weeks (n = 22; TE only)
GT4, 5, 6	M13-583	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 121)
	M14-867	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 32)
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 58)
TN and TE Subjects with Cirrhosis		
GT1, 2, 4, 5, 6	M14-172	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 146)
GT3	M14-868	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 64; TN only) or 16 weeks (n = 51; TE only)
Subjects with CKD Stages 4 – 5 With or Without Cirrhosis		
GT1 – 6	M15-462	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 104)
NS5A Inhibitor and/or PI-Experienced Subjects With or Without Cirrhosis		
GT1, 4	M15-410	GLE/PIB 300 mg/120 mg QD for 12 (n = 66) or 16 weeks (n = 47)

CKD = chronic kidney disease; DCV = daclatasvir; GLE = glecaprevir; GT = genotype; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; PIB = pibrentasvir; QD = once daily; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naïve

Efficacy

In treatment-naïve (TN) or IFN, pegIFN, RBV, and/or SOF treatment experienced (TE-PRS) subjects, the pooled overall SVR_{12} rates with GLE/PIB were > 97% across GT1, 2, 4, 5 and 6 regardless of treatment experience, treatment duration, including any degree of renal impairment, presence of compensated cirrhosis, or HIV coinfection (Table 2).

Among subjects with GT3 infection, the pooled SVR_{12} rates across durations were 95.2% among all subjects, 96.6% among cirrhotic subjects, and 100% among subjects with CKD Stages 4 – 5. The SVR_{12} rates among subjects previously treated with a PI and/or NS5A inhibitor were ≥ 89.0% for GT1 and GT4.

Table 2. SVR_{12} Rates by Treatment Experience and HCV Genotype – GT1 – 6 (ITT Population, Phase 2 and 3 Analysis Set)

Genotype	TN n/N (%) 95% CI[a]	TE-PRS n/N (%) 95% CI[a]	TN + TE-PRS			TE-NS5A and/or PIs n/N (%) 95% CI[a]	Overall n/N (%) 95% CI[a]
			All[a]	Cirrhotic n/N (%) 95% CI[b]	CKD 4 – 5 n/N (%) 95% CI[b]		
Phase 2 and 3 Analysis Set	1604/1640 (**97.8**) 97.1, 98.5	602/616 (**97.7**) 96.6, 98.9	2206/2256 (**97.8**) 97.2, 98.4	274/281 (**97.5**) 95.7, 99.3	102/104 (**98.1**) 95.4, 100.0	101/113 (**89.4**) 83.7, 95.1	2307/2369 (**97.4**) 96.7, 98.0
GT1	555/561 (**98.9**) 98.1, 99.8	326/328 (**99.4**) 98.5, 100.0	881/889 (**99.1**) 98.5, 99.7	98/101 (**97.0**) 93.7, 100.0	53/55 (**96.4**) 91.4, 100.0	97/109 (**89.0**) 83.1, 94.9	978/998[c] (**98.0**) 97.1, 98.8
GT2	365/369 (**98.9**) 97.9, 100.0	95/97 (**97.9**) 95.1, 100.0	460/466 (**98.7**) 97.7, 99.7	35/35 (**100**) 100.0, 100.0	16/16 (**100**) 100.0, 100.0	N/A	460/466 (**98.7**) 97.7, 99.7
GT3	499/521 (**95.8**) 94.0, 97.5	113/122 (**92.6**) 88.0, 97.3	612/643 (**95.2**) 93.5, 96.8	112/116 (**96.6**) 93.2, 99.9	11/11 (**100**) 100.0, 100.0	N/A	612/643 (**95.2**) 93.5, 96.8
GT4	119/122 (**97.5**) 94.8, 100.0	55/56 (**98.2**) 94.7, 100.0	174/178 (**97.8**) 95.6, 99.9	20/20 (**100**) 100.0, 100.0	20/20 (**100**) 100.0, 100.0	4/4 (**100**) 100.0, 100.0	178/182 (**97.8**) 95.7, 99.9
GT5	26/26 (**100**) 100.0, 100.0	6/6 (**100**) 100.0, 100.0	32/32 (**100**) 100.0, 100.0	2/2 (**100**) 100.0, 100.0	1/1 (**100**) 100.0, 100.0	N/A	32/32 (**100**) 100.0, 100.0
GT6	40/41 (**97.6**) 92.8, 100.0	7/7 (**100**) 100.0, 100.0	47/48 (**97.9**) 93.8, 100.0	7/7 (**100**) 100.0, 100.0	1/1 (**100**) 100.0, 100.0	N/A	47/48 (**97.9**) 93.8, 100.0

CI = confidence interval; CKD = chronic kidney disease; GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat; N/A = not applicable; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SVR_{12} = sustained virologic response 12 weeks postdosing; TE = treatment-experienced; TN = treatment-naïve; TE-NS5A and/or PI = TE with NS5A inhibitor and/or PI

a. CI was calculated using a stratum-weighted proportion and variance.

b. CI was calculated using the normal approximation to the binomial distribution.

c. Eleven subjects were classified by the central laboratory and treated as GT2 but included here as GT1 due to being identified as such by phylogenetic analysis; all 11 subjects achieved SVR_{12}.

Cross reference: Summary of Clinical Efficacy R&D/16/0146: Table 1.2__2.2

Impact of Baseline Polymorphisms on Treatment Outcome

The association between baseline polymorphisms in NS3 and NS5A and treatment outcome in subjects who received GLE 300 mg QD with PIB 120 mg QD in the registrational or supportive Phase 2 studies was evaluated by conducting an integrated analysis of baseline sequence data. Next-generation sequencing (NGS) was conducted on all baseline samples, data was analyzed at the 15% detection threshold, and baseline polymorphisms at amino acid positions 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A were examined for impact on SVR_{12}.

In subjects who were TN or TE-PRS, baseline polymorphisms in NS3 were detected in 1.1% (9/845), 0.8% (3/398), 1.6% (10/613), 1.2% (2/164), 41.9% (13/31), and 2.9% (1/34) of subjects with HCV genotype 1, 2, 3, 4, 5 and 6 infection, respectively. Baseline polymorphisms in NS5A were detected in 26.8% (225/841), 79.8% (331/415), 22.1% (136/615), 49.7% (80/161), 12.9% (4/31), and 54.1% (20/37) of subjects with HCV genotype 1, 2, 3, 4, 5, and 6 infection, respectively.

The presence of baseline polymorphisms in NS3 and/or NS5A did not have an impact on SVR_{12} rates for GT1-, 2-, 4-, 5-, or 6-infected subjects.

Within GT3-infected subjects, baseline polymorphisms in NS3 did not have an impact on treatment outcome. The NS5A polymorphisms at positions 24, 28, 31, 58, 92, or 93 (including Y93H) did not have an impact on treatment outcome, whereas the A30K polymorphism was associated with a slightly decreased SVR_{12} rate. Given the low prevalence of A30K (6.3%; 39/615) and that the majority of subjects with A30K achieved SVR_{12}, its impact on overall SVR is expected to be minimal.

Amino Acid Substitutions in Subjects Experiencing Virologic Failure

Among TN and TE-PRS subjects without cirrhosis or with compensated cirrhosis treated for 8, 12, or 16 weeks, 23 subjects experienced virologic failure (2 with GT1, 2 with GT2, and 19 with GT3). A GT3-infected subject experiencing virologic failure was determined to have been reinfected with GT3a virus distinct from the one present at baseline.

Therefore, baseline polymorphisms and treatment-emergent substitutions were analyzed for 22 subjects experiencing virologic failure.

Among the 2 GT1-infected subjects, 1 had treatment-emergent substitutions A156V in NS3 and Q30R/L31M/H58D in NS5A, and 1 had treatment-emergent Q30R/H58D (while Y93N was present at baseline and post-treatment) in NS5A.

Among the 2 GT2-infected subjects, no treatment-emergent substitutions were observed in NS3 or NS5A; the prevalent M31 polymorphism in NS5A was present at baseline and post-treatment in both subjects.

Among the 18 GT3-infected subjects, the majority of subjects had treatment-emergent substitutions at the time of failure in NS3 (61.1%, 11/18) and NS5A (88.9%, 16/18). Treatment emergent NS3 substitutions Y56H/N, Q80K/R, A156G, and Q168L/R were observed in 11 subjects, and A166S or Q168R was present at both baseline and post-treatment in 5 subjects. Treatment-emergent NS5A substitutions M28G, A30G/K, L31F, P58T, or Y93H were observed in 16 subjects, and 13 subjects had A30K (n = 9) or Y93H (n = 5) at both baseline and post-treatment.

Integrated Safety Results

A summary of treatment-emergent adverse events (AEs) from pooled analyses of the registrational studies and supportive Phase 2 studies are presented in Table 3. Given the severity of the underlying renal disease and its associated comorbidities in patients with CKD Stages 4 and 5, the frequency and severity of the AEs in subjects enrolled Study M15-462 were expected to be higher than in subjects enrolled in the other registrational studies. Therefore, the summary of adverse events reported in Table 3 does not include the results of Study M15-462.

As shown in Table 3, AEs occurring with a frequency > 5% are headache, fatigue, nausea and diarrhea. The majority of subjects experienced an AE, which were mostly considered to be mild in severity by the investigator (Grade 1). Rates of AEs that were serious, led to premature study drug discontinuation or had a severity Grade ≥ 3 were low. Including

data from Study M15-462, there were 7 deaths, none of which were related to study drug, and the majority occurred several months after the last dose of study drug.

Table 3. Adverse Events Reported for ≥ 5.0% of Subjects (Phase 2 and 3 Analysis Set)

	Phase 2 and 3 Analysis Set[a] (N = 2,265) n (%)	
	All Adverse Events	DAA-Related Adverse Events[b]
Any AE	1,529 (67.5)	929 (41.0)
An AE Grade ≥ 3	65 (2.9)	4 (0.2)
Any SAE	48 (2.1)	1 (< 0.1)
Discontinuation of study drug due to any AE	8 (0.4)	3 (0.1)
All deaths[c]	6 (0.3)	0
Preferred Term		
Headache	410 (18.1)	298 (13.2)
Fatigue	330 (14.6)	259 (11.4)
Nausea	208 (9.2)	172 (7.6)
Diarrhea	146 (6.4)	86 (3.8)

AE = adverse event; DAA = direct-acting antiviral agent; GLE = glecaprevir; PIB = pibrentasvir; SAE = serious adverse event

a. Excludes Study M15-462.

b. DAAs = GLE, PIB, or GLE/PIB.

c. Includes nontreatment-emergent deaths. One additional death occurred in Study M15-462.

Cross reference: Summary of Clinical Safety R&D/16/0147: Table 2.2__2.2, Table 2.2__3.2

Adverse events in subjects without cirrhosis (n = 1,977) were similar in type, frequency, and severity compared with subjects with compensated cirrhosis (n = 288). The safety profile in subjects with HCV/HIV-1 coinfection (n = 33) was similar to that in HCV monoinfected subjects. Overall, the safety profile of GLE/PIB in the elderly population (≥ 65 years old, n = 328) was comparable to the safety profile in the non-elderly population (n = 2,041).

In Study M15-462, GLE/PIB was generally well-tolerated in subjects with CKD Stage 4 and 5 as evidenced by a treatment discontinuation rate of 1.9% (2/104) due to AEs that were considered DAA-related. No subject experienced a serious AE that was assessed as DAA-related. The safety profile in subjects (n = 104) in Study M15-462 was consistent with underlying severe renal impairment and its associated comorbidities. Pruritus was the most common AE among subjects (20.2%) in this study followed by fatigue (14.4%) and nausea (11.5%). Pruritus was not an unexpected finding, as it is commonly observed in patients with severe renal impairment.[15] Laboratory abnormalities were infrequent with no subject experiencing a Grade 3 or higher elevation in ALT or AST and 1 subject experiencing a Grade 3 elevation in total bilirubin. No safety signal or toxicity related to GLE/PIB specific to subjects with CKD Stage 4 and 5 has been identified.

The frequency and severity of hepatic-related AEs as well as liver chemistry abnormalities evaluating potential hepatotoxicity were low across the Phase 2 and 3 studies (excluding Study M15-462). Liver-related safety results indicated that:

- Four subjects had post-nadir Grade 3 ALT abnormalities or Grade 2 ALT with total bilirubin $\geq 2 \times$ ULN. None of these subjects prematurely discontinued study drug due to an ALT or bilirubin increase.
  - ALT abnormalities in 3 of these 4 subjects were not clinically significant
  - One subject experienced concurrent ALT $> 3 \times$ ULN (increased from nadir grade) and total bilirubin $\geq 2 \times$ ULN in the context of multiple gallstones that was not consistent with drug-induced liver injury
- Based on exposure-response analyses, no GLE/PIB exposure-dependent ALT increases were observed in subjects with ALT abnormalities
- Grade 3 increases in bilirubin were infrequent (0.4%) and without bilirubin-related AEs; none were associated with liver disease progression
- No subjects experienced drug-related hepatic decompensation. One subject with cirrhosis (Study M14-172) who had known esophageal varices experienced an episode of esophageal varices hemorrhage that was considered not related to study drug. Treatment was continued without clinical or laboratory signs of liver disease progression.

- A total of 6 (0.3%) subjects experienced a de novo event of HCC. In all 6 subjects, the events were considered related to subject's medical history of underlying liver disease and not to GLE/PIB.
- There were no cases consistent with drug-induced liver injury.

In summary, GLE/PIB demonstrated a favorable safety profile that was similar across durations of 8, 12, and 16 weeks. The regimen was well tolerated across a broad and diverse population of subjects, including subjects with compensated cirrhosis, HIV co-infection, and CKD Stage 4 or 5.

Common GLE/PIB-related AEs (ADRs) occurring in ≥ 5% of subjects were headache, fatigue, nausea. Adverse drug reactions were mostly Grade 1 (mild) in severity. Serious AEs and AEs leading to premature study drug discontinuation were rare.

There were no hematological or blood chemistry findings of concern or considered likely to be related to treatment. Unlike other protease inhibitors, no liver-related toxicities and no cases consistent with drug-induced liver injury were identified.

3.1 Differences Statement

The GLE/PIB fixed dose combination for 8 and 12 weeks was explored in treatment-naïve and -experienced HCV GT1 – 6 infected subjects, without cirrhosis or with compensated cirrhosis including subjects with HIV/HCV co-infection and subjects with CKD Stage 4 or 5 in several Phase 3 studies conducted in a randomized, controlled, double-blind or open-label fashion.

This is the first Phase 3b study designed to evaluate HCV GT1 – 6 treatment-naïve subjects without cirrhosis (Metavir F2 – F3) and with compensated cirrhosis (Metavir F4) treated with GLE/PIB for 8 or 12 weeks, respectively, in Brazil. This country did not participate in the Global GLE/PIB program.

3.2 Benefits and Risks

Benefits of treatment with GLE/PIB include: potent and pangenotypic antiviral activity in vitro, higher genetic barrier to development of drug resistance across genotypes compared to first generation DAA protease and NS5A inhibitors, no need for RBV, 8 or 12 weeks of treatment for NS5AI and PI naive, and the convenience of a once daily regimen. The combination of GLE/PIB has been evaluated in six Phase 3 registration studies and three Phase 2b supportive studies. The results of these studies show high SVR_{12} rates among subjects with HCV GT 1 – 6 infection who receive treatment with GLE/PIB.

Adverse events that are known, and those not previously identified, may occur with GLE/PIB as detailed in the informed consent of this study. In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures. Additional safety data for each DAA alone and the combination of PIB/GLE are detailed in Section 3.0 and in the Investigator's Brochure.[14]

Risks associated with GLE/PIB, including the risks of adverse reactions, virologic failure, and development of resistance-associated substitutions (Section 5.3.4), appear to be limited and manageable based upon the available data. Given the potential for high SVR_{12} rates in populations of HCV-infected subjects, including HIV/HCV co-infected, and with CKD 4 – 5, the risk-benefit profile for GLE/PIB is favorable.

4.0 Study Objective

4.1 Primary Objectives

The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving SVR_{12} (HCV RNA < LLOQ 12 weeks following therapy) and safety of GLE/PIB combination in treatment-naïve adults in Brazil with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis. The efficacy endpoints will be analyzed based on combined

treatment duration and genotypes and safety analysis will be done by individual treatment groups.

4.2 Secondary Objectives

The secondary objectives are to assess efficacy of GLE/PIB based on overall population (i.e., across treatment durations and genotypes) by evaluating the following:

- The percentages of subjects with HCV on-treatment virologic failure (OTVF);
- The percentages of subjects with HCV virologic relapse.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of GLE/PIB for an 8- or 12-week treatment duration in adults in Brazil with chronic HCV GT1 – 6 infection, without cirrhosis or with compensated cirrhosis with a METAVIR System Fibrosis Score of F2, F3 or F4 (F2-F4) or equivalent,[16] who are HCV treatment-naïve. Approximately 100 subjects meeting the eligibility criteria will be enrolled. The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of approximately 35 GT1 and 35 GT3 subjects and 2) approximately 80 F2 – 3 and a maximum of approximately 20 F4 subjects.

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

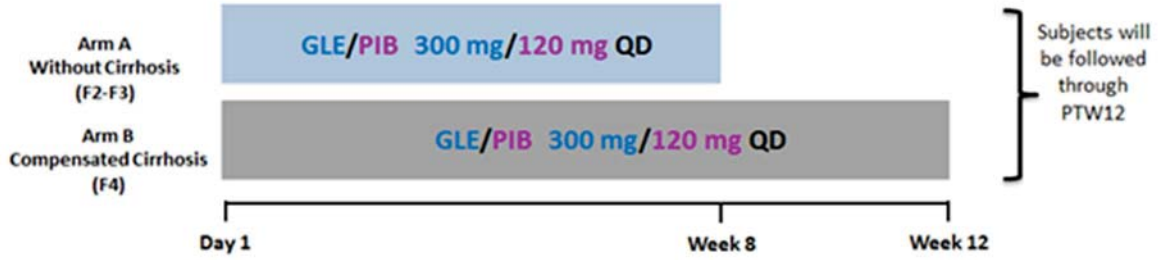
Screening Period: Subjects will have up to 35 days following the Screening Visit to confirm eligibility and enroll in the study.

Treatment Period: Eligible subjects will be enrolled to receive GLE/PIB 300 mg/120 mg once daily (QD) for an 8 (Arm A) or 12 (Arm B) week treatment duration based on cirrhosis status.

Post-Treatment Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 12 weeks to monitor HCV RNA levels to evaluate efficacy and the emergence and persistence of resistance-associated substitutions.

A study schematic is shown below in Figure 1.

Figure 1. Study Design



* **The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of approximately 35 GT1 and 35 GT3 subjects and 2) approximately 80 F2 – F3 and a maximum of approximately 20 F4 subjects.**

Approximately 100 eligible subjects will be enrolled into one of the following treatment arms:

- Arm A: HCV GT 1 – 6 without cirrhosis (F2 – F3) subjects will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks.
- Arm B: HCV GT 1 – 6 subjects with compensated cirrhosis (F4) will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 12 weeks.

The study was designed to enroll approximately 100 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening may not be enrolled.

5.1.1 Screening Period

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study-specific procedures will receive a unique subject number via the Interactive Response Technology (IRT) system. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through Study Day 1 prior to dosing, and will record the results of this assessment and the details of the informed consent process in the subject's medical records. Eligible subjects have up to 35 days following the Screening Visit to enroll into the study.

5.1.1.1 Rescreening

Subjects who at Screening have any of the following are not eligible to rescreen or retest:

- A positive Hepatitis B surface antigen (HBsAg);
- HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti-HBs); or
- If Woman of Childbearing Potential (WOCBP), a positive serum pregnancy test;
- Development of decompensated liver disease during the screening period, as defined by the Exclusion Criterion 6.

Otherwise subjects may be retested or rescreened only once unless approved by the Primary Therapeutic Area Medical Director.

Subjects who have exclusionary laboratory parameter(s) are allowed to retest on the related panel(s) (e.g., exclusionary ALT requires a repeat chemistry panel) within the same screening period and must meet all eligibility laboratory criteria on any panel that is repeated. If any of the retest result(s) are exclusionary, the subject may not be rescreened again.

Subjects that exceed the initial 35 day screening period should be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary during the first screening attempt (with the exception of HIV, HBV, HCV genotype and subtype, follicle stimulating hormone (FSH), which do not need to be repeated). The FibroScan and liver biopsy do not need to be repeated for rescreened subjects provided that the date of the liver biopsy is within 24 months of the rescreening date and the FibroScan is within 6 months of the rescreening date (Section 5.1.1).

Subjects who rescreen or subjects not meeting the study eligibility criteria must be identified by site personnel as a screen failure in both IRT and EDC systems.

5.1.2 Treatment Period

After meeting the eligibility criteria, subjects will be enrolled via IRT on Study Day 1. Subjects will be administered study drug at the site on Study Day 1, and provided dosing instructions.

Study visits and procedures during the Treatment Period are detailed in Appendix C. Safety and tolerability will be assessed throughout the study. Laboratory testing will include chemistry and hematology as specified in Table 5. Plasma samples for pharmacokinetic analysis and HCV RNA analysis will be collected as detailed in Section 5.3 and Section 5.3.1.1.

All subjects will continue to return to the site on an outpatient basis as outlined in Appendix C. Sites should ensure that subjects adhere to all study visits. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

HCV virologic failure criteria will be evaluated and applied by the investigator as detailed in Section 5.4.1.1.

Subjects who prematurely discontinue from the Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined in Appendix C and as described in Section 5.4.1. Subjects who prematurely discontinue from study treatment will continue to be followed in the Post-Treatment Period (see Section 5.1.3).

5.1.3 Post-Treatment Period

All subjects who received at least one dose of study drug will be monitored in the Post-Treatment Period for 12 weeks following the last dose of study drug for safety, HCV RNA, and the emergence and persistence of HCV resistance-associated substitutions.

The Post-Treatment Period will begin the day following the last dose of study drug. Study visits during the Post-Treatment period are detailed in Appendix D and Section 5.3.1.1.

Subjects who prematurely discontinue during the Post-Treatment Period should return to the site for a Post-Treatment discontinuation visit as outlined in Appendix D.

5.2 Selection of Study Population

The study population consists of male and female adults aged 18 years or older with chronic HCV GT1 – 6 infection with METAVIR equivalent fibrosis stage of F2 – F4 (without cirrhosis or with compensated cirrhosis) who are HCV treatment naïve (i.e., subject has never received a single dose of any approved or investigational anti-HCV medication). Subjects with HIV/HCV co-infection and subjects at all CKD stages (CKD Stages 1 – 5) are allowed to participate. Subjects who meet all inclusion criteria and none of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

1. Male or female, at least 18 years of age at time of Screening.
2. If female, subject must be either

Postmenopausal defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause; or
- Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L; or
- Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

OR

- A WOCBP practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 through at least 30 days after the last dose of study drug.

3. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.

   Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing.

4. Screening laboratory result indicating HCV GT1-, 2-, 3-, 4-, 5- and/or 6-infection. Mixed and indeterminate genotypes are acceptable.

5. Subject has positive plasma HCV antibody and HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.

6. Subjects who are known to be HCV/HIV co-infected may enroll if they have a positive test result for anti-Human Immunodeficiency Virus antibody at Screening and are:

   Naïve to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study), or on a stable, qualifying HIVART regimen for at least 8 weeks prior to Baseline. (Substituting TDF for TAF as part of the combination regimen is allowed at any time.)

The HIVART regimen must include at least one of the following ARV agents:

- Raltegravir (RAL)
- Dolutegravir (DTG)
- Rilpivirine (RPV)
- Elvitegravir/cobicistat (EVG/COBI)

In addition to the above medications, HIV Ab positive subjects (both without cirrhosis or with compensated cirrhosis) may take a nucleoside/nucleotide reverse transcriptase inhibitor (N(t)RTI) backbone containing any of the following:

- Tenofovir disoproxil fumarate (TDF)
- Tenofovir alafenamide (TAF)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Lamivudine (3TC)

Subjects receiving any other HIV ART in addition to those noted above are not eligible for enrollment in the study.

Subjects on stable HIV ART must have Plasma HIVRNA below 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once during the 12 months prior to Screening (by an approved plasma HIVRNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTi*m*e HIV-1 assay).

7. Subject must be documented as without cirrhosis with METAVIR equivalent fibrosis stage of F2 – 3 or with compensated cirrhosis (F4) based on results of a liver biopsy, or FibroScan, or FibroTest score (as described in Section 5.3.1.1).

8. Subjects with compensated cirrhosis only: Absence of hepatocellular carcinoma (HCC) 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. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.
9. Subject must voluntarily sign and date an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to the initiation of any Screening or study specific procedures.
10. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.
11. Subjects requiring dialysis should have been receiving dialysis for at least 1 month prior to enrollment, and may be on hemodialysis or peritoneal dialysis.

Rationale for Inclusion Criteria

1, 4 – 11	In order to select the appropriate subject population with appropriate disease characteristics for evaluation
2, 3	The impact of GLE and PIB on human pregnancies has not been established. However, assessment of the completed nonclinical reproductive toxicology studies indicates that there is no drug-related effect on teratogenicity/fetotoxicity. In addition, the compounds are non-genotoxic
10	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.

2. Current HBV infection on screening tests, defined as:
   - A positive HBsAg, or;
   - HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti-HBs)
3. Requirement for and inability or unwillingness to safely discontinue the medications or supplements listed in Table 4 at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of any study drug.
4. Requirement for 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).
5. 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.
6. Any current or past clinical evidence of Child-Pugh B or C classification (score of > 6) or clinical history of liver decompensation including ascites on physical exam, including hepatic encephalopathy or variceal bleeding. Prophylactic use of beta blockers is not exclusionary (see Section 5.3.1.1).
7. Laboratory parameters exclusions:
   - ALT > 10 × ULN; AST > 10 × ULN
   - Total Bilirubin > 3.0 mg/dL
   - Albumin < LLN (without cirrhosis); < 2.8 mg/dL (with compensated cirrhosis)
   - Platelets < 90,000 10^3/µL (without cirrhosis); < 60,000 10^3/µL (with compensated cirrhosis)
8. History of solid organ transplantation, unless the implanted organ has since been removed, or is non-functional, and subject is no longer on immunosuppressive medication. If the organ is non-functional, the subject must be clinically stable off of immunosuppressive medication for a minimum of 6 months prior to screening. This only applies to subjects with CKD Stage 4 or 5.

9. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks (whichever is longer) prior to study drug administration.
10. Receipt of any investigational or commercially available anti-HCV agents examples include, but are not limited to: interferon, pegylated interferon ribavirin, sofosbuvir, telaprevir, boceprevir, simeprevir, asunaprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, voxilaprevir, velpatasvir or dasabuvir.
11. History of severe, life-threatening or other significant sensitivity to any excipients of the study drug.
12. Treatment for an AIDS-Defining Conditions (ADC) (Appendix E) within 6 months of Screening.
13. Subjects who cannot participate in the study per local law.

Rationale for Exclusion Criteria

1, 3, 4, 6 – 13	In order to ensure safety of the subjects throughout the study
2, 5	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal 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 drugs. 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 serious adverse event (SAE) will be recorded in EDC. The AbbVie Primary Therapeutic Area Medical Director should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior HCV Therapy

Subjects must be HCV treatment-naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication).

5.2.3.2 Prior and Concomitant HIV Therapy

Subject on an HIV ART regimen must include ARV agents as defined in Inclusion Criterion 6 (Section 5.2.1).

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

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

Subjects receiving any other HIV ART in addition to those listed in Inclusion Criterion 6 (Section 5.2.1) would not be eligible for enrollment in the study.

5.2.3.3 Concomitant Therapy

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

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 drugs, if applicable.

Flu shots and other vaccinations are allowed during Screening through the Post-Treatment Period for all subjects. Flu shots and vaccinations may affect plasma HIV RNA levels.

5.2.3.4 Prohibited Therapy

Medications or supplements prohibited to be administered with ABT-493/ABT-530 are listed in Table 4. For subjects in the study in countries where ABT-493/ABT-530 (glecapravir/pibrentasvir) has received marketing authorization, any medications in the local label that are contraindicated to be administered with ABT-493/ABT-530 (glecapravir/pibrentasvir) are also considered to be prohibited medications. Subjects must be able to safely discontinue any prohibited medications or supplements 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 drugs.

Table 4. Prohibited Medications and Supplements

Medication or Supplement Name
Red yeast rice (monacolin K), St. John's Wort
Carbamazepine, efavirenz, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin*
Astemizole, cisapride, terfenadine
Ethinyl estradiol

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drug. After signing the informed consent form, 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) 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 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 either 1) reduce or limit the pravastatin or rosuvastatin dose in accordance with the ABT-493/ABT-530 product label (if approved in the country); or 2) reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drug if ABT-493/ABT-530 is not yet approved in the country.

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

The chronic use of systemic immunosuppressants is prohibited from 2 weeks prior to the first dose of study drug and until 30 days after the last dose of study drug including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab).

For HCV/HIV coinfected subjects, the investigator must refer to the current package insert(s) or product label(s) of a subject's ART regimen for a complete list of medications prohibited to be used with those drugs, which should not be used at least 2 weeks prior to the first dose of any study drug and not use these during the entire Treatment Period and for 30 days following discontinuation of study drugs.

5.2.4 Contraception Recommendations

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a Woman of Childbearing Potential, practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 30 days after the last dose of study drug:

- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- 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, symptom-thermal, post-ovulation methods] and withdrawal are not acceptable).

For male study subjects, no contraception is required.

5.3 Efficacy, Pharmacokinetic, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C (Treatment Period) and Appendix D (Post-Treatment Period).

5.3.1.1 Study Procedures

Informed Consent

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Medical History

A complete medical history, including history of tobacco, alcohol and drug use, will be taken from each subject at Screening Visit. The subject's medical history will be updated at the Study Day 1 Visit. This updated medical history will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will be performed at visits specified in Appendix C, or upon subject discontinuation. A symptom-directed physical examination may be performed at any other visit, when necessary.

The physical examination performed on Study Day 1 will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after the first dose will be recorded as adverse events.

Height will be measured only at Screening.

Vital Signs and Weight

Body temperature, blood pressure, pulse, and body weight will be measured at each study visit as specified in Appendix C and Appendix D. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes. The subject should wear lightweight clothing and no shoes during weighing. The vital signs performed on Day 1 of the Treatment Period will serve as the baseline for clinical assessment.

12-Lead Electrocardiogram

A 12-lead resting ECG will be obtained at the visits indicated in Appendix C. The ECG should be performed prior to blood collection.

The ECG will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign, and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 5 at the visits indicated in Appendix C and Appendix D.

Blood samples for serum chemistry tests should be collected following a minimum 8-hour fast prior to study drug intake (with the exception of the Screening Visit, which may be non-fasting). Subjects whose visits occur prior to the morning dose of study drug should

be instructed to fast after midnight until the blood sample is collected in the morning and thereafter take their study medications with food. Subjects whose visits occur following the morning dose of study drug should be instructed to fast after breakfast until the study visit occurs. At the Study Day 1 visit, a fasting blood sample should be collected prior to the first dose of study drug. Blood samples should still be drawn if the subject did not fast for at least 8 hours. Fasting or non-fasting status will be recorded in the source documents and on the laboratory requisition. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

A central laboratory will be utilized to process and provide results for the clinical laboratory tests.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study. The certified laboratory chosen for this study is Covance. Samples will be sent to the following addresses:

Covance
8211 SciCor Drive
Indianapolis, IN 46214 USA

Table 5. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Additional Tests
Hematocrit	Blood Urea Nitrogen (BUN)	Anti-HCV Ab[a]
Hemoglobin	Creatinine	HCV RNA
Red Blood Cell (RBC) count	Total bilirubin	HCV genotype and subtype[a]
White Blood Cell (WBC) count	Direct and indirect bilirubin	HIV Ab[a]
Neutrophils	Alanine transaminase (ALT)	HIV RNA[b]
Bands, if detected	Aspartate transaminase (AST)	Hepatitis B Panel (Anti-HB[c]
Lymphocytes	Alkaline phosphatase	Total, Anti-HBs and HBsAg)[c]
Monocytes	Sodium	Anti-HBc IgM[c]
Basophils	Potassium	Anti-HBc Total[c]
Eosinophils	Calcium	Anti-HBs[c]
Platelet count (estimate not acceptable)	Inorganic phosphorus	Anti-HAV
Prothrombin Time/INR[a]	Total protein	IgM[d]
Activated partial thromboplastin time (aPTT)	Glucose	Anti_HAV Total[d]
	Albumin	Anti-HEV IgG[d]
	Chloride	Anti-HEV IgM[d]
	Bicarbonate	HEV RNA[d]
	Magnesium	HBV DNA[e]
	Gamma-glutamyl transferase (GGT)	Follicle Stimulating Hormone (FSH)[f]
		Urine and Serum Human Chorionic Gonadotropin (hCG) for females[g]
		Alpha2-macroglobulin[h]
		Haptoglobin[h]
		Apolipoprotein A1[h]
		CD4, CD4%[b]
		CD8, CD8%[b]
		CD4:CD8[b]

a. Performed only at Screening.

b. Only for known HCV/HIV co-infected subjects.

c. Performed at Screening for all subjects and also performed for management of transaminase elevations (Section 6.1.7.1).

d. Performed for management of transaminase elevation (Section 6.1.7.1).

e. Performed at Screening for subjects who have occult HBV infection (positive Anti-HBc Total with negative HBsAg and Anti-HBs) and also performed for management of transaminase elevation (Section 6.1.7.1).

f. Only performed if requested during screening for post-menopausal women < 55 to verify FSH level if site does not have a previous result available.

g. Required only for females of child bearing potential.

h. Component of FibroTest and collected only if required for FibroTest calculation during the Screening Period.

For any laboratory test value outside the reference range that the investigator considers to be clinically significant:

- The investigator will repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.
- A laboratory test value that requires a subject to be discontinued from the study or study drug or requires a subject to receive treatment will be recorded as an adverse event.

The management of laboratory abnormalities that may occur during the study is described in Section 6.1.7.

Pregnancy Testing

- WOCBP must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.
- Monthly pregnancy testing should be performed during treatment, including at the last dose and until 30 days of last study drug dose, as indicated in Appendix C and Appendix D.
- Subjects with borderline pregnancy tests at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
- Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in the inclusion criteria) at Screening do not require pregnancy testing.

Concomitant Medication Assessment

Please refer to Section 5.2.3.2.

Hepatitis B, Hepatitis C Virus and HIV Screen

HBsAg, anti-HBc and anti-HBs, anti-HCV Ab and anti-HIV Ab will be performed at Screening. The investigator must discuss any local reporting requirements to local health

agencies with the subject. The site will report these results per local regulations, if necessary. The HIV results will not be reported by the central laboratory to the clinical database.

Liver Diagnostic Testing

Subjects will be considered to be without cirrhosis or with compensated cirrhosis based on the definitions below:

Without Cirrhosis (F2 and F3)

- A liver biopsy within 24 months prior to or during Screening demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of 2 – 3, Ishak fibrosis score of 3 or 4; or
- A FibroScan® score of 8.8 to < 12.5 kPa within ≤ 6 months of Screening or during Screening period (FibroScan® must be approved by the local regulatory agency to qualify for entrance criteria); or
- A Screening FibroTest score of 0.49 to 0.72 (inclusive).[17]

With Compensated Cirrhosis (F4)

- 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 or on a liver biopsy conducted during Screening; or
- A FibroScan® score of ≥ 12.5 kPa within ≤ 6 months of Screening or during Screening period (FibroScan® must be approved by the local regulatory agency to qualify for entrance criteria); or
- A Screening FibroTest result that is ≥ 0.73.

The result of the liver biopsy supersedes the results of FibroScan and FibroTest and result of FibroScan supersedes the results of FibroTest. At Screening, it is recommended that subjects should otherwise meet all other inclusion criteria and none of the exclusion criteria before undergoing a liver biopsy.

Child-Pugh Score and Category

Subjects with compensated cirrhosis will have Child-Pugh scores assessed, except those who are on ongoing use of anticoagulants. The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments) as shown in Table 6. Child-Pugh score will be determined at the visits indicated in Appendix C and Appendix D.

Table 6. Child-Pugh Classification of Severity of Cirrhosis

	Points Assigned for Observed Findings		
Parameter	**1**	**2**	**3**
Total bilirubin, µmol/L (mg/dL)	< 34.2 (< 2)	34.2 – 51.3 (2 – 3)	> 51.3 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28 – 35 (2.8 – 3.5)	< 28 (< 2.8)
INR	< 1.7	1.7 – 2.3	> 2.3
Ascites**	None	Slight	Moderate to severe
Hepatic encephalopathy*	None	Grade 1 or 2 (or suppressed with medication)	Grade 3 or 4 (or refractory)

Child-Pugh category A: 5 – 6 points; Child-Pugh category B: 7 – 9 points; Child-Pugh category C: 10 – 15 points.

* Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.
Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

** None.
Slight ascites = Ascites detectable only by ultrasound examination.
Moderate ascites = Ascites manifested by moderate symmetrical distension of the abdomen.
Severe ascites = Large or gross ascites with marked abdominal distension.

Clinical Assessment of Hepatic Decompensation

A clinical assessment of hepatic encephalopathy and ascites will be performed at Study Day 1 prior to dosing to confirm the subject has not progressed to hepatic decompensation since Screening for all subjects who have compensated cirrhosis. Grading system guidelines for ascites are listed above in Table 6. Subjects who present symptoms and

signs of hepatic decompensation including assessment at Day 1 prior to receiving study drug, will not be enrolled into the trial.

Hepatocellular Carcinoma Screening: Liver Ultrasound

HCC screening will be required as a protocol-specified study procedure only at the Screening Visit and at the last Post-Treatment Study Visit, as indicated in Appendix C and Appendix D, for subjects with compensated cirrhosis only. In-between those visits, HCC screening should be performed according to standard of care.

At the Screening Visit and at the last Post-Treatment Study Visit, subjects with compensated cirrhosis will be required to undergo a liver ultrasound to screen for HCC, unless the subject has a historical liver ultrasound, CT scan or MRI performed for HCC screening within 3 months prior to those visits, in which case the result of the historical ultrasound, CT scan or MRI will be used as the result for the Study Visit assessment. A positive ultrasound result suspicious of HCC will be confirmed with CT scan or MRI. Alternate methods of screening for HCC (i.e., CT scan or MRI) at a study visit should be discussed with the study designated physician.

Patient Reported Outcomes (PRO) Instruments (Questionnaires)

Subjects will complete the self-administered PRO instruments on the study visits specified in Appendix C and Appendix D. Subjects should be instructed to follow the instructions provided with each instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaires to them. Site personnel should encourage completion of each instrument at all specified visits and should ensure that a response is entered for all items.

Short Form 36 – Version 2 Health Survey (SF-36v2)

The SF-36v2 is a general Health Related Quality of Life (HRQoL) instrument with extensive use broad variety of health conditions and is the standard in literature for HCV.

The SF-36v2 instrument comprises 36 total items (questions) targeting a subject's functional health and well-being in 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). Domain scores are also aggregated into a Physical Component Summary score and a Mental Component Summary score. Higher SF-36v2 scores indicate a better state of health. The SF-36v2 should require approximately 10 minutes to complete.

Treatment Satisfaction Questionnaire-Medicine (TSQM)

The TSQM is a 14-item instrument and includes assessments of satisfaction with a medication's effectiveness (Effectiveness, three items), lack of side effects (Side Effects; five items), convenience (three items) and the subject's global satisfaction (Global Satisfaction; three items).

The subject should complete the questionnaire before site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response. TSQM scores range from 0 – 100 with higher scores indicating better satisfaction. The TSQM should require approximately 5 minutes to complete.

EuroQol-5 Dimensions-3 Level (EQ-5D-3L)

The EQ-5D-3L is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-3L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on 3 levels of severity. Responses to the 5 items encode a discrete health state which is mapped to a preference (utility) specific for different societies. Subjects also rate their perception of their overall health on a separate visual analogue scale (VAS). The EQ-5D-3L should require approximately 5 minutes to complete.

PRO instruments should be consistently presented so that subjects complete the questionnaires in the following order: the SF-36v2, TSQM, and EQ-5D-3L. PRO instruments should be completed prior to drug administration on Day 1 and prior to any

discussion of adverse events or any review of laboratory findings, including HCV RNA levels, at all study specified visits listed in Appendix C and Appendix D. The TSQM is the only PRO assessment that will not be performed at Day 1.

Enrollment and Assignment of Subject Numbers

All Screening activities must be completed and reviewed prior to enrollment. Subjects who meet all the Inclusion Criteria and none of the Exclusion Criteria at Screening will proceed to enrollment via the IRT system on Study Day 1.

Subject numbers will be unique 4 digit numbers and will begin with 1001 with the first two digits representing the investigative site, and the last two digits representing the subjects at that site. Enrolled subjects will keep their subject number throughout the study. Subjects will be enrolled on Study Day 1 as described in Section 5.5.4.

Study Drug Compliance for Kits

Individual bottles of GLE/PIB will be provided for subject dosing to the site. Each subject will have compliance documented by the site in the subject's source notes for GLE/PIB. At each Study Drug Accountability Visit in Appendix C, the overall number of tablets of GLE/PIB remaining in each bottle will be recorded and entered in the IRT system along with the date of reconciliation.

Additional information regarding treatment compliance can be found in Section 5.5.6.

HCV Genotype and Subgenotype

Plasma samples for HCV genotype and subtype determination will be collected at Screening. Genotype and subtype will be assessed using the Versant® HCV Genotype Inno LiPA Assay, Version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY) by the central laboratory. If the LiPA assay is unable to genotype a sample, its genotype and subtype will be evaluated by a Sanger sequencing assay of a region of the NS5B gene by the central laboratory.

HCV RNA Levels

Plasma samples for HCV RNA levels will be collected as indicated in Appendix C and Appendix D. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan HCV Quantitative Test, v2.0. The lower limit of detection (LLOD) and lower limit of quantification (LLOQ) for this assay (regardless of genotype) are both 15 IU/mL.

HCV Resistance Testing Sample

A plasma sample for HCV resistance testing will be collected prior to dosing on Day 1 and at the study visits indicated in Appendix C and Appendix D. Specific instructions for preparation and storage of HCV RNA and HCV resistance samples will be provided by the central laboratory, AbbVie, or its designee.

Study Drug Dosing Card

Subjects will be provided with self-administration instructions and study drug dosing cards to record the exact date, time (record to the nearest minute) and number of tablets of study drug administration (GLE/PIB) for the last 2 doses of study drug taken prior to the scheduled pharmacokinetic sample collection visits during the Treatment Period as detailed in Appendix C.

The site staff will record the information about the last 2 doses taken prior to the scheduled pharmacokinetic sample collection from the study drug dosing card into the eCRF. In the event that the dosing card is not available, the site may obtain dosing information via patient interview and record this information in the source notes and the eCRF.

To facilitate proper dosing of study drug before pharmacokinetic evaluation blood samples are taken, the following procedures should be performed:

- The Investigator or designee should make sure the subject is given the dosing card at the visits listed in Appendix C.

- The Investigator or designee will contact the subject approximately 2 days before the scheduled visit date to review the importance of proper study drug administration relative to the pharmacokinetic blood collection and documentation of dosing times on the dosing card. The date and time of the contact will be entered into the subject's source documents.
- The completed dosing card will be collected by the Investigator or designee on the day of the visit and be kept as a source record of dosage administration times documented in the eCRF.

Flow Cytometry, HIV RNA and HIV Resistance Testing Samples

For subjects with HCV/HIV coinfection, samples for plasma HIV RNA levels and flow cytometry (including but not limited to CD4+ T-cell and CD8+ T-cell counts [absolute and percent]) will be obtained at the times specified in Appendix C and Appendix D. Plasma HIV-1 RNA will be measured by the central laboratory using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, version 2.0 HIV-1 Assay. Results below the LLOD are reported as: "Not Detected." HIV treatment failure is defined as detectable HIV RNA after 6 months of highly active antiretroviral therapy (HAART) or HIV RNA detectable after a period of undetectable measurement following use of HAART.

If a HIV RNA level result of subject on stable HIV ART is ≥ 200 copies/mL, the subject's HIV RNA is to be repeated as noted in Section 5.4.1.2. At the time the repeat plasma HIV RNA is drawn, a sample should be obtained for HIV genotypic resistance testing. If the subject's repeat HIV RNA is ≥ 500 copies/mL, the sample obtained for HIV genotypic resistance testing will be analyzed.

HIV protease (PR), reverse transcriptase (RT) and integrase (IN) sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assay.

If the subject's repeat HIV RNA is < 200 copies/mL, then the subject will resume routine plasma HIV RNA assessments as shown in Appendix C and Appendix D, and described in Section 5.4.1.2.

Specific instructions for preparation and storage of flow cytometry, plasma HIV RNA, and HIV resistance samples will be provided by the central laboratory, AbbVie, or its designee.

5.3.1.2 Meals and Dietary Requirements

Study drug (GLE/PIB) tablets should be dosed together and taken with food.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic assay of GLE, PIB, and their possible metabolites will be collected by venipuncture at each study visit indicated below and in Appendix C.

- At all Treatment-Period visits, except Day 1, a single blood sample for pharmacokinetic analysis will be collected without regard to the time of dosing. The date and time of blood sample collection and the two previous doses of the study drug will be recorded to the nearest minute in the source documents. Additionally, the date and time of the two previous doses of the study drug will be recorded to the nearest minute on the eCRF.

5.3.2.2 Handling/Processing of Samples

Specific instructions for collection of blood samples and subsequent preparation and storage of plasma samples for the pharmacokinetic assays of GLE, PIB, and their possible metabolites will be provided by the central laboratory, AbbVie, or its designee.

5.3.2.3 Disposition of Samples

The frozen plasma samples for the pharmacokinetic assays of GLE, PIB, and their possible metabolites will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory.

The central laboratory will then ship the GLE and PIB samples to AbbVie or the reference laboratories following separately provided instructions.

5.3.2.4 Measurement Methods

Plasma concentrations of GLE and PIB will be determined using a validated assay methods in the Drug Analysis Department at AbbVie. Plasma concentrations of any possible GLE and PIB metabolites may also be determined using either validated or non-validated methods.

5.3.3 Efficacy Variables

Virologic response will be assessed by plasma HCV RNA levels in IU/mL at various time points from Day 1 through 12 weeks after completion or discontinuation of study drug.

5.3.3.1 Primary Variable

The primary efficacy variable is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

5.3.3.2 Secondary Variables

The secondary efficacy variables are:

- The percentage of subjects with HCV OTVF.
- The percentage of subjects with HCV virologic relapse.

5.3.3.3 HCV Resistance Variables

For all subjects receiving GLE/PIB and with available samples, baseline polymorphisms at signature resistance associated amino acid positions identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA ≥ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the baseline sequence, 2) the amino acid substitutions in available post-baseline samples at signature resistance associated positions identified by NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of resistance-associated substitutions by NGS.

5.3.4 Safety Variables

The following safety evaluations will be performed during the study: adverse events, vital signs, physical examination, ECG, and laboratory tests assessments.

5.3.5 Pharmacokinetic Variables

Individual plasma concentrations of GLE, PIB, and their potential metabolites, if measured, will be tabulated and summarized.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.

If, during the course of study drug administration, the subject prematurely discontinues, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Appendix C and Appendix D. 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. The last dose of any study drug and reason for discontinuation will be recorded in the EDC (electronic data capture) system. 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 substitutions.

If a subject is discontinued from study drug or in 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.

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. Specific instructions regarding subject pregnancy can be found in Section 6.1.6. If a subject is discontinued, subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

5.4.1.1 HCV Virologic Failure Criteria

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.
- 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 resistance-associated viral substitutions until 12 weeks post-treatment. Alternative management will only be considered with the approval of TA MD.

5.4.1.2 Failure to Maintain HIV Virologic Suppression

HIV RNA will be assessed at each scheduled study visit during the Treatment and Post Treatment Period, as detailed in Appendix C and Appendix D.

The criteria for failure to maintain HIV virologic suppression among subjects on stable ARTs is as follows:

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

Subjects should remain on HCV study drug treatment and his/her current ART regimen while the failure to maintain HIV virologic suppression is being confirmed. A confirmatory HIV RNA and HIV genotypic resistance blood draw can be done as an unscheduled visit. However, if this blood draw falls on the date of a scheduled study visit (Appendix C and Appendix D), only a single HIV RNA and HIV genotypic resistance blood draw needs to be performed at this visit.

At the time a confirmatory HIV RNA is drawn, a sample for HIV genotypic resistance testing should also be obtained; this sample will be analyzed if the subject's repeat plasma HIV RNA is ≥ 500 copies/mL. Subjects should remain on HCV study drug treatment and his/her current ART regimen while the failure to maintain HIV virologic suppression is being confirmed. A confirmatory HIV RNA and HIV genotypic resistance blood draw can be done as an unscheduled visit. However, if this blood draw falls on the date of a scheduled study visit (Appendix C and Appendix D), only a single HIV RNA and HIV genotypic resistance blood draw needs to be performed at this visit.

During the Treatment Period, subjects with confirmed failure to maintain HIV RNA suppression should continue HCV study drug treatment unless there is a requirement for prohibited concomitant medications (Section 5.2.3.2) to construct a new HIV ART regimen.

Clinical management of failure to maintain HIV virologic suppression during the study (Treatment and Post-Treatment Period) will be handled by the Investigator according to current HIV treatment guidelines and local standard of care. Subject's change of HIV ART regimen must be discussed with the AbbVie TA MD prior to the change being made, unless the change is being made to address an immediate safety concern.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Each dose of GLE/PIB will be dispensed in the form of film-coated co-formulated tablets at the visits listed in Appendix C. Subjects will be instructed to take study drug at the same time every day with food. Please refer to Section 5.3.1.1 and Section 5.3.2.1 for more details.

GLE/PIB will be provided by AbbVie as 100 mg/40 mg film-coated tablets. GLE/PIB will be taken orally at GLE 300 mg/PIB 120 mg (three × GLE 100 mg/PIB 40 mg tablets) QD and with food.

Beginning with Study Day 1, the site will use the IRT system to obtain the study drug kit numbers to dispense at the study visits specified in Appendix C. Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. The site will also contact the IRT system to provide study drug return information for each kit at the visits specified in Appendix C. At the end of the Treatment Period or at the Premature D/C Visit from the Treatment Period, the site will contact the IRT system to provide the discontinuation visit date information and study drug return information for each kit (Section 5.5.7).

All subjects who receive at least one dose of study drug and meet the HCV virologic failure criteria defined in Section 5.4.1.1 will be discontinued from treatment.

5.5.2 Identity of Investigational Products

Information about the study drug to be used in this study is presented in Table 7.

Table 7. Identity of Investigational Products

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
Glecaprevir/Pibrentasvir	AbbVie	Oral	Film-coated tablet	100 mg/ 40 mg

5.5.2.1 Packaging and Labeling

Study drug will be supplied in bottles. Each bottle will be labeled as required per country requirements. Labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to subject.

5.5.2.2 Storage and Disposition of Study Drug

Study Drug	Storage Conditions
Glecaprevir/Pibrentasvir bottles	15° to 25°C (59° to 77°F)

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be

maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to AbbVie (or designee).

5.5.3 Method of Assigning Subjects to Treatment Groups

At the Screening Visit, all subjects will be assigned a unique subject number through the use of IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number, assigned at the Screening Visit, throughout the study. For enrollment of eligible subjects into the study, the site will utilize the IRT system in order to receive the treatment assignment. Enrolled subjects will be assigned to either Arm A (8 weeks of treatment) or Arm B (12 weeks of treatment) based on cirrhosis status. The study drug kit numbers will be assigned according to schedules computer-generated before the start of the study by the AbbVie Statistics Department.

Contact information and user guidelines for IRT use will be provided to each site. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Subjects meeting the eligibility criteria will be enrolled as described in Section 8.3.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.6.4. Study drug dosing will be initiated at the Study Day 1 Visit.

All tablets of GLE/PIB will be dosed together (three tablets once daily). All subjects should take all doses of study medications with food.

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

At the start of the study, each subject should receive counseling regarding the importance of dosing compliance with the treatment regimen with regard to HCV virologic response and potential development of resistance due to poor compliance.

At each study visit after Day 1 during the Treatment Period, subjects will be instructed to bring all bottles of study drug (full, partial, or empty) for assessment of treatment compliance. At Study Drug Accountability visits denoted in Appendix C, study site personnel will assess subject compliance by inspecting the contents of the bottles and record the status of each one, as well as the exact number of remaining tablets of GLE/PIB in IRT. Treatment compliance will be based on the number of tablets dispensed, as recorded in IRT, and the number of remaining tablets. If poor compliance is noted, the subject should be counseled and this should be documented in the subject's source.

5.5.7 Drug Accountability

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt (POR) or similar document and via recording in the IRT system. A current (running) and accurate inventory of study drug will be kept by the investigator and will include lot number, kit number, number of tablets dispensed, subject number, initials of person who dispensed study drug, and date dispensed for each subject. An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the Treatment Period. The monitor will review study drug accountability on an ongoing basis. Final accountability will be verified by the monitor at the end of study drug treatment at the site.

During the study, should an enrolled subject misplace or damage a study drug bottle of GLE/PIB the IRT system must be contacted and informed of the misplaced or damaged study drug. If the bottle is damaged, the subject will be requested to return the remaining study drug to the site. Replacement study drug may only be dispensed to the subject by contacting the IRT system. Study drug replacement(s) and an explanation of the reason for the misplaced or damaged study drug(s) will be documented within the IRT system. The study drug start date and the last dose of the regimen will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each bottle, number of tablets remaining in each one returned, and the date of reconciliation will be documented in the IRT system. The monitor will review study drug accountability on an ongoing basis.

Upon completion of or discontinuation from the Treatment Period, all original study drug bottles (containing unused study drug) will be returned to AbbVie (or designee) or destroyed on site. All destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of drug accountability procedures. Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The GLE/PIB combination regimen for 8- and 12-weeks in HCV treatment-naïve subjects without cirrhosis and with compensated cirrhosis respectively, was evaluated in HCV GT1 – 6 infected subjects in the Phase 3 studies discussed in detail in Section 3.0. A high (> 97%) efficacy and positive safety profile was demonstrated in these studies. AbbVie plans to evaluate the same combination regimen at the proposed label durations in a similar HCV GT1 – 6 infected population in Brazil. The study is designed to include subpopulations of HCV-infected patients (e.g., GT1 and GT3; severe renal disorder and HIV/HCV co-infected population) that represents the unmet clinical treatment need in Brazil. The selection of a two arm study design is appropriate so that treatment naïve

GT1 – 6 Brazilian subjects receive the proposed label treatment duration based on their cirrhosis status.

In view of the expected high SVR rate in this study and the established safety profile of GLE/PIB in patients with advanced fibrosis, a control arm would be of limited value for efficacy comparison. In this context, an open-label study is appropriate to adequately describe the efficacy and safety of this regimen administered for the proposed global label recommended durations for treatment naïve subjects.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study. HCV RNA assays are standard and validated. Next generation sequencing (NGS) methods are experimental.

5.6.3 Suitability of Subject Population

This study is intended to enroll HCV treatment-naïve adults in Brazil with chronic HCV genotype 1 – 6 without cirrhosis and with compensated cirrhosis with METAVIR equivalent fibrosis stage F2-F4. Patients with HCV/HIV co-infection and CKD Stages 1 – 5 may participate in the study. The study population includes subpopulations of HCV-infected patients (e.g., GT1 and GT3; severe CKD and HIV/HCV co-infected populations) with high unmet clinical treatment need currently in Brazil.

5.6.4 Selection of Doses in the Study

5.6.4.1 Rationale for Dose Selections

The dose GLE/PIB 300 mg/120 mg 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.

5.6.4.1.1 GLE and PIB Dose and Treatment Duration

GLE/PIB is proposed to be indicated for the treatment of chronic HCV infection in adults. In DAA-treatment naïve adults, the recommended oral dose of GLE/PIB is three 100 mg/40 mg tablets QD with food (total daily dose of 300 mg/120 mg) for 8 weeks in subjects without cirrhosis and for 12 weeks in subjects with compensated cirrhosis based on the ITT SVR_{12} rates in the registrational studies. Only HCV treatment naïve subjects will be enrolled in this study. The efficacy in subjects with CKD4 – 5 did not differ from those without CKD. Similar efficacy result was observed on HCV/HIV co-infected subjects and HCV monoinfected subjects. The recommended durations for all HCV treatment naive patients of all HCV genotypes are summarized in Table 8, and SVR_{12} is summarized by GT in Table 9. These are recommendations for all HCV-infected patients, including those co-infected with HIV and patients with any degree of renal impairment.

A favorable safety profile has been observed in HCV-infected subjects without cirrhosis or with compensated cirrhosis who received the GLE + PIB 300 mg + 120 mg dose combination. No dose response relationship was observed for adverse events, or for treatment-emergent post-nadir alanine aminotransferase elevations.

The maximum dose of ABT-493/ABT-530 will not exceed 300 mg/120 mg per day for 12 weeks.

Table 8. Recommended GLE/PIB Duration for TN Patients

	Recommended Treatment Duration	
Patient Population	**No Cirrhosis**	**Cirrhosis**
Genotype 1 – 6	8 weeks	12 weeks

GLE = glecaprevir; PIB = pibrentasvir; TN = treatment-naïve

Table 9. Summary of SVR_{12} Rates for TN and TE-PR, SOF/R or PI by Subject Population (Phase 2 and 3 Analysis Set)

	SVR_{12}%										
	GT1		GT2		GT3		GT4 – 6		GT1 – 6		
	No Cirr	Cirr	No Cirr	Cirr	No Cirr	Cirr	No Cirr	Cirr	No Cirr	Cirr	All
TN[a] + TE-P/R, SOF/R or PI[b]	99.0	97.2	98.0	100	95.2	96.6	93.1	100	97.4	97.6	97.5

cirr = cirrhosis; GT = genotype; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; P/R = regimens containing interferon, pegylated interferon, and/or ribavirin; SOF/R = regimens containing sofosbuvir and ribavirin; SVR_{12} = sustained virologic response 12 weeks postdosing; TE = treatment-experienced; TN = treatment-naive

a. Recommended treatment duration for subjects without cirrhosis is 8 weeks and with cirrhosis is 12 weeks.

b. Recommended treatment duration for GT1, 2, 4 – 6 subjects without cirrhosis is 8 weeks and with cirrhosis is 12 weeks. Recommended treatment duration for GT3 subjects is 16 weeks.

Cross reference: AbbVie. R&D16/0146. Summary of Clinical Efficacy for Glecaprevir/Pibrentasvir in HCV. 2016.

6.0 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 after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.7.1. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other" cause of the event. For adverse events to be

considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (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 accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (see Section 6.1.7 regarding toxicity management) and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during the study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been 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 adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) 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.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4).

The table of clinical toxicity grades "National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4" is available from the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf and is to be used in the grading of adverse events. Below are the general grading categories. However, the investigator should always search NCI CTC AE for a given diagnostic/symptomatic AE term to identify and apply specific grading details for that AE entity.

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.

6.1.3 Relationship to Study Drug

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

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

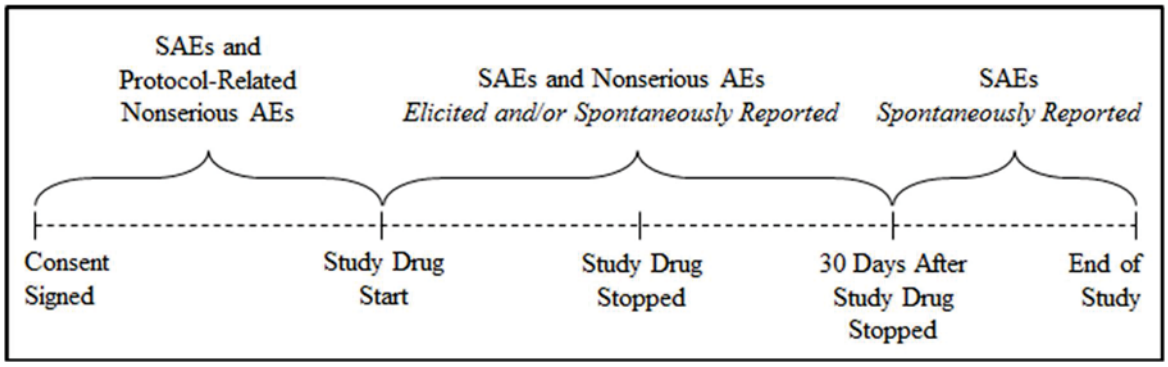
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All serious adverse events as well as protocol-related nonserious adverse events (e.g., infection at liver biopsy site) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days following discontinuation of study treatment has elapsed, all adverse events will be collected, whether solicited or spontaneously reported by the subject. After 30 days following completion of study treatment and throughout the Post-Treatment Period, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected).

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the

electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Antiviral Safety Team at:

[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Email: [redacted]

For any subject safety concerns, please contact the physician listed below:

[redacted]

[redacted]
Infectious Disease Development
1500 Seaport Blvd, Suite 289H
Redwood City, CA 94063

Telephone Contact Information:
Office: [redacted]
Mobile:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: [redacted]

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming 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 5.4.1). If a subject is discontinued, the subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

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 end of treatment.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the investigator. All adverse events 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 "National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4" is to be used in the grading of adverse events and laboratory abnormalities, which is available on the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Specific toxicity management guidelines apply to the instances of increases in ALT (Section 6.1.7.1).

6.1.7.1 Management of Increases in ALT

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 the hepatic questionnaire.
- Evaluate for an alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain Anti-HAV IgM, Anti-HAV Total, Anti-HBc IgM, Anti-HBc Total, Anti-HBs, HBV DNA, HBsAG, Anti-HEV IgM, Anti-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 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 liver failure.
  - At the discretion of the investigator.

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

6.1.8 Collection of Data Regarding Known AIDS-Defining Conditions

HIV infected subjects participating in clinical trials may develop infections typically associated with AIDS. A list of these known AIDS-Defining Conditions (ADC) is presented in Appendix E. The events listed in Appendix E will be summarized as HIV-related events, not as adverse events. These ADCs will be collected from the time of study drug administration until 30 days following discontinuation of study drug.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) 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.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 1 business day of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. 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 adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitors:

Primary Contact:

[redacted]
AbbVie
[redacted]
North Chicago, IL 60064
USA

Office: [redacted]
Email:

Alternate Contact:

[redacted]
AbbVie
[redacted]
North Chicago, IL 60064
USA

Office: [redacted]
Cell:
Email:

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

An interim data lock may occur in the study if interim study results are needed for regulatory interaction purposes. No changes to the study design or treatment of subjects would result from this interim analysis, so adjustment for multiplicity is needed.

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

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

Safety and demographic analyses will be performed on all subjects who receive at least one dose of study drug.

Efficacy analyses will be performed on the intention-to-treat (ITT) population defined as all enrolled subjects who receive at least one dose of study drug, unless otherwise specified.

Sensitivity analyses of the primary efficacy endpoint, when applicable, will be performed on the intention-to-treat population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-VF).

No data will be imputed for any efficacy or safety analysis except for analyses of SVR endpoints (HCV RNA data). HCV RNA values will be selected for the analyses of all SVR endpoints (e.g., SVR_4 and SVR_{12}) based on defined visit windows. A backward imputation method will be used to impute missing responses for SVR analyses.

8.1.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all treated subjects by Arm (A and B), and overall. Demographics include age, weight, height, body mass index (BMI), gender, race, and ethnicity. Baseline characteristics include HCV genotype subtype, CKD stage, baseline HCV RNA level, fibrosis stage (F2, F3, F4), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no), use of stable opiate substitution, history of diabetes, baseline metabolic syndrome, history of bleeding disorders, history of depression or bipolar disorder, history of cardiovascular disease, geographic region, and HIV coinfection status.

All the demographics and baseline characteristics will be summarized as continuous or categorical variables where appropriate. Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and BMI), and the number and percentage of subjects will be presented for categorical variables (e.g., sex and race).

Treatment compliance to study drug will be calculated based on the percentage of tablets taken relative to the total tablets expected to be taken. A subject is considered to be compliant if the percentage is between 80% and 120%. Compliance will be calculated for each subject and summarized with the mean, median, standard deviation, minimum, and maximum. The percentage of compliant subjects will be summarized.

8.1.2 Efficacy

All efficacy analyses will be performed on the ITT population, unless otherwise specified.

The efficacy analyses will be performed across all treatment durations and genotypes.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. The notation "HCV RNA < LLOQ" is used to represent all HCV RNA values

< 15 IU/mL, regardless of whether the HCV RNA is detectable or not. HCV RNA ≥ LLOQ are all quantifiable values.

8.1.2.1 Primary Efficacy Endpoints

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) within all genotypes (GT1 – 6 subjects) will be analyzed on combined treatment groups. The primary endpoint will be analyzed based on intention to treat (ITT) population. The number and percentage of subjects achieving SVR_{12} will be summarized with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless the number of SVR_{12} non-responders is less than 5, in which case the Wilson's score method will be used for the confidence interval instead.

A summary of reason for SVR_{12} non-response (e.g., OTVF, relapse, other) will be provided.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The percentage of subjects with HCV OTVF (defined as confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and
- The percentage of subjects with post-treatment HCV virologic relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment; excluding subjects who have been shown to be reinfected)

For the analysis of post-treatment HCV virologic relapse, completion of treatment is defined as any subject with study drug duration of 52 days and 77 days or greater for subjects allocated to treatment durations of 8 weeks and 12 weeks, respectively.

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

8.1.2.3 Sensitivity Analysis

As sensitivity analyses, the number and percentage of subjects in the mITT-VF population achieving SVR_{12}, as applicable, will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution and a two-sided 95% confidence interval using the Wilson's score method.

The two-sided 95% confidence interval using Wilson's score method will also be calculated as a sensitivity analysis for the primary endpoint of SVR_{12} based on ITT population.

8.1.2.4 Subgroup Analysis

The subgroup analyses will be performed based on the combined treatment groups. The percentage of subjects with SVR_{12} will be calculated, as will the corresponding two sided 95% Wilson score intervals, for the following subgroups:

- HCV genotype and available subtype
- Sex
- Age
- Race
- Baseline HCV RNA level
- Baseline fibrosis stage
- Baseline cirrhosis status
- Baseline platelet count
- Baseline albumin
- Chronic Kidney Disease Stage
- HIV co-infection
- HIV ART regimen (for HIV coinfected)

- Baseline CD4+ count (for HIV coinfected)

Further details about subgroup analysis will be described in the statistical analysis plan.

8.1.2.5 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized by genotype:

- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of subjects who achieve SVR_4 4 weeks after the last actual dose of study drug (SVR_4);

The number and percentage of subjects meeting each additional efficacy endpoint will be summarized along with a two-sided 95% confidence interval using the Wilson's score interval.

8.1.3 Patient Reported Outcomes

The handling of missing data for patient reported outcomes (PROs) will be as follows. If a respondent answers at least 50% of the items in a multi-item scale of the SF-36v2, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing. The Mental and Physical Component Summary measures will not be computed if any domain is missing. For TSQM, if a respondent answers at least 2 items in the 3 item scales of Side Effects or Effectiveness, the missing items will be imputed with the average score of the answered items in the same scale. For EQ-5D-3L, health state index and VAS scores no imputation will be performed for missing items.

The mean change from baseline to each applicable post-baseline timepoint in the SF-36v2 Mental Component Summary (SF-36-MCS) and Physical Component Summary

(SF-36-PCS) scores; EQ5D-3L health state index and VAS score will be summarized descriptively at each applicable visit and for change from baseline to each applicable visit.

For each of these scores, mean change from Baseline to Final Treatment Visit and from Baseline to Post-Treatment Week 12 will be summarized using an analysis of covariance (ANCOVA) model with baseline score as a covariate.

The following analyses of patient reported outcomes (PROs) also will be performed:

- Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable timepoint of greater than or equal to 3 points in the SF-36 MCS and PCS;
- Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable timepoint of greater than or equal to 5 points in the SF-36 MCS and PCS;
- Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable timepoint of greater than or equal to 5 points in the SF-36 domain scores;

TSQM Effectiveness, Side Effects, Convenience, and Global Satisfaction scores will be summarized descriptively at each applicable visit.

Additional analyses of PROs will be performed as useful and appropriate.

8.1.4 HCV Resistance Analyses

For all subjects with an available sample, full length NS3/4A or NS5A from baseline samples will be sequenced by NGS. For subjects who experience virologic failure (OTVF or post-treatment relapse), full length NS3/4A and NS5A genes from the first available sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS. An appropriate subtype specific prototypic reference sequence will be used for comparison with sequences from samples. Subjects treated with study drug who do not achieve SVR_{12} due to reasons other than virologic failure but have a time point with

HCV RNA ≥ 1000 IU/mL after treatment discontinuation, will have the sample at that time point sequenced.

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore, if the HCV RNA level at the time of HCV virologic failure or treatment discontinuation is < 1000 IU/mL, the sample closest in time after HCV virologic failure/treatment discontinuation with an HCV RNA level ≥ 1000 IU/mL will be used.

The following definitions will be used in the resistance analyses:

- Baseline polymorphism: a polymorphism by NGS in a baseline sample (≥ 2% or ≥ 15% prevalence within a subject's viral population depending on polymorphism frequency threshold utilized) that was not present in the appropriate prototypic reference amino acid sequence for a given DAA target (NS3/4A or NS5A).
- Polymorphism/substitution at a signature amino acid position: polymorphism (relative to reference) present in a baseline sample or substitution (relative to baseline) present in a post-baseline sample at a signature amino acid position.
- Post-baseline substitution: an amino acid substitution in a post-baseline time point sample that was not detected at baseline (< 2%) in the subject and is detectable in ≥ 2% of the sequences from the post-baseline sample.
- Enriched polymorphism: polymorphism present in both the baseline and a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post-baseline % – baseline %) ≥ 20].
- Treatment-emergent substitution by NGS: A post-baseline substitution or an enriched polymorphism detected by NGS.

Analysis 1: The following analyses will be provided for all subjects, separated by HCV subtype:

- A listing of all baseline polymorphisms (2% detection threshold) at signature resistance-associated amino acid positions for each DAA target (NS3/4A and NS5A).
- A listing of all baseline polymorphisms (15% detection threshold) at non-signature resistance-associated amino acid positions for each DAA target (NS3/4A and NS5A) for subjects who experience virologic failure.
- The number and percentage of subjects with baseline polymorphisms at signature amino acid positions at detection thresholds of 2% and 15%.

Analysis 2: The impact of baseline polymorphisms on treatment outcome will be assessed as follows: for each polymorphism, the SVR_{12} rate will be calculated for subjects with and without the polymorphism and the 2 rates will be compared. Analysis will be grouped by HCV subtype and DAA target (NS3/4A or NS5A).

The following will be included in the analyses of impact of baseline polymorphisms on treatment outcome:

- For each signature amino acid position, presence of any polymorphism at that position (vs no polymorphism at that position), using detection thresholds of both 2% and 15%.
- Each individual polymorphism at each signature amino acid position (vs not that polymorphism) using detection thresholds of 2% and 15%.
- Polymorphisms at each non-signature amino acid position at a detection threshold of 15%.

Analysis 3: The following analyses will be performed for subjects who do not achieve SVR_{12} and who have post-baseline resistance data available:

- Listings by subject of all treatment-emergent substitutions relative to the baseline amino acid sequences will be provided for each DAA target (NS3/4A and NS5A).

- Listings by subject and time point of all post-baseline substitutions at signature amino acid position relative to the baseline amino acid sequence will be provided for each DAA target (NS3/4A and NS5A).

HCV Genotype/Subtype

Phylogenetic analysis will be conducted on HCV NS3/4A and/or NS5A sequence from baseline samples from all subjects in order to accurately determine genotype/subtype. If the phylogenetic analysis is not available, then the result from Sanger sequencing of a region of NS5B by AbbVie or by the Central laboratory will be used to determine the subject's HCV genotype/subtype, if available. Finally, if neither the phylogenetic analysis result nor the Sanger sequencing assay results is available, then the Inno-LIPA assay results from the Central laboratory will be used to categorize the subject. This final HCV genotype subtype will be used in efficacy subgroup analyses.

8.1.5 HIV Resistance Analyses

If a subject develops a confirmed, plasma HIV RNA level ≥ 500 copies/mL after starting the study, the subject's HIV PR, RT, and/or IN sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assays. The number of subjects who demonstrate HIV genotypic resistance and the genotypic resistance mutations detected in the samples obtained from these subjects will be tabulated and summarized. Resistance will be defined as described by the IAS-USA Panel.[18]

8.1.6 Safety

Safety summaries will be provided by the treatment arm (i.e., study drug duration assigned by cirrhosis status) and overall. All subjects who receive at least one dose of study drug will be included in the safety analyses.

8.1.6.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term. The tabulation of the number of subjects with treatment-emergent adverse events by severity grade (Grades 1 – 5) and relationship to each study drug will also be provided. Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe grade for the severity grade table and the most related for the relationship to study drug tables. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC.

Additional analyses will be described in the statistical analysis plan.

8.1.6.2 Clinical Laboratory Data

Clinical laboratory tests will be summarized at each visit. The baseline value will be the last non-missing measurement prior to the initial dose of study drug. Mean changes from baseline to each post-baseline visit, including Final Treatment Visit, will be summarized descriptively. Changes from baseline to maximum post-baseline CTCAE grade of laboratory values will also be summarized.

8.1.6.3 Vital Signs Data

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each post-baseline visit, including Final Treatment Visit, will be summarized descriptively. The number and percentage of subjects with post-baseline values meeting pre-defined criteria for Potentially Clinically Significant (PCS) vital signs values will be summarized.

8.1.6.4 HCV/HIV Co-Infection

The following additional safety data will be summarized and analyzed for subjects with HCV/HIV co-infection overall and in each treatment arm:

- The percentage of subjects with plasma HIV RNA suppression at the end of treatment and at Post-Treatment Week 12 using the FDA Snapshot Algorithm;
- The number and percentage of subjects with plasma HIV RNA < 20 copies/mL at each applicable time point;
- Change from baseline in CD4+ T-cell count (absolute and percent) to each applicable post-baseline time point;
- Change from baseline in lymphocytes (count and percentage) and CD8+ T-cell counts (absolute and percent) to each applicable post-baseline time point;
- The listing of subjects with a plasma HIV RNA value ≥ 200 copies/mL at any baseline or post-baseline visit during the study.

The analysis of change from baseline in CD4+ T-cell count (absolute and percent), lymphocytes (count and percentage) and CD8+ T-cell counts (absolute and percent) will report the mean and median values at baseline and at each applicable post-baseline visit, as well as N, mean, median, standard deviation (SD), minimum and maximum values for the change from baseline overall and within each treatment arm.

8.1.7 Pharmacokinetic and Exposure-Response Analyses

Plasma concentrations of GLE, PIB, and their possible metabolites, if measured, will be tabulated for each subject and group. Summary statistics will be computed for each time and visit.

Plasma concentration data from this study may be combined with data from other studies and analyzed using the following general methodology:

Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (version VII, or higher version). The

structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. Apparent oral clearance (CL/F) and apparent volume of distribution (V/F) of the PK analytes will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis. Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM.

Relationship between exposure (noncompartmental or population pharmacokinetic model based values of concentrations over time, AUC, C_{trough} or some other appropriate measure of exposure) and clinical observations (antiviral activity or virologic end points, such as SVR_{12} response) may be explored, if appropriate.

Exposure-response relationships for primary and secondary efficacy variables and/or some safety measures of interest may also be explored. Exposure response relationships will utilize a logistic regression analysis and/or a semi-mechanistic viral dynamic model. Additionally, relationship between exposure and safety endpoints of interest may also be explored. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

It is anticipated that a total of approximately 100 HCV infected treatment naïve GT1 – 6 subjects will be enrolled in this study. No formal hypothesis is being tested. If the observed SVR_{12} rate in this study is 97% among 100 HCV GT1 – 6 treatment naive subjects, then the half-width of 2-sided 95% normal approximation interval is 3.3%.

8.3 Randomization Methods

This study is not randomized. Eligible subjects will be allocated to a treatment arm according to their cirrhosis status (presence/absence).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific, and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information, and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain, and archive study essential documents according to ICH GCP and all other applicable regulatory requirements.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on 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 clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

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

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

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

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the

investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

Any research that may be done using optional exploratory research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from optional exploratory research may be provided to investigators and used in scientific publications or presented at medical conventions. Optional exploratory research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the

investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

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

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for GLE/PIB Fixed-Dose Combination.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection

Protocol Date: 08 November 2017

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
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., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
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 investigation and all 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. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Pharmacokinetics
		Clinical
		Clinical
		Clinical
		Statistics
		Bioanalysis
		Clinical

Appendix C. Study Activities – Treatment Period

Activity	Screening	Day 1[a]	Wk 4	Wk 8 (Arm B Only)	EOT (Arm A and Arm B) or Premature D/C from Treatment[b]
Informed Consent[c]	X				
Dispense/Review Study Drug Dosing Card		X (Dispense only)	X	X	X (Review only)
Medical History[d]	X	X			
Physical Exam[e]	X	X			X
Vital Signs, Weight, Height[f]	X	X	X	X	X
ECG	X				
Hematology/Chemistry[g]/Coagulation Panel	X	X	X	X	X
Pregnancy Test (serum [s] urine [u])[h]	X (s)	X (u)	X (u)	X (u)	X (u)
Anti-HCV Ab, Anti-HIV Ab	X				
Hepatitis B Panel	X				
HCV Genotype and Subgenotype	X				
FibroTest or FibroScan® or Liver Biopsy[i]	X				
Concomitant Medication Assessment	X	X	X	X	X
Adverse Event Assessment[k]	X	X	X	X	X
Study Drug Dispensed		X	X	X[k]	
HCV RNA Samples	X	X	X	X	X
Study Drug Accountability and Review of Study Drug Adherence			X	X	X[l]
HCV Resistance Sample		X	X	X	X

Activity	Screening	Day 1[a]	Wk 4	Wk 8 (Arm B Only)	EOT (Arm A and Arm B) or Premature D/C from Treatment[b]
Pharmacokinetic Samples[m]			X	X	X
Child-Pugh Score (subjects with compensated cirrhosis only)[n]	X				X
Clinical Assessment of Hepatic Decompensation (subjects with compensated cirrhosis only)[n]		X			
HCC Screening Liver ultrasound (subjects with compensated cirrhosis only)[n]	X				
Patient Reported Outcomes Instruments (PROs)[o]		X			X
Flow cytometry sample[p]	X	X			X
HIV RNA[p]	X	X	X	X	X

Wk = Week; EOT = End of treatment; D/C = Discontinuation

* The EOT visit can be at Week 8 or 12 in accordance with treatment duration as described in Section 5.1.

a. All procedures to be performed prior to first dose.

b. Subjects who prematurely discontinue during the Treatment Period should return to the site to complete the Premature D/C Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy).

c. Subjects need to sign an IRB/IEC approved informed consent for the study (prior to performing any Screening or study-specific procedures).

d. A complete medical history will be taken at Screening and will be updated at the Study Day 1 Visit.

e. A symptom-directed physical examination may be performed at any other visit, when necessary. Any significant physical examination findings after the first dose will be recorded as adverse events.

f. Height will be measured at the Screening Visit only.

g. Blood samples for serum chemistry tests should be collected following a minimum 8-hour fast prior to study drug intake (with the exception of the Screening Visit, which may be non-fasting).

h. Pregnancy testing is not required for women not of childbearing potential as defined in Section 5.2.4.

i. For subjects who have not had a qualifying liver biopsy within the previous 24 months for subjects without cirrhosis or at any time for subjects with compensated cirrhosis) or a qualifying FibroScan® within the previous 6 months for subjects without cirrhosis or at any time prior to Screening for subjects with compensated cirrhosis).

j. Subjects with a historical negative Liver Ultrasound, CT or MRI (within 3 months prior to screening) are not required to have a screening Liver Ultrasound performed. If additional Liver Ultrasound testing is required it should be completed as an unscheduled visit. A positive ultrasound result suspicious of HCC will be confirmed with CT scan or MRI. A liver ultrasound should be performed at the end of treatment visit if it has been 6 months or more since the historical evaluation.

k. See specific information regarding adverse event collection in Section 6.1.1.1.

l. Dispensation at Week 8 and Study Drug Accountability at Week 12 are only applicable to Arm B. Subjects should bring all study drug to every visit for the site to review adherence. However, the site will record the number of tablets returned only at the Study Drug Accountability Visits at Weeks 4, 8, 12 (if applicable) or Premature D/C.

m. PK samples will be collected at each scheduled study visit. Detail regarding timing of samples is provided in Section 5.3.2.1.

n. Child-Pugh Score, Clinical Assessment of Hepatic Decompensation, and Liver Ultrasound are only performed for subjects in Arm B (compensated cirrhotic) as described in Section 5.3.1.1.

o. PROs should be administered before any study procedures in the order listed in Section 5.3.1.1. TSQM will be the only PRO not administered at Day 1.

p. For HCV/HIV co-infected subjects.

Appendix D. Study Activities – Post-Treatment (PT) Period

Activity	PT Wk 4	PT Wk 12	PT D/C[a]
Vital Signs and Weight	X	X	X
Hematology/Chemistry/Coagulation Panel	X	X[b]	X[c]
Pregnancy Test (urine)[d]	X (u)		X (u)[c]
Concomitant Medication Assessment[e]	X	X[e]	X[e]
Child-Pugh Score (subjects with compensated cirrhosis only)		X	X
Adverse Event Assessment[f]	X[f]	X[g]	X[g]
HCV RNA Samples	X	X	X
HCV Resistance Sample	X	X	X
Patient Reported Outcomes Instruments (PROs)[h]		X	X
Flow cytometry sample[h]	X	X	
HIV RNA[i]	X	X	
HCC Screening: Liver Ultrasound[j]		X	X

Wk = Week; PT D/C = Post-Treatment Discontinuation

a. Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C Visit procedures.

b. Chemistry/Coagulation panel will only be collected at PT Wk 12 for subjects in Arm B (compensated cirrhosis).

c. Hematology/Chemistry/Coagulation Panel and Pregnancy Test are not required at PT Wk 12, but only at PT D/C if subject discontinues prior to PT Wk 4.

d. Women of childbearing potential do not require pregnancy testing beyond PTW4. Pregnancy testing will be performed at PT D/C visit only if the subject discontinues prior to PTW4. Pregnancy testing in PT Period is not required for females of non-childbearing potential as defined in Section 5.2.4.

e. Only medications taken for SAEs and treatment of HCV will be collected after 30 days post-dosing.

f. Nonserious AEs and all SAEs will be collected until 30 days post dosing. All spontaneously reported SAEs will be collected thereafter. See specific information regarding adverse event collection in Section 6.1.4.

g. Only SAEs will be collected thereafter as described in Section 6.1.4.

h. PROs should be administered before any study procedures in the order listed in Section 5.3.1.1.

i. For HCV/HIV co-infected subjects.

j. HCC Screening Liver Ultrasound performed only subjects in Arm B (compensated cirrhosis) as described in Section 5.3.1.1.

Note: Day 1 of the Post-Treatment Period will be defined as the day after the last dose of study drug.

Appendix E. List of AIDS-Defining Conditions

Collection of data regarding known AIDS-Defining Conditions is covered in Section 6.1.8.

AIDS-Defining Conditions:

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus†
- Cervical cancer, invasive§
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age > 1 month
- Cytomegalovirus retinitis (with loss of vision)†
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (> 1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi sarcoma†
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*,†
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary†

- Mycobacterium tuberculosis of any site, pulmonary,[†,§] disseminated,[†] or extrapulmonary[†]
- Mycobacterium, other species or unidentified species, disseminated[†] or extrapulmonary[†]
- Pneumocystis jirovecii pneumonia[†]
- Pneumonia, recurrent[†,§]
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age > 1 month[†]
- Wasting syndrome attributed to HIV

* Only among children aged < 13 years. (CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43[No. RR-12].)

† Condition that might be diagnosed presumptively.

§ Only among adults and adolescents aged > 13 years. (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41[No. RR-17].)

Cross reference: Morbidity and Mortality Weekly Report (MMWR). AIDS Defining Conditions. 2008. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2 htm.

Appendix F. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.0 Title Page
"Sponsor/Emergency Contact:"
Add:

Emergency 24 hour Number: +1 973-784-6402

Section 1.1 Synopsis
Subsection Objective:
Second bullet previously read:

The secondary objectives are to assess efficacy of GLE/PIB by hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis by evaluating the percentages of subjects with HCV on-treatment virologic failure and HCV virologic relapse across treatment durations and genotypes.

Has been changed to read:

The secondary objectives are to assess efficacy of GLE/PIB by hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis by evaluating the percentages of subjects with HCV on-treatment virologic failure (OTVF) and HCV virologic relapse across treatment durations and genotypes.

Section 1.1 Synopsis
Subsection Study Sites:
Previously read:

Approximately 12

Has been changed to read:

Approximately 14

Section 1.1 Synopsis
Subsection Statistical Methods:
Heading "Efficacy:"
First paragraph, third, fourth and fifth sentence previously read:

The number and percentage of subjects achieving SVR_{12} will be summarized with a two-sided 95% confidence interval. If the SVR_{12} is less than 100%, then the normal approximation for the binomial distribution will be used as a confidence interval. If the SVR_{12} rate is 100%, the Wilson's score method will be used to calculate the confidence interval.

Has been changed to read:

The number and percentage of subjects achieving SVR_{12} will be summarized with a two-sided 95% confidence interval based on the normal approximation of the binomial distribution unless the number of SVR_{12} non-responders is less than 5, in which case the Wilson's score method will be used to calculate the confidence interval.

Section 1.1 Synopsis
Subsection Statistical Methods:
Heading "Efficacy:"
First bullet previously read:

The percentage of subjects with on-treatment HCV virologic failure

Has been changed to read:

The percentage of subjects with OTVF.

Section 1.1 Synopsis
Subsection Statistical Methods:
Heading "PROs:"
Previously read:

Change from baseline to each applicable visit in the patient reported outcome summary measures will be summarized.

Has been changed to read:

Change from baseline to each applicable visit in the patient reported outcome summary measures for SF-36 and EQ-5D-3L will be summarized. Summary measures at each applicable visit will be summarized for the TSQM.

Section 1.3 List of Abbreviations and Definition of Terms
Add:

ADC AIDS-Defining Conditions

OTVF On-treatment virologic failure

Section 4.2 Secondary Objectives
First bullet previously read:

The percentages of subjects with HCV on-treatment virologic failure;

Has been changed to read:

The percentages of subjects with HCV on-treatment virologic failure (OTVF);

Section 5.2.1 Inclusion Criteria
Criterion 3, first paragraph previously read:

Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine or serum pregnancy test at Study Day 1.

Has been changed to read:

Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.

Section 5.2.2 Exclusion Criteria
Criterion 6, first sentence previously read:

Any current or past clinical evidence of Child-Pugh B or C classification or clinical history, including on Day 1 prior to dose, of liver decompensation including hepatic

encephalopathy or variceal bleeding, radiographic evidence of small ascites, or empiric use of lactulose/rifaximin.

Has been changed to read:

Any current or past clinical evidence of Child-Pugh B or C classification (score of > 6) or clinical history of liver decompensation including ascites on physical exam, including hepatic encephalopathy or variceal bleeding.

Section 5.2.2 Exclusion Criteria
Criterion 12 previously read:

Treatment for an AIDS-associated opportunistic infection (OI) (Appendix E) within 6 months of Screening.

Has been changed to read:

Treatment for an AIDS-Defining Conditions (ADC) (Appendix E) within 6 months of Screening.

Section 5.2.3.4 Prohibited Therapy
First paragraph previously read:

Subjects must be able and willing to safely discontinue any prohibited medications or supplements listed in Table 4 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. For medications contraindicated with ABT-493/ABT-530 (glecapravir/pibrentasvir), refer to the recommended prescribing information section of the approval local product label where the regimen has received marketing authorization. If locally approved labels are not available, refer to Table 4.

Has been changed to read:

Medications or supplements prohibited to be administered with ABT-493/ABT-530 are listed in Table 4. For subjects in the study in countries where ABT-493/ABT-530 (glecapravir/pibrentasvir) has received marketing authorization, any medications in the

local label that are contraindicated to be administered with ABT-493/ABT-530 (glecapravir/pibrentasvir) are also considered to be prohibited medications. Subjects must be able to safely discontinue any prohibited medications or supplements 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 drugs.

Table 4. Prohibited Medications and Supplements
Second row
Add:

efavirenz,

Table 4. Prohibited Medications and Supplements
Table note "*" previously read:

Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with study drugs. Subjects receiving these statins should either switch to pravastatin or rosuvastatin prior to the first dose of study drugs or may interrupt statin therapy throughout the treatment period 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 drugs.

Has been changed to read:

Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drug. After signing the informed consent form, 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) 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 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 either 1) reduce or limit the

pravastatin or rosuvastatin dose in accordance with the ABT-493/ABT-530 product label (if approved in the country); or 2) reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drug if ABT-493/ABT-530 is not yet approved in the country.

Section 5.2.3.4 Prohibited Therapy
Second paragraph previously read:

Use of ethinyl estradiol containing oral contraceptives with GLE/PIB was associated with ALT increases in some healthy female subjects. Hormonal contraceptives (including oral, topical [including vaginal rings], injectable, or implantable varieties) containing ethinyl estradiol may not be used from 14 days prior to the first dose of GLE/PIB until 14 days after the end of GLE/PIB dosing. Progestin-only contraceptives such as those containing norethindrone, desogestrel, or levonorgestrel, without ethinyl estradiol, may be used with GLE/PIB. Post-menopausal hormone replacement therapy, i.e., estradiol, esterified or conjugated estrogens, as long as they do not contain ethinyl estradiol, may be used with GLE/PIB at the discretion of the Investigator.

Has been changed to read:

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

Section 5.3.1.1 Study Procedures
Subsection <u>Clinical Laboratory Tests</u>
Fourth paragraph, address previously read:

Covance
8211 SciCor Drive
Indianapolis, IN 46214 USA
(For sites in North America)

Has been changed to read:

Covance
8211 SciCor Drive
Indianapolis, IN 46214 USA

Section 5.3.1.1 Study Procedures
Subsection Pregnancy Testing
First bullet previously read:

WOCBP must have a negative serum pregnancy test result at Screening, and a negative serum or urine pregnancy test at Study Day 1.

Has been changed to read:

WOCBP must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.

Section 5.3.1.1 Study Procedures
Subsection Hepatocellular Carcinoma Screening: Liver Ultrasound
Previously read:

In order to monitor for the presence of hepatocellular carcinoma (HCC), an ultrasound of the liver will be performed as indicated in Appendix C for subjects with compensated cirrhosis only. Subjects with compensated cirrhosis who do not have a historical qualifying liver ultrasound, CT, or MRI within the past 3 months will have an ultrasound performed during Screening. A positive ultrasound result suspicious for HCC will be confirmed with CT scan or MRI during Screening. Suspicious ultrasound lesions confirmed by CT or MRI are exclusionary.

Has been changed to read:

HCC screening will be required as a protocol-specified study procedure only at the Screening Visit and at the last Post-Treatment Study Visit, as indicated in Appendix C and Appendix D, for subjects with compensated cirrhosis only. In-between those visits, HCC screening should be performed according to standard of care.

At the Screening Visit and at the last Post-Treatment Study Visit, subjects with compensated cirrhosis will be required to undergo a liver ultrasound to screen for HCC, unless the subject has a historical liver ultrasound, CT scan or MRI performed for HCC screening within 3 months prior to those visits, in which case the result of the historical ultrasound, CT scan or MRI will be used as the result for the Study Visit assessment. A positive ultrasound result suspicious of HCC will be confirmed with CT scan or MRI. Alternate methods of screening for HCC (i.e., CT scan or MRI) at a study visit should be discussed with the study designated physician.

Section 5.3.1.1 Study Procedures
Subsection Patient Reported Outcomes (PRO) Instruments (Questionnaires)
Heading "EuroQol-5 Dimensions-3 Level (EQ-5D-3L)"
Last paragraph
Add: new last sentence

The TSQM is the only PRO assessment that will not be performed at Day 1.

Section 5.3.3 Efficacy Variables
Previously read:

Virologic response will be assessed by plasma HCV RNA levels in IU/mL at various time points from Day 1 through 24 weeks after completion or discontinuation of the study.

Has been changed to read:

Virologic response will be assessed by plasma HCV RNA levels in IU/mL at various time points from Day 1 through 12 weeks after completion or discontinuation of study drug.

Section 5.3.3.2 Secondary Variables
First bullet previously read:

The percentage of subjects with HCV on-treatment virologic failure.

Has been changed to read:

The percentage of subjects with HCV OTVF.

Section 6.0 Complaints
Last paragraph, last sentence previously read:

For product complaints, please refer to Section 6.1.8.

Has been changed to read:

For product complaints, please refer to Section 6.2.

Section 6.1.7.1 Management of Increases in ALT
First paragraph, second bullet previously read:

Evaluate for an alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain Anti-HAV IgM, Anti-HAV IgG, Anti-HBc IgM, Anti-HBc Total, Anti-HBs, HBV DNA, HBsAG, Anti-HEV IgM, Anti-HEV IgG and HEV RNA, and other additional tests, as appropriate.

Has been changed to read:

Evaluate for an alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain Anti-HAV IgM, Anti-HAV Total, Anti-HBc IgM, Anti-HBc Total, Anti-HBs, HBV DNA, HBsAG, Anti-HEV IgM, Anti-HEV IgG and HEV RNA, and other additional tests, as appropriate.

Section 6.1.8 Collection of Data Regarding Known AIDS-Associated Opportunistic Infections
Section title and text previously read:

6.1.8 Collection of Data Regarding Known AIDS-Associated Opportunistic Infections

HIV infected subjects participating in clinical trials may develop infections typically associated with AIDS. A list of these known AIDS-associated opportunistic infections (OI) is presented in Appendix E. The events listed in Appendix E will be summarized as HIV-related events, not as adverse events. These OIs will be collected from the time of study drug administration until 30 days following discontinuation of study drug.

Has been changed to read:

6.1.8 Collection of Data Regarding Known AIDS-Defining Conditions

HIV infected subjects participating in clinical trials may develop infections typically associated with AIDS. A list of these known AIDS-Defining Conditions (ADC) is presented in Appendix E. The events listed in Appendix E will be summarized as HIV-related events, not as adverse events. These ADCs will be collected from the time of study drug administration until 30 days following discontinuation of study drug.

Section 6.2.2 Reporting
First paragraph, first sentence previously read:

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form.

Has been changed to read:

Product Complaints concerning the investigational product must be reported to the Sponsor within 1 business day of the study site's knowledge of the event via the Product Complaint form.

Section 7.0 Protocol Deviations
"Alternate Contact:" previously read:

[redacted]
AbbVie
[redacted]
North Chicago, IL 60064
USA

Office: [redacted]
Email: [redacted]

Has been changed to read:

[redacted]
AbbVie
[redacted]
North Chicago, IL 60064
USA

Office:
Cell:
Email: [redacted]

Section 8.1 Statistical and Analytical Plans
First paragraph, last sentence previously read:

No changes to the study design or treatment of subjects would result from this interim analyses, so adjustment for multiplicity is needed.

Has been changed to read:

No changes to the study design or treatment of subjects would result from this interim analysis, so adjustment for multiplicity is needed.

Section 8.1.1 Demographics and Baseline Characteristics
First paragraph, last sentence previously read:

Baseline characteristics include HCV genotype subtype, prior HCV treatment history, CKD stage, baseline HCV RNA level, fibrosis stage (F2, F3, F4), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no), use of stable opiate substitution, history of diabetes, baseline metabolic syndrome, history of bleeding disorders, history of depression or bipolar disorder, history of cardiovascular disease, geographic region, and HIV coinfection status.

Has been changed to read:

Baseline characteristics include HCV genotype subtype, CKD stage, baseline HCV RNA level, fibrosis stage (F2, F3, F4), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no), use of stable opiate substitution, history of diabetes, baseline metabolic syndrome, history of bleeding disorders, history of depression or bipolar disorder, history of cardiovascular disease, geographic region, and HIV coinfection status.

Section 8.1.2.1 Primary Efficacy Endpoints
Third, fourth and fifth sentence previously read:

The number and percentage of subjects achieving SVR_{12} will be summarized with a two-sided 95% confidence interval. If the SVR_{12} is less than 100%, then the normal approximation of the binomial distribution will be used as a confidence interval. If the SVR_{12} rate is 100%, the Wilson's score method will be used to calculate the confidence interval.

Has been changed to read:

The number and percentage of subjects achieving SVR_{12} will be summarized with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless the number of SVR_{12} non-responders is less than 5, in which case the Wilson's score method will be used for the confidence interval instead.

A summary of reason for SVR_{12} non-response (e.g., OTVF, relapse, other) will be provided.

Section 8.1.2.2 Secondary Efficacy Endpoints
First bullet previously read:

The percentage of subjects with HCV on-treatment virologic failure (defined as confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA

≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and

Has been changed to read:

The percentage of subjects with HCV OTVF (defined as confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and

Section 8.1.2.2 Secondary Efficacy Endpoints
Last paragraph previously read:

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

Has been changed to read:

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

Section 8.1.2.5 Additional Efficacy Endpoints
Delete: last bullet

The percentage of subjects who relapse after achieving SVR_{12}.

Section 8.1.3 Patient Reported Outcomes
Second paragraph previously read:

The mean change from baseline to each applicable post-baseline timepoint in the SF-36v2 Mental Component Summary (SF-36-MCS) and Physical Component Summary (SF-36-PCS) scores; EQ5D-3L health state index and VAS score; TSQM Effectiveness, Side Effects, Convenience, and Global Satisfaction scores will be summarized descriptively at each applicable visit and for change from baseline to each applicable visit. For each of these scores, mean change from Baseline to Final Treatment Visit and from

Baseline to Post-Treatment Week 12 will be summarized using an analysis of covariance (ANCOVA) model with baseline score as a covariate.

Has been changed to read:

The mean change from baseline to each applicable post-baseline timepoint in the SF-36v2 Mental Component Summary (SF-36-MCS) and Physical Component Summary (SF-36-PCS) scores; EQ5D-3L health state index and VAS score will be summarized descriptively at each applicable visit and for change from baseline to each applicable visit.

For each of these scores, mean change from Baseline to Final Treatment Visit and from Baseline to Post-Treatment Week 12 will be summarized using an analysis of covariance (ANCOVA) model with baseline score as a covariate.

Section 8.1.3 Patient Reported Outcomes
Add: new sixth paragraph

TSQM Effectiveness, Side Effects, Convenience, and Global Satisfaction scores will be summarized descriptively at each applicable visit.

Section 8.1.4 HCV Resistance Analyses
Second sentence previously read:

For subjects who experience virologic failure (on-treatment virologic failure or post-treatment relapse), full length NS3/4A and NS5A genes from the first available sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS.

Has been changed to read:

For subjects who experience virologic failure (OTVF or post-treatment relapse), full length NS3/4A and NS5A genes from the first available sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS.

Section 9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Second paragraph, last sentence previously read:

The investigator will be required to submit, maintain, and archive study essential documents according to ICH GCP.

Has been changed to read:

The investigator will be required to submit, maintain, and archive study essential documents according to ICH GCP and all other applicable regulatory requirements.

Section 10.1 Source Documents
First paragraph
Add: new fourth and fifth sentence

The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

Section 13.0 Completion of the Study
Second paragraph, first sentence previously read:

The investigator must retain any records related to the study according to local requirements.

Has been changed to read:

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements.

Appendix B. List of Protocol Signatories

Previously read:

Name	Title	Functional Area
[redacted]		Pharmacokinetics
		Clinical
		Clinical
		Clinical
		Statistics
		Clinical
		Clinical Drug Supply Management

Has been changed to read:

Name	Title	Functional Area
[redacted]		Pharmacokinetics
		Clinical
		Clinical
		Clinical
		Statistics
		Bioanalysis
		Clinical

Appendix C. Study Activities – Treatment Period
Activity "Pregnancy Test (serum [s] urine [u])[h]," "Child-Pugh Score (subjects with compensated cirrhosis only)," "Clinical Assessment of Hepatic Decompensation (subjects with compensated cirrhosis only)" and "HCC Screening Liver ultrasound (subjects with compensated cirrhosis only)" previously read:

Activity	Screening	Day 1[a]	Wk 4	Wk 8 (Arm B Only)	EOT (Arm A and Arm B) or Premature D/C from Treatment[b]
Pregnancy Test (serum [s] urine [u])[h]	X (s)	X (u, s)	X (u)	X (u)	X (u)
Child-Pugh Score (subjects with compensated cirrhosis only)	X	X			X
Clinical Assessment of Hepatic Decompensation (subjects with compensated cirrhosis only)		X			
HCC Screening Liver ultrasound (subjects with compensated cirrhosis only)	X				

Has been changed to read:

Activity	Screening	Day 1[a]	Wk 4	Wk 8 (Arm B Only)	EOT (Arm A and Arm B) or Premature D/C from Treatment[b]
Pregnancy Test (serum [s] urine [u])[h]	X (s)	X (u)	X (u)	X (u)	X (u)
Child-Pugh Score (subjects with compensated cirrhosis only)[n]	X				X
Clinical Assessment of Hepatic Decompensation (subjects with compensated cirrhosis only)[n]		X			
HCC Screening Liver ultrasound (subjects with compensated cirrhosis only)[n]	X				

Appendix C. Study Activities – Treatment Period
Add: new table note "n."

Child-Pugh Score, Clinical Assessment of Hepatic Decompensation, and Liver Ultrasound are only performed for subjects in Arm B (compensated cirrhotic) as described in Section 5.3.1.1.

Appendix C. Study Activities – Treatment Period
Tablenote "o."
Add: new last sentence

TSQM will be the only PRO not administered at Day 1.

Appendix D. Study Activities – Post-Treatment (PT) Period
Previously read:

Activity	PT Wk 4	PT Wk 12	PT D/C[a]
Vital Signs and Weight	X	X	X
Hematology/Chemistry/Coagulation Panel	X		X[b]
Pregnancy Test (urine)[c]	X (u)		X (u)[b]
Concomitant Medication Assessment[d]	X	X[d]	X[d]
Child-Pugh Score (subjects with compensated cirrhosis only)		X	X
Adverse Event Assessment[e]	X[e]	X[f]	X[f]
HCV RNA Samples	X	X	X
HCV Resistance Sample	X	X	X
Patient Reported Outcomes Instruments (PROs)[g]		X	X
Flow cytometry sample[h]	X	X	
HIV RNA[h]	X	X	

Wk = Week; PT D/C = Post-Treatment Discontinuation

a. Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C Visit procedures.

b. Hematology/Chemistry /Coagulation Panel and Pregnancy Test are not required at PT Wk 12, but only at PT D/C if subject discontinues prior to PT Wk 4.

c. Women of childbearing potential do not require pregnancy testing beyond PTW4. Pregnancy testing will be performed at PT D/C visit only if the subject discontinues prior to PTW4. Pregnancy testing in PT Period is not required for females of non-childbearing potential as defined in Section 5.2.4.

d. Only medications taken for SAEs and treatment of HCV will be collected after 30 days post-dosing.

e. Nonserious AEs and all SAEs will be collected until 30 days post dosing. All spontaneously reported SAEs will be collected thereafter. See specific information regarding adverse event collection in Section 6.1.4.

f. Only SAEs will be collected thereafter as described in Section 6.1.4.

g. PROs should be administered before any study procedures in the order listed in Section 5.3.1.1.

h. For HCV/HIV co-infected subjects.

Note: Day 1 of the Post-Treatment Period will be defined as the day after the last dose of study drug.

Has been changed to read:

Activity	PT Wk 4	PT Wk 12	PT D/C[a]
Vital Signs and Weight	X	X	X
Hematology/Chemistry/Coagulation Panel	X	X[b]	X[c]
Pregnancy Test (urine)[d]	X (u)		X (u)[c]
Concomitant Medication Assessment[e]	X	X[e]	X[e]
Child-Pugh Score (subjects with compensated cirrhosis only)		X	X
Adverse Event Assessment[f]	X[f]	X[g]	X[g]
HCV RNA Samples	X	X	X
HCV Resistance Sample	X	X	X
Patient Reported Outcomes Instruments (PROs)[h]		X	X
Flow cytometry sample[h]	X	X	
HIV RNA[i]	X	X	
HCC Screening: Liver Ultrasound[j]		X	X

Wk = Week; PT D/C = Post-Treatment Discontinuation

a. Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C Visit procedures.

b. Chemistry/Coagulation panel will only be collected at PT Wk 12 for subjects in Arm B (compensated cirrhosis).

c. Hematology/Chemistry/Coagulation Panel and Pregnancy Test are not required at PT Wk 12, but only at PT D/C if subject discontinues prior to PT Wk 4.

d. Women of childbearing potential do not require pregnancy testing beyond PTW4. Pregnancy testing will be performed at PT D/C visit only if the subject discontinues prior to PTW4. Pregnancy testing in PT Period is not required for females of non-childbearing potential as defined in Section 5.2.4.

e. Only medications taken for SAEs and treatment of HCV will be collected after 30 days post-dosing.

f. Nonserious AEs and all SAEs will be collected until 30 days post dosing. All spontaneously reported SAEs will be collected thereafter. See specific information regarding adverse event collection in Section 6.1.4.

g. Only SAEs will be collected thereafter as described in Section 6.1.4.

h. PROs should be administered before any study procedures in the order listed in Section 5.3.1.1.

i. For HCV/HIV co-infected subjects.

j. HCC Screening Liver Ultrasound performed only subjects in Arm B (compensated cirrhosis) as described in Section 5.3.1.1.

Note: Day 1 of the Post-Treatment Period will be defined as the day after the last dose of study drug.

Appendix E. List of AIDS-Associated Opportunistic Infections
Appendix title and text previously read:

Appendix E. List of AIDS-Associated Opportunistic Infections

Collection of data regarding known AIDS-associated opportunistic infections is covered in Section 6.1.8.

AIDS-Defining Conditions:

- Aspergillosis
- Bartonellosis
- Candidiasis (*Bronchi; *Esophagus; *Lungs; Oropharyngeal [Thrush]; *Trachea; Vulvovaginal [Persistent, Frequent, or Poorly Responsive to Therapy])
- *Coccidioidomycosis
- *Cryptococcosis
- *Cryptosporidiosis
- Cytomegalovirus (*Retinitis; *Cytomegalovirus Disease [other than liver, spleen or nodes])
- Enteric infections, Recurrent (Bacterial)
- Herpes Simplex Virus (*Bronchitis; *Esophagitis; *Pneumonitis; *Chronic Ulcer(s) [> 1 month in duration])
- *Histoplasmosis
- Human Herpesvirus-8 Disease (Kaposi Sarcoma, Primary Effusion Lymphoma, Multicentric Castleman's Disease)
- Human Papilloma Virus Infections
- *Isosporiasis (Cystoisosporiasis)
- Microsporidiosis
- *Mycobacterium avium – Complex Disease (Disseminated)
- *Mycobacterium tuberculosis – Infection and Disease
- *Pneumonia

- *Pneumonia, recurrent bacterial (and/or other respiratory infections including sinusitis, bronchitis, otitis)
- *Progressive multifocal leukoencephalopathy (JC Virus Infection)
- Syphilis
- *Toxoplasma Gondii Encephalitis
- Varicella Zoster Virus Diseases

* AIDS-defining event as described by CDC Surveillance Case Definition of 1993.

Cross reference: Guidelines for Prevention and Treatment of Opportunistic Infections in HIV Infected Adults and Adolescents. Available from: http://aidsinfo nih.gov/guidelines.

Has been changed to read:

Appendix E. List of AIDS-Defining Conditions

Collection of data regarding known AIDS-Defining Conditions is covered in Section 6.1.8.

AIDS-Defining Conditions:

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus†
- Cervical cancer, invasive§
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age > 1 month
- Cytomegalovirus retinitis (with loss of vision)†
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (> 1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 month)
- Histoplasmosis, disseminated or extrapulmonary

- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi sarcoma†
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*,†
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary†
- Mycobacterium tuberculosis of any site, pulmonary,†,§ disseminated,† or extrapulmonary†
- Mycobacterium, other species or unidentified species, disseminated† or extrapulmonary†
- Pneumocystis jirovecii pneumonia†
- Pneumonia, recurrent†,§
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age > 1 month†
- Wasting syndrome attributed to HIV

* Only among children aged < 13 years. (CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43[No. RR-12].)

† Condition that might be diagnosed presumptively.

§ Only among adults and adolescents aged > 13 years. (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41[No. RR-17].)

Cross reference: Morbidity and Mortality Weekly Report (MMWR). AIDS Defining Conditions. 2008. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2 htm.

Document Approval

Study M16156 - A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection - Amendment 1 - 08Nov2017

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Signed by:	Date:	Meaning Of Signature:
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1.0 Title Page

Clinical Study Protocol M16-156

A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection

AbbVie Investigational Product:	Glecaprevir/Pibrentasvir
Date:	16 February 2017
Development Phase:	3b
Study Design:	This is an open-label, multicenter study
Investigators:	Multicenter Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc. (AbbVie)*
Sponsor/Emergency Contact:	[redacted] Infectious Disease Development 1500 Seaport Blvd, Suite 289H Redwood City, CA 94063 Phone: Mobile: Fax: [redacted]

* 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.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Synopsis

AbbVie Inc.	**Protocol Number:** M16-156
Name of Study Drug: Glecaprevir, Pibrentasvir	**Phase of Development:** 3b
Name of Active Ingredient: Glecaprevir, Pibrentasvir	**Date of Protocol Synopsis:** 16 February 2017
Protocol Title: A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection	
Objectives: • The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving SVR_{12} (HCV RNA < LLOQ 12 weeks following therapy) and safety of GLE/PIB combination in treatment-naïve adults in Brazil with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis. The efficacy endpoints will be analyzed based on combined treatment duration and genotypes and safety analysis will be done by individual treatment groups. • The secondary objectives are to assess efficacy of GLE/PIB by hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis by evaluating the percentages of subjects with HCV on-treatment virologic failure and HCV virologic relapse across treatment durations and genotypes.	
Investigators: Multicenter, single country (Brazil)	
Study Sites: Approximately 12	
Study Population: Chronic HCV GT 1 – 6-infected male and female adults with Metavir equivalent fibrosis stage of F2 – F4, at least 18 years of age, without cirrhosis or with compensated cirrhosis, who are HCV treatment-naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication).	
Number of Subjects to be Enrolled: Approximately 100 subjects	
Methodology: This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of GLE/PIB combination for an 8 or 12-week treatment duration in adults in Brazil with chronic HCV GT1 – 6 infection, without cirrhosis (F2 – F3) or with compensated cirrhosis (F4), who are HCV treatment-naïve. Approximately 100 subjects meeting the eligibility criteria will be enrolled. The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of 35 GT1 and 35 GT3 subjects and 2) approximately 80 F2 – F3 and a maximum of approximately 20 F4 subjects.	

Methodology (Continued):

Approximately 100 eligible subjects will be enrolled into one of the following treatment arms:

- Arm A: HCV GT 1 – 6 without cirrhosis (F2 and F3) subjects will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks.
- Arm B: HCV GT 1 – 6 subjects with compensated cirrhosis (F4) will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 12 weeks.

The study will consist of a Screening Period, Treatment Period and Post Treatment Period:

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

Treatment Period: Eligible subjects will be enrolled to receive GLE/PIB 300 mg/120 mg once daily (QD) for an 8 (Arm A) or 12 (Arm B) week treatment duration based on their cirrhosis status.

Scheduled visits for subjects in the Treatment Period consist of Day 1 and Weeks 4 and 8 for all subjects and an additional Week 12 visit for subjects in Arm B. Study procedures, including assessment of adverse events, vital signs, study medication adherence, concomitant medications, HCV RNA, HCV resistance, and clinical laboratory tests, will be conducted at each visit.

Post-Treatment (PT) Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 12 weeks to monitor safety, HCV RNA levels and the emergence and persistence of resistance-associated substitutions.

During the Post-Treatment Period, all subjects will have visits at PT Weeks 4 and 12, following completion of the Treatment Period. Study procedures to monitor safety, HCV RNA, and the emergence and persistence of resistant viral variants will be conducted during these visits.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject has positive plasma HCV antibody and HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.
2. Subject must be documented as without cirrhosis with METAVIR equivalent fibrosis stage of F2 – F3 or with compensated cirrhosis (F4) based on results of a liver biopsy, or FibroScan, or FibroTest score (as described in Section 5.3.1.1).
4. Subjects who are known to be HCV/HIV co-infected may enroll if they have a positive test result for anti-Human Immunodeficiency Virus antibody at Screening and are:

   Naïve to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study), or

   On a stable, qualifying HIV ART regimen for at least 8 weeks prior to Baseline.

   Subjects on stable HIV ART must have Plasma HIVRNA below 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once during the 12 months prior to Screening (by an approved plasma HIVRNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTi*m*e HIV-1 assay).
5. Subjects requiring dialysis should have been receiving dialysis for at least 1 month prior to enrollment, and may be on hemodialysis or peritoneal dialysis.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

6. Subjects With Compensated Cirrhosis Only: Absence of hepatocellular carcinoma (HCC) 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. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.

Main Exclusion:

1. Female subject who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Current HBV infection on screening tests, defined as:
   - A positive HBsAg, or;
   - HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti-HBs)
3. History of severe, life-threatening, or other significant sensitivity to any excipients of the study drug.
4. Any current or past clinical evidence of Child-Pugh B or C classification or clinical history, including on Day 1 prior to dose, of liver decompensation including hepatic encephalopathy or variceal bleeding, radiographic evidence of small ascites, or empiric use of lactulose/rifaximin. Prophylactic use of beta blockers is not exclusionary (see Section 5.3.1.1).
5. Laboratory parameters exclusions:
   - ALT > 10 × ULN; AST > 10 × ULN
   - Total Bilirubin > 3.0 mg/dL
   - Albumin < LLN (without cirrhosis); < 2.8 mg/dL (with compensated cirrhosis)
   - Platelets < 90,000 10^3/μL (without cirrhosis); < 60,000 10^3/μL (with compensated cirrhosis)
6. Receipt of any investigational or commercially available anti-HCV agents examples include, but are not limited to: interferon, pegylated interferon, ribavirin, sofosbuvir, telaprevir, boceprevir, simeprevir, asunaprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, voxilaprevir, velpatasvir or dasabuvir.

Investigational Products:	Glecaprevir/Pibrentasvir 100 mg/40 mg Film-coated tablet
Doses:	Glecaprevir/Pibrentasvir 300 mg/120 mg QD (3 tablets)
Mode of Administration:	Oral with food.
Reference Therapy:	N/A
Doses:	N/A
Mode of Administration:	N/A

Duration of Treatment: Subjects without cirrhosis will receive GLE/PIB for 8 weeks, while subjects with compensated cirrhosis will receive GLE/PIB for 12 weeks.

Criteria for Evaluation:

Efficacy:

Plasma HCV RNA (IU/mL) will be assessed at each Treatment and Post-Treatment Visit.

Criteria for Evaluation (Continued):

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests, and vital signs.

Patient Reported Outcomes (PROs):

The Short Form 36 Version 2 Health Status Survey (SF-36v2) will be used to assess the functional health and well-being of subjects. The Treatment Satisfaction Questionnaire (TSQM) will be used to assess treatment satisfaction with the GLE/PIB combined regime. EuroQol-5 Dimensions-3 Level (EQ-5D-3L) is a health state utility instrument that evaluates preference for health status (utility); subjects also rate their perception of their overall health on a separate visual analogue scale (VAS).

Resistance:

The following information will be tabulated and summarized: 1) for all subjects with available samples, baseline polymorphisms at signature resistance-associated amino acid positions relative to the appropriate prototypic reference sequences; and 2) for subjects who do not achieve SVR_{12}, post-baseline substitutions relative to the corresponding baseline sequence in available samples.

Pharmacokinetic:

Individual plasma concentrations of GLE, PIB, and their possible metabolites will be tabulated and summarized.

Statistical Methods:

Efficacy:

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 all genotypes (GT1 – 6 subjects) and treatment groups. The primary endpoint will be analyzed based on intention to treat (ITT) population. The number and percentage of subjects achieving SVR_{12} will be summarized with a two-sided 95% confidence interval. If the SVR_{12} is less than 100%, then the normal approximation for the binomial distribution will be used as a confidence interval. If the SVR_{12} rate is 100%, the Wilson's score method will be used to calculate the confidence interval.

The secondary efficacy endpoints are:

- The percentage of subjects with on-treatment HCV virologic failure.
- The percentage of subjects with post-treatment HCV virologic relapse.

Subgroup analysis based on the treatment arm (i.e., without cirrhosis/with compensated cirrhosis) will be performed. For the secondary efficacy endpoints and subgroup analysis, the two-sided 95% confidence interval will be calculated using Wilson's score method.

PROs:

Change from baseline to each applicable visit in the patient reported outcome summary measures will be summarized.

Statistical Methods (Continued):

Safety:

Safety summaries will be provided by the treatment arm (i.e., cirrhosis status/study drug duration) and overall. All subjects who receive at least one dose of study drug will be included in the safety analyses. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by MedDRA System Organ Class (SOC) and preferred term. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by grade and relationship to study drug.

Resistance:

For all subjects receiving study drug, baseline polymorphisms at signature resistance-associated amino acid positions identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the baseline sequences, 2) the amino acid substitutions in available post baseline samples at signature resistance-associated positions identified by NGS, and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral substitutions by NGS.

Pharmacokinetic:

Individual plasma concentrations of GLE, PIB, and their possible metabolites will be tabulated and summarized. Pharmacokinetic data from this study may be combined with data from other studies for the population pharmacokinetic analyses using a non-linear mixed-effect modeling approach with the NONMEM software. Relationships between exposure and clinical observations (antiviral activity) may be explored.

1.2 List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Anti-HBc	Anti-Hepatitis B core antibody
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ART	Antiretroviral therapy
AUC	Area under the plasma concentration-time curve
BMI	Body mass index
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
CL/F	Apparent oral plasma clearance
CR/CL	Creatinine clearance
CRF	Case report form
CT	Computed tomography
C_{trough}	Pre-dose trough plasma concentration
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EQ-5D-3L	EuroQol-5 Dimensions-3 Level
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GT	Genotype
HBsAg	Hepatitis B surface antigen
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B Virus

HCC	Hepatocellular carcinoma
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention To Treat
IU	International units
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NGS	Next generation sequence
NONMEM	Non-linear mixed-effect modeling
NS5A	Nonstructural viral protein 5A
PegIFN	Pegylated-interferon alfa-2a or alfa-2b
PegIFN/RBV	Combination of pegylated-interferon alfa-2a or alfa-2b and ribavirin
PI	Protease Inhibitor
PK	Pharmacokinetic
POR	Proof of receipt
P/R	pegIFN/RBV
PRO	Patient reported outcome
PT	Post-Treatment
QD	Once daily
RBC	Red blood cells

RBV	Ribavirin
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Standard Deviation
SF-36v2	Short Form 36 – Version 2 Health Survey
SOC	System Organ Class/Standard of Care
SOF	Sofosbuvir
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
SVR_4	Sustained virologic response 4 weeks post dosing
SVR_{12}	Sustained virologic response 12 weeks post dosing
TE	Treatment Experienced
TN	Treatment-naïve
TSQM	Treatment Satisfaction Questionnaire-Medicine
ULN	Upper limit of normal
VAS	Visual Analog Scale
V/F	Apparent Volume of distribution
WBC	White blood cells
WOCBP	Women of child bearing potential

Definition of Terms

Study Drug	glecaprevir/pibrentasvir
Study Day 1	First day of study drug dosing
Treatment Period	Day 1 through last dose of study drug
Post-Treatment Period	Day after the last dose of study drug through Post-Treatment Week 12 or Post-Treatment Discontinuation

2.0 Table of Contents

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3.0 Introduction

Hepatitis C virus (HCV) infection is a global health problem, with over 184 million individuals infected worldwide.[1] There are 7 identified HCV genotypes, with genotype 1 (GT1) being the most prevalent worldwide. HCV genotypes 2 (GT2) and 3 (GT3) infections are more common in Latin America (5% to 30%), Europe (20% to 40%) and Asia (30% to 45%).[2-4] HCV GT4 is commonly found in parts of Africa and the Middle East, particularly in Egypt, GT5 is primarily found in South Africa, and GT6 is primarily found in south-east Asia, and GT7 has recently been described in Central Africa.[5] Genotype 1 (GT1) is the most frequent in all regions in Brazil (65%), followed by genotype 3 (30%) and GT2 (5%). Genotypes 4 to 6 are rarely reported (0.3%) in the country.[6]

Depending on various risk factors, between 10% and 40% of all patients with chronic HCV infection will develop cirrhosis. Death related to the complications of cirrhosis may occur at an incidence of approximately 4% per year; hepatocellular carcinoma (HCC) occurs in this population at an estimated incidence of 1% to 5% per year. Patients diagnosed with hepatocellular carcinoma have a 33% probability of death during the first year.[7] Successful treatment of HCV has been shown to significantly reduce the risk of disease progression and related mortality as well as the development of hepatocellular carcinoma.[8,9]

At the time of initiation of this study, therapy for HCV had improved considerably with the approval of several interferon (IFN)-free direct-acting antiviral agent (DAA) regimens (ledipasvir [LDV]/sofosbuvir [SOF], SOF plus simeprevir [SMV], SOF plus daclatasvir [DCV], ombitasvir [OBV]/paritaprevir [PTV]/ritonavir [r] ± dasabuvir [DSV], elbasvir [EBR]/grazoprevir [GZR], and SOF/velpatasvir [VEL]).[10,11] In Brazil, the National HCV Program provides specific regimens to a subset of subjects with confirmed HCV and specific GT infection. The mono HCV infected subjects must have confirmed Metavir F3 and F4 fibrosis stage, and the HCV/HIV co-infected should be treated regardless of liver fibrosis staging. A treatment guideline recommends SOF + DCV or SOF + SMV for

GT1; SOF + RBV for GT2; SOF + pegIFN or SOF + DCV for GT3; and SOF + pegIFN + RBV or SOF + DCV for GT4. Duration of treatment is based on history of monoinfection with HCV, or co-infection with HIV, GT subtype and fibrosis staging. These regimens are available across the country and prescribed free of charge within the country's universal health care system.

However, these approved and recommended regimens are not equally potent across all HCV genotypes and subpopulations. Additional limitations of several current regimens include the requirement of ribavirin (RBV) for certain populations, significant drug to drug interactions, limited options for subjects with renal insufficiency, reduced efficacy in patients with baseline amino acid polymorphisms associated with reduced susceptibility to the HCV nonstructural 5A (NS5A) inhibitors (NS5AI) or NS3/4A protease inhibitors (PI), and limited options for patients who have failed regimens containing an NS5AI and/or PI. Efficacy in GT3-infected patients, particularly those who are treatment-experienced (TE) and/or cirrhotic, is also substantially lower than what is observed for other genotypes.[12]

AbbVie has developed two "next generation" DAAs, glecaprevir (GLE, formerly known as ABT-493), an HCV NS3/4A PI, and pibrentasvir (PIB, formerly known as ABT-530), an NS5AI, for use in combination for the treatment of HCV. GLE and PIB each has potent in vitro antiviral activity against genotypes 1 through 6[13] and a high genetic barrier to resistance, with no or little loss of potency against common resistant-associated substitutions. Additive or synergistic in vitro anti-HCV activity has been demonstrated with the combination of GLE and PIB. GLE 100 mg and PIB 40 mg are co-formulated into a fixed-dose combination tablet (hereafter referred to as GLE/PIB), which provides patients with a convenient once-daily (QD), fixed-dose combination treatment regimen of three tablets QD to maximize treatment compliance.

A detailed discussion of the preclinical pharmacology and toxicology, in vitro virology and metabolism, and clinical data can be found in the Investigator's Brochure.[14]

GLE/PIB

Overview of GLE/PIB Registrational Program and Supportive Phase 2 Studies

The GLE/PIB registrational program included a broad subject population including subjects with compensated liver disease and subjects with severe renal insufficiency across GT1 – 6 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 (TN) and TE subjects to any combination of pegylated IFN (pegIFN), RBV, SOF, NS5A inhibitors, or PIs were allowed in the program. In addition, the program included subjects with human immunodeficiency virus (HIV) coinfection (Study M13-590), subjects with chronic kidney disease [CKD] 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 (Table 1).

Table 1. Overview of Clinical Studies by Subject Population

Genotype	Clinical Study	Summary of Study Design
TN and TE Subjects Without Cirrhosis		
GT1	M13-590	GLE/PIB 300 mg/120 mg QD for 8 (n = 351) or 12 weeks (n = 352)
	M14-867	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 34)
GT2	M15-464	GLE/PIB 300 mg/120 mg QD (n = 202) or placebo (n = 100) for 12 weeks
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 199) or 12 weeks (n = 25)
GT3	M13-594	GLE/PIB 300 mg/120 mg QD for 8 (n = 157) or 12 weeks (n = 233) or SOF 400 mg + DCV 60 mg QD for 12 weeks (n = 115) (all subjects in study were TN)
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 29; TN only), 12 weeks (n = 76), or 16 weeks (n = 22; TE only)
GT4, 5, 6	M13-583	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 121)
	M14-867	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 32)
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 58)
TN and TE Subjects with Cirrhosis		
GT1, 2, 4, 5, 6	M14-172	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 146)
GT3	M14-868	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 64; TN only) or 16 weeks (n = 51; TE only)
Subjects with CKD Stages 4 – 5 With or Without Cirrhosis		
GT1 – 6	M15-462	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 104)
NS5A Inhibitor and/or PI-Experienced Subjects With or Without Cirrhosis		
GT1, 4	M15-410	GLE/PIB 300 mg/120 mg QD for 12 (n = 66) or 16 weeks (n = 47)

CKD = chronic kidney disease; DCV = daclatasvir; GLE = glecaprevir; GT = genotype; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; PIB = pibrentasvir; QD = once daily; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naïve

Efficacy

In treatment-naïve (TN) or IFN, pegIFN, RBV, and/or SOF treatment experienced (TE-PRS) subjects, the pooled overall SVR_{12} rates with GLE/PIB were > 97% across GT1, 2, 4, 5 and 6 regardless of treatment experience, treatment duration, including any degree of renal impairment, presence of compensated cirrhosis, or HIV coinfection (Table 2).

Among subjects with GT3 infection, the pooled SVR_{12} rates across durations were 95.2% among all subjects, 96.6% among cirrhotic subjects, and 100% among subjects with CKD Stages 4 – 5. The SVR_{12} rates among subjects previously treated with a PI and/or NS5A inhibitor were ≥ 89.0% for GT1 and GT4.

Table 2. SVR_{12} Rates by Treatment Experience and HCV Genotype – GT1 – 6 (ITT Population, Phase 2 and 3 Analysis Set)

Genotype	TN n/N (%) 95% CI[a]	TE-PRS n/N (%) 95% CI[a]	TN + TE-PRS			TE-NS5A and/or PIs n/N (%) 95% CI[a]	Overall n/N (%) 95% CI[a]
			All[a]	Cirrhotic n/N (%) 95% CI[b]	CKD 4 – 5 n/N (%) 95% CI[b]		
Phase 2 and 3 Analysis Set	1604/1640 (**97.8**) 97.1, 98.5	602/616 (**97.7**) 96.6, 98.9	2206/2256 (**97.8**) 97.2, 98.4	274/281 (**97.5**) 95.7, 99.3	102/104 (**98.1**) 95.4, 100.0	101/113 (**89.4**) 83.7, 95.1	2307/2369 (**97.4**) 96.7, 98.0
GT1	555/561 (**98.9**) 98.1, 99.8	326/328 (**99.4**) 98.5, 100.0	881/889 (**99.1**) 98.5, 99.7	98/101 (**97.0**) 93.7, 100.0	53/55 (**96.4**) 91.4, 100.0	97/109 (**89.0**) 83.1, 94.9	978/998[c] (**98.0**) 97.1, 98.8
GT2	365/369 (**98.9**) 97.9, 100.0	95/97 (**97.9**) 95.1, 100.0	460/466 (**98.7**) 97.7, 99.7	35/35 (**100**) 100.0, 100.0	16/16 (**100**) 100.0, 100.0	N/A	460/466 (**98.7**) 97.7, 99.7
GT3	499/521 (**95.8**) 94.0, 97.5	113/122 (**92.6**) 88.0, 97.3	612/643 (**95.2**) 93.5, 96.8	112/116 (**96.6**) 93.2, 99.9	11/11 (**100**) 100.0, 100.0	N/A	612/643 (**95.2**) 93.5, 96.8
GT4	119/122 (**97.5**) 94.8, 100.0	55/56 (**98.2**) 94.7, 100.0	174/178 (**97.8**) 95.6, 99.9	20/20 (**100**) 100.0, 100.0	20/20 (**100**) 100.0, 100.0	4/4 (**100**) 100.0, 100.0	178/182 (**97.8**) 95.7, 99.9
GT5	26/26 (**100**) 100.0, 100.0	6/6 (**100**) 100.0, 100.0	32/32 (**100**) 100.0, 100.0	2/2 (**100**) 100.0, 100.0	1/1 (**100**) 100.0, 100.0	N/A	32/32 (**100**) 100.0, 100.0
GT6	40/41 (**97.6**) 92.8, 100.0	7/7 (**100**) 100.0, 100.0	47/48 (**97.9**) 93.8, 100.0	7/7 (**100**) 100.0, 100.0	1/1 (**100**) 100.0, 100.0	N/A	47/48 (**97.9**) 93.8, 100.0

CI = confidence interval; CKD = chronic kidney disease; GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat; N/A = not applicable; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SVR_{12} = sustained virologic response 12 weeks postdosing; TE = treatment-experienced; TN = treatment-naïve; TE-NS5A and/or PI = TE with NS5A inhibitor and/or PI

a. CI was calculated using a stratum-weighted proportion and variance.

b. CI was calculated using the normal approximation to the binomial distribution.

c. Eleven subjects were classified by the central laboratory and treated as GT2 but included here as GT1 due to being identified as such by phylogenetic analysis; all 11 subjects achieved SVR_{12}.

Cross reference: Summary of Clinical Efficacy R&D/16/0146: Table 1.2__2.2

Impact of Baseline Polymorphisms on Treatment Outcome

The association between baseline polymorphisms in NS3 and NS5A and treatment outcome in subjects who received GLE 300 mg QD with PIB 120 mg QD in the registrational or supportive Phase 2 studies was evaluated by conducting an integrated analysis of baseline sequence data. Next-generation sequencing (NGS) was conducted on all baseline samples, data was analyzed at the 15% detection threshold, and baseline polymorphisms at amino acid positions 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A were examined for impact on SVR_{12}.

In subjects who were TN or TE-PRS, baseline polymorphisms in NS3 were detected in 1.1% (9/845), 0.8% (3/398), 1.6% (10/613), 1.2% (2/164), 41.9% (13/31), and 2.9% (1/34) of subjects with HCV genotype 1, 2, 3, 4, 5 and 6 infection, respectively. Baseline polymorphisms in NS5A were detected in 26.8% (225/841), 79.8% (331/415), 22.1% (136/615), 49.7% (80/161), 12.9% (4/31), and 54.1% (20/37) of subjects with HCV genotype 1, 2, 3, 4, 5, and 6 infection, respectively.

The presence of baseline polymorphisms in NS3 and/or NS5A did not have an impact on SVR_{12} rates for GT1-, 2-, 4-, 5-, or 6-infected subjects.

Within GT3-infected subjects, baseline polymorphisms in NS3 did not have an impact on treatment outcome. The NS5A polymorphisms at positions 24, 28, 31, 58, 92, or 93 (including Y93H) did not have an impact on treatment outcome, whereas the A30K polymorphism was associated with a slightly decreased SVR_{12} rate. Given the low prevalence of A30K (6.3%; 39/615) and that the majority of subjects with A30K achieved SVR_{12}, its impact on overall SVR is expected to be minimal.

Amino Acid Substitutions in Subjects Experiencing Virologic Failure

Among TN and TE-PRS subjects without cirrhosis or with compensated cirrhosis treated for 8, 12, or 16 weeks, 23 subjects experienced virologic failure (2 with GT1, 2 with GT2, and 19 with GT3). A GT3-infected subject experiencing virologic failure was determined to have been reinfected with GT3a virus distinct from the one present at baseline.

Therefore, baseline polymorphisms and treatment-emergent substitutions were analyzed for 22 subjects experiencing virologic failure.

Among the 2 GT1-infected subjects, 1 had treatment-emergent substitutions A156V in NS3 and Q30R/L31M/H58D in NS5A, and 1 had treatment-emergent Q30R/H58D (while Y93N was present at baseline and post-treatment) in NS5A.

Among the 2 GT2-infected subjects, no treatment-emergent substitutions were observed in NS3 or NS5A; the prevalent M31 polymorphism in NS5A was present at baseline and post-treatment in both subjects.

Among the 18 GT3-infected subjects, the majority of subjects had treatment-emergent substitutions at the time of failure in NS3 (61.1%, 11/18) and NS5A (88.9%, 16/18). Treatment emergent NS3 substitutions Y56H/N, Q80K/R, A156G, and Q168L/R were observed in 11 subjects, and A166S or Q168R was present at both baseline and post-treatment in 5 subjects. Treatment-emergent NS5A substitutions M28G, A30G/K, L31F, P58T, or Y93H were observed in 16 subjects, and 13 subjects had A30K (n = 9) or Y93H (n = 5) at both baseline and post-treatment.

Integrated Safety Results

A summary of treatment-emergent adverse events (AEs) from pooled analyses of the registrational studies and supportive Phase 2 studies are presented in Table 3. Given the severity of the underlying renal disease and its associated comorbidities in patients with CKD Stages 4 and 5, the frequency and severity of the AEs in subjects enrolled Study M15-462 were expected to be higher than in subjects enrolled in the other registrational studies. Therefore, the summary of adverse events reported in Table 3 does not include the results of Study M15-462.

As shown in Table 3, AEs occurring with a frequency > 5% are headache, fatigue, nausea and diarrhea. The majority of subjects experienced an AE, which were mostly considered to be mild in severity by the investigator (Grade 1). Rates of AEs that were serious, led to premature study drug discontinuation or had a severity Grade ≥ 3 were low. Including

data from Study M15-462, there were 7 deaths, none of which were related to study drug, and the majority occurred several months after the last dose of study drug.

Table 3. Adverse Events Reported for ≥ 5.0% of Subjects (Phase 2 and 3 Analysis Set)

	Phase 2 and 3 Analysis Set[a] (N = 2,265) n (%)	
	All Adverse Events	DAA-Related Adverse Events[b]
Any AE	1,529 (67.5)	929 (41.0)
An AE Grade ≥ 3	65 (2.9)	4 (0.2)
Any SAE	48 (2.1)	1 (< 0.1)
Discontinuation of study drug due to any AE	8 (0.4)	3 (0.1)
All deaths[c]	6 (0.3)	0
Preferred Term		
Headache	410 (18.1)	298 (13.2)
Fatigue	330 (14.6)	259 (11.4)
Nausea	208 (9.2)	172 (7.6)
Diarrhea	146 (6.4)	86 (3.8)

AE = adverse event; DAA = direct-acting antiviral agent; GLE = glecaprevir; PIB = pibrentasvir; SAE = serious adverse event

a. Excludes Study M15-462.

b. DAAs = GLE, PIB, or GLE/PIB.

c. Includes nontreatment-emergent deaths. One additional death occurred in Study M15-462.

Cross reference: Summary of Clinical Safety R&D/16/0147: Table 2.2__2.2, Table 2.2__3.2

Adverse events in subjects without cirrhosis (n = 1,977) were similar in type, frequency, and severity compared with subjects with compensated cirrhosis (n = 288). The safety profile in subjects with HCV/HIV-1 coinfection (n = 33) was similar to that in HCV monoinfected subjects. Overall, the safety profile of GLE/PIB in the elderly population (≥ 65 years old, n = 328) was comparable to the safety profile in the non-elderly population (n = 2,041).

In Study M15-462, GLE/PIB was generally well-tolerated in subjects with CKD Stage 4 and 5 as evidenced by a treatment discontinuation rate of 1.9% (2/104) due to AEs that were considered DAA-related. No subject experienced a serious AE that was assessed as DAA-related. The safety profile in subjects (n = 104) in Study M15-462 was consistent with underlying severe renal impairment and its associated comorbidities. Pruritus was the most common AE among subjects (20.2%) in this study followed by fatigue (14.4%) and nausea (11.5%). Pruritus was not an unexpected finding, as it is commonly observed in patients with severe renal impairment.[15] Laboratory abnormalities were infrequent with no subject experiencing a Grade 3 or higher elevation in ALT or AST and 1 subject experiencing a Grade 3 elevation in total bilirubin. No safety signal or toxicity related to GLE/PIB specific to subjects with CKD Stage 4 and 5 has been identified.

The frequency and severity of hepatic-related AEs as well as liver chemistry abnormalities evaluating potential hepatotoxicity were low across the Phase 2 and 3 studies (excluding Study M15-462). Liver-related safety results indicated that:

- Four subjects had post-nadir Grade 3 ALT abnormalities or Grade 2 ALT with total bilirubin ≥ 2 × ULN. None of these subjects prematurely discontinued study drug due to an ALT or bilirubin increase.
  - ALT abnormalities in 3 of these 4 subjects were not clinically significant
  - One subject experienced concurrent ALT > 3 × ULN (increased from nadir grade) and total bilirubin ≥ 2 × ULN in the context of multiple gallstones that was not consistent with drug-induced liver injury
- Based on exposure-response analyses, no GLE/PIB exposure-dependent ALT increases were observed in subjects with ALT abnormalities
- Grade 3 increases in bilirubin were infrequent (0.4%) and without bilirubin-related AEs; none were associated with liver disease progression
- No subjects experienced drug-related hepatic decompensation. One subject with cirrhosis (Study M14-172) who had known esophageal varices experienced an episode of esophageal varices hemorrhage that was considered not related to study drug. Treatment was continued without clinical or laboratory signs of liver disease progression.

- A total of 6 (0.3%) subjects experienced a de novo event of HCC. In all 6 subjects, the events were considered related to subject's medical history of underlying liver disease and not to GLE/PIB.
- There were no cases consistent with drug-induced liver injury.

In summary, GLE/PIB demonstrated a favorable safety profile that was similar across durations of 8, 12, and 16 weeks. The regimen was well tolerated across a broad and diverse population of subjects, including subjects with compensated cirrhosis, HIV co-infection, and CKD Stage 4 or 5.

Common GLE/PIB-related AEs (ADRs) occurring in ≥ 5% of subjects were headache, fatigue, nausea. Adverse drug reactions were mostly Grade 1 (mild) in severity. Serious AEs and AEs leading to premature study drug discontinuation were rare.

There were no hematological or blood chemistry findings of concern or considered likely to be related to treatment. Unlike other protease inhibitors, no liver-related toxicities and no cases consistent with drug-induced liver injury were identified.

3.1 Differences Statement

The GLE/PIB fixed dose combination for 8 and 12 weeks was explored in treatment-naïve and -experienced HCV GT1 – 6 infected subjects, without cirrhosis or with compensated cirrhosis including subjects with HIV/HCV co-infection and subjects with CKD Stage 4 or 5 in several Phase 3 studies conducted in a randomized, controlled, double-blind or open-label fashion.

This is the first Phase 3b study designed to evaluate HCV GT1 – 6 treatment-naïve subjects without cirrhosis (Metavir F2 – F3) and with compensated cirrhosis (Metavir F4) treated with GLE/PIB for 8 or 12 weeks, respectively, in Brazil. This country did not participate in the Global GLE/PIB program.

3.2 Benefits and Risks

Benefits of treatment with GLE/PIB include: potent and pangenotypic antiviral activity in vitro, higher genetic barrier to development of drug resistance across genotypes compared to first generation DAA protease and NS5A inhibitors, no need for RBV, 8 or 12 weeks of treatment for NS5AI and PI naive, and the convenience of a once daily regimen. The combination of GLE/PIB has been evaluated in six Phase 3 registration studies and three Phase 2b supportive studies. The results of these studies show high SVR_{12} rates among subjects with HCV GT 1 – 6 infection who receive treatment with GLE/PIB.

Adverse events that are known, and those not previously identified, may occur with GLE/PIB as detailed in the informed consent of this study. In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures. Additional safety data for each DAA alone and the combination of PIB/GLE are detailed in Section 3.0 and in the Investigator's Brochure.[14]

Risks associated with GLE/PIB, including the risks of adverse reactions, virologic failure, and development of resistance-associated substitutions (Section 5.3.4), appear to be limited and manageable based upon the available data. Given the potential for high SVR_{12} rates in populations of HCV-infected subjects, including HIV/HCV co-infected, and with CKD 4 – 5, the risk-benefit profile for GLE/PIB is favorable.

4.0 Study Objective

4.1 Primary Objectives

The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving SVR_{12} (HCV RNA < LLOQ 12 weeks following therapy) and safety of GLE/PIB combination in treatment-naïve adults in Brazil with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis. The efficacy endpoints will be analyzed based on combined

treatment duration and genotypes and safety analysis will be done by individual treatment groups.

4.2 Secondary Objectives

The secondary objectives are to assess efficacy of GLE/PIB based on overall population (i.e., across treatment durations and genotypes) by evaluating the following:

- The percentages of subjects with HCV on-treatment virologic failure;
- The percentages of subjects with HCV virologic relapse.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of GLE/PIB for an 8- or 12-week treatment duration in adults in Brazil with chronic HCV GT1 – 6 infection, without cirrhosis or with compensated cirrhosis with a METAVIR System Fibrosis Score of F2, F3 or F4 (F2-F4) or equivalent,[16] who are HCV treatment-naïve. Approximately 100 subjects meeting the eligibility criteria will be enrolled. The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of approximately 35 GT1 and 35 GT3 subjects and 2) approximately 80 F2 – 3 and a maximum of approximately 20 F4 subjects.

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

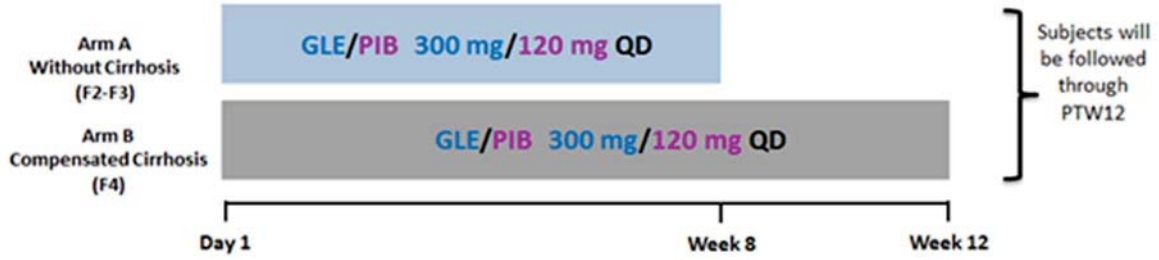
Screening Period: Subjects will have up to 35 days following the Screening Visit to confirm eligibility and enroll in the study.

Treatment Period: Eligible subjects will be enrolled to receive GLE/PIB 300 mg/120 mg once daily (QD) for an 8 (Arm A) or 12 (Arm B) week treatment duration based on cirrhosis status.

Post-Treatment Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 12 weeks to monitor HCV RNA levels to evaluate efficacy and the emergence and persistence of resistance-associated substitutions.

A study schematic is shown below in Figure 1.

Figure 1. Study Design



* **The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of approximately 35 GT1 and 35 GT3 subjects and 2) approximately 80 F2 – F3 and a maximum of approximately 20 F4 subjects.**

Approximately 100 eligible subjects will be enrolled into one of the following treatment arms:

- Arm A: HCV GT 1 – 6 without cirrhosis (F2 – F3) subjects will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks.
- Arm B: HCV GT 1 – 6 subjects with compensated cirrhosis (F4) will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 12 weeks.

The study was designed to enroll approximately 100 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening may not be enrolled.

5.1.1 Screening Period

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study-specific procedures will receive a unique subject number via the Interactive Response Technology (IRT) system. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through Study Day 1 prior to dosing, and will record the results of this assessment and the details of the informed consent process in the subject's medical records. Eligible subjects have up to 35 days following the Screening Visit to enroll into the study.

5.1.1.1 Rescreening

Subjects who at Screening have any of the following are not eligible to rescreen or retest:

- A positive Hepatitis B surface antigen (HBsAg);
- HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti-HBs); or
- If Woman of Childbearing Potential (WOCBP), a positive serum pregnancy test;
- Development of decompensated liver disease during the screening period, as defined by the Exclusion Criterion 6.

Otherwise subjects may be retested or rescreened only once unless approved by the Primary Therapeutic Area Medical Director.

Subjects who have exclusionary laboratory parameter(s) are allowed to retest on the related panel(s) (e.g., exclusionary ALT requires a repeat chemistry panel) within the same screening period and must meet all eligibility laboratory criteria on any panel that is repeated. If any of the retest result(s) are exclusionary, the subject may not be rescreened again.

Subjects that exceed the initial 35 day screening period should be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary during the first screening attempt (with the exception of HIV, HBV, HCV genotype and subtype, follicle stimulating hormone (FSH), which do not need to be repeated). The FibroScan and liver biopsy do not need to be repeated for rescreened subjects provided that the date of the liver biopsy is within 24 months of the rescreening date and the FibroScan is within 6 months of the rescreening date (Section 5.1.1).

Subjects who rescreen or subjects not meeting the study eligibility criteria must be identified by site personnel as a screen failure in both IRT and EDC systems.

5.1.2 Treatment Period

After meeting the eligibility criteria, subjects will be enrolled via IRT on Study Day 1. Subjects will be administered study drug at the site on Study Day 1, and provided dosing instructions.

Study visits and procedures during the Treatment Period are detailed in Appendix C. Safety and tolerability will be assessed throughout the study. Laboratory testing will include chemistry and hematology as specified in Table 5. Plasma samples for pharmacokinetic analysis and HCV RNA analysis will be collected as detailed in Section 5.3 and Section 5.3.1.1.

All subjects will continue to return to the site on an outpatient basis as outlined in Appendix C. Sites should ensure that subjects adhere to all study visits. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

HCV virologic failure criteria will be evaluated and applied by the investigator as detailed in Section 5.4.1.1.

Subjects who prematurely discontinue from the Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined in Appendix C and as described in Section 5.4.1. Subjects who prematurely discontinue from study treatment will continue to be followed in the Post-Treatment Period (see Section 5.1.3).

5.1.3 Post-Treatment Period

All subjects who received at least one dose of study drug will be monitored in the Post-Treatment Period for 12 weeks following the last dose of study drug for safety, HCV RNA, and the emergence and persistence of HCV resistance-associated substitutions.

The Post-Treatment Period will begin the day following the last dose of study drug. Study visits during the Post-Treatment period are detailed in Appendix D and Section 5.3.1.1.

Subjects who prematurely discontinue during the Post-Treatment Period should return to the site for a Post-Treatment discontinuation visit as outlined in Appendix D.

5.2 Selection of Study Population

The study population consists of male and female adults aged 18 years or older with chronic HCV GT1 – 6 infection with METAVIR equivalent fibrosis stage of F2 – F4 (without cirrhosis or with compensated cirrhosis) who are HCV treatment naïve (i.e., subject has never received a single dose of any approved or investigational anti-HCV medication). Subjects with HIV/HCV co-infection and subjects at all CKD stages (CKD Stages 1 – 5) are allowed to participate. Subjects who meet all inclusion criteria and none of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

1. Male or female, at least 18 years of age at time of Screening.
2. If female, subject must be either

Postmenopausal defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause; or
- Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L; or
- Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

OR

- A WOCBP practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 through at least 30 days after the last dose of study drug.

3. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine or serum pregnancy test at Study Day 1.

   Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing.

4. Screening laboratory result indicating HCV GT1-, 2-, 3-, 4-, 5- and/or 6-infection. Mixed and indeterminate genotypes are acceptable.

5. Subject has positive plasma HCV antibody and HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.

6. Subjects who are known to be HCV/HIV co-infected may enroll if they have a positive test result for anti-Human Immunodeficiency Virus antibody at Screening and are:

   Naïve to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study), or on a stable, qualifying HIVART regimen for at least 8 weeks prior to Baseline. (Substituting TDF for TAF as part of the combination regimen is allowed at any time.)

The HIVART regimen must include at least one of the following ARV agents:

- Raltegravir (RAL)
- Dolutegravir (DTG)
- Rilpivirine (RPV)
- Elvitegravir/cobicistat (EVG/COBI)

In addition to the above medications, HIV Ab positive subjects (both without cirrhosis or with compensated cirrhosis) may take a nucleoside/nucleotide reverse transcriptase inhibitor (N(t)RTI) backbone containing any of the following:

- Tenofovir disoproxil fumarate (TDF)
- Tenofovir alafenamide (TAF)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Lamivudine (3TC)

Subjects receiving any other HIV ART in addition to those noted above are not eligible for enrollment in the study.

Subjects on stable HIV ART must have Plasma HIVRNA below 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once during the 12 months prior to Screening (by an approved plasma HIVRNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTi*m*e HIV-1 assay).

7. Subject must be documented as without cirrhosis with METAVIR equivalent fibrosis stage of F2 – 3 or with compensated cirrhosis (F4) based on results of a liver biopsy, or FibroScan, or FibroTest score (as described in Section 5.3.1.1).

8. Subjects with compensated cirrhosis only: Absence of hepatocellular carcinoma (HCC) 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. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.
9. Subject must voluntarily sign and date an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to the initiation of any Screening or study specific procedures.
10. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.
11. Subjects requiring dialysis should have been receiving dialysis for at least 1 month prior to enrollment, and may be on hemodialysis or peritoneal dialysis.

Rationale for Inclusion Criteria

1, 4 – 11	In order to select the appropriate subject population with appropriate disease characteristics for evaluation
2, 3	The impact of GLE and PIB on human pregnancies has not been established. However, assessment of the completed nonclinical reproductive toxicology studies indicates that there is no drug-related effect on teratogenicity/fetotoxicity. In addition, the compounds are non-genotoxic
10	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.

2. Current HBV infection on screening tests, defined as:
   - A positive HBsAg, or;
   - HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti-HBs)
3. Requirement for and inability or unwillingness to safely discontinue the medications or supplements listed in Table 4 at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of any study drug.
4. Requirement for 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).
5. 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.
6. Any current or past clinical evidence of Child-Pugh B or C classification or clinical history, including on Day 1 prior to dose, of liver decompensation including hepatic encephalopathy or variceal bleeding, radiographic evidence of small ascites, or empiric use of lactulose/rifaximin. Prophylactic use of beta blockers is not exclusionary (see Section 5.3.1.1).
7. Laboratory parameters exclusions:
   - ALT > 10 × ULN; AST > 10 × ULN
   - Total Bilirubin > 3.0 mg/dL
   - Albumin < LLN (without cirrhosis); < 2.8 mg/dL (with compensated cirrhosis)
   - Platelets < 90,000 10^3/µL (without cirrhosis); < 60,000 10^3/µL (with compensated cirrhosis)

8. History of solid organ transplantation, unless the implanted organ has since been removed, or is non-functional, and subject is no longer on immunosuppressive medication. If the organ is non-functional, the subject must be clinically stable off of immunosuppressive medication for a minimum of 6 months prior to screening. This only applies to subjects with CKD Stage 4 or 5.
9. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks (whichever is longer) prior to study drug administration.
10. Receipt of any investigational or commercially available anti-HCV agents examples include, but are not limited to: interferon, pegylated interferon ribavirin, sofosbuvir, telaprevir, boceprevir, simeprevir, asunaprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, voxilaprevir, velpatasvir or dasabuvir.
11. History of severe, life-threatening or other significant sensitivity to any excipients of the study drug.
12. Treatment for an AIDS-associated opportunistic infection (OI) (Appendix E) within 6 months of Screening.
13. Subjects who cannot participate in the study per local law.

Rationale for Exclusion Criteria

1, 3, 4, 6 – 13	In order to ensure safety of the subjects throughout the study
2, 5	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal 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 drugs. 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 serious adverse event (SAE) will be recorded in EDC. The AbbVie Primary Therapeutic Area Medical Director should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior HCV Therapy

Subjects must be HCV treatment-naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication).

5.2.3.2 Prior and Concomitant HIV Therapy

Subject on an HIV ART regimen must include ARV agents as defined in Inclusion Criterion 6 (Section 5.2.1).

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

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

Subjects receiving any other HIV ART in addition to those listed in Inclusion Criterion 6 (Section 5.2.1) would not be eligible for enrollment in the study.

5.2.3.3 Concomitant Therapy

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

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 drugs, if applicable.

Flu shots and other vaccinations are allowed during Screening through the Post-Treatment Period for all subjects. Flu shots and vaccinations may affect plasma HIV RNA levels.

5.2.3.4 Prohibited Therapy

Subjects must be able and willing to safely discontinue any prohibited medications or supplements listed in Table 4 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.

Table 4. Prohibited Medications and Supplements

Medication or Supplement Name
Red yeast rice (monacolin K), St. John's Wort
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin*
Astemizole, cisapride, terfenadine
Ethinyl estradiol

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with study drugs. Subjects receiving these statins should either switch to pravastatin or rosuvastatin prior to the first dose of study drugs or may interrupt statin therapy throughout the treatment period 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 drugs.

Use of ethinyl estradiol containing oral contraceptives with GLE/PIB was associated with ALT increases in some healthy female subjects. Hormonal contraceptives (including oral, topical [including vaginal rings], injectable, or implantable varieties) containing ethinyl estradiol may not be used from 14 days prior to the first dose of GLE/PIB until 14 days after the end of GLE/PIB dosing. Progestin-only contraceptives such as those containing norethindrone, desogestrel, or levonorgestrel, without ethinyl estradiol, may be used with GLE/PIB. Post-menopausal hormone replacement therapy, i.e., estradiol, esterified or conjugated estrogens, as long as they do not contain ethinyl estradiol, may be used with GLE/PIB at the discretion of the Investigator.

The chronic use of systemic immunosuppressants is prohibited from 2 weeks prior to the first dose of study drug and until 30 days after the last dose of study drug including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab).

For HCV/HIV coinfected subjects, the investigator must refer to the current package insert(s) or product label(s) of a subject's ART regimen for a complete list of medications prohibited to be used with those drugs, which should not be used at least 2 weeks prior to the first dose of any study drug and not use these during the entire Treatment Period and for 30 days following discontinuation of study drugs.

5.2.4 Contraception Recommendations

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a Woman of Childbearing Potential, practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 30 days after the last dose of study drug:

- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- 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, symptom-thermal, post-ovulation methods] and withdrawal are not acceptable).

For male study subjects, no contraception is required.

5.3 Efficacy, Pharmacokinetic, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C (Treatment Period) and Appendix D (Post-Treatment Period).

5.3.1.1 Study Procedures

Informed Consent

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Medical History

A complete medical history, including history of tobacco, alcohol and drug use, will be taken from each subject at Screening Visit. The subject's medical history will be updated at the Study Day 1 Visit. This updated medical history will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will be performed at visits specified in Appendix C, or upon subject discontinuation. A symptom-directed physical examination may be performed at any other visit, when necessary.

The physical examination performed on Study Day 1 will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after the first dose will be recorded as adverse events.

Height will be measured only at Screening.

Vital Signs and Weight

Body temperature, blood pressure, pulse, and body weight will be measured at each study visit as specified in Appendix C and Appendix D. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes. The subject should wear lightweight clothing and no shoes during weighing. The vital signs performed on Day 1 of the Treatment Period will serve as the baseline for clinical assessment.

12-Lead Electrocardiogram

A 12-lead resting ECG will be obtained at the visits indicated in Appendix C. The ECG should be performed prior to blood collection.

The ECG will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign, and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 5 at the visits indicated in Appendix C and Appendix D.

Blood samples for serum chemistry tests should be collected following a minimum 8-hour fast prior to study drug intake (with the exception of the Screening Visit, which may be non-fasting). Subjects whose visits occur prior to the morning dose of study drug should be instructed to fast after midnight until the blood sample is collected in the morning and thereafter take their study medications with food. Subjects whose visits occur following the morning dose of study drug should be instructed to fast after breakfast until the study visit occurs. At the Study Day 1 visit, a fasting blood sample should be collected prior to the first dose of study drug. Blood samples should still be drawn if the subject did not fast for at least 8 hours. Fasting or non-fasting status will be recorded in the source documents and on the laboratory requisition. The baseline laboratory test results for

clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

A central laboratory will be utilized to process and provide results for the clinical laboratory tests.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study. The certified laboratory chosen for this study is Covance. Samples will be sent to the following addresses:

Covance
8211 SciCor Drive
Indianapolis, IN 46214 USA
(For sites in North America)

Table 5. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Additional Tests
Hematocrit	Blood Urea Nitrogen (BUN)	Anti-HCV Ab[a]
Hemoglobin	Creatinine	HCV RNA
Red Blood Cell (RBC) count	Total bilirubin	HCV genotype and subtype[a]
White Blood Cell (WBC) count	Direct and indirect bilirubin	HIV Ab[a]
Neutrophils	Alanine transaminase (ALT)	HIV RNA[b]
Bands, if detected	Aspartate transaminase (AST)	Hepatitis B Panel (Anti-HB[c]
Lymphocytes	Alkaline phosphatase	Total, Anti-HBs and HBsAg)[c]
Monocytes	Sodium	Anti-HBc IgM[c]
Basophils	Potassium	Anti-HBc Total[c]
Eosinophils	Calcium	Anti-HBs[c]
Platelet count (estimate not acceptable)	Inorganic phosphorus	Anti-HAV
Prothrombin Time/INR[a]	Total protein	IgM[d]
Activated partial thromboplastin time (aPTT)	Glucose	Anti_HAV Total[d]
	Albumin	Anti-HEV IgG[d]
	Chloride	Anti-HEV IgM[d]
	Bicarbonate	HEV RNA[d]
	Magnesium	HBV DNA[e]
	Gamma-glutamyl transferase (GGT)	Follicle Stimulating Hormone (FSH)[f]
		Urine and Serum Human Chorionic Gonadotropin (hCG) for females[g]
		Alpha2-macroglobulin[h]
		Haptoglobin[h]
		Apolipoprotein A1[h]
		CD4, CD4%[b]
		CD8, CD8%[b]
		CD4:CD8[b]

a. Performed only at Screening.

b. Only for known HCV/HIV co-infected subjects.

c. Performed at Screening for all subjects and also performed for management of transaminase elevations (Section 6.1.7.1).

d. Performed for management of transaminase elevation (Section 6.1.7.1).

e. Performed at Screening for subjects who have occult HBV infection (positive Anti-HBc Total with negative HBsAg and Anti-HBs) and also performed for management of transaminase elevation (Section 6.1.7.1).

f. Only performed if requested during screening for post-menopausal women < 55 to verify FSH level if site does not have a previous result available.

g. Required only for females of child bearing potential.

h. Component of FibroTest and collected only if required for FibroTest calculation during the Screening Period.

For any laboratory test value outside the reference range that the investigator considers to be clinically significant:

- The investigator will repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.
- A laboratory test value that requires a subject to be discontinued from the study or study drug or requires a subject to receive treatment will be recorded as an adverse event.

The management of laboratory abnormalities that may occur during the study is described in Section 6.1.7.

Pregnancy Testing

- WOCBP must have a negative serum pregnancy test result at Screening, and a negative serum or urine pregnancy test at Study Day 1.
- Monthly pregnancy testing should be performed during treatment, including at the last dose and until 30 days of last study drug dose, as indicated in Appendix C and Appendix D.
- Subjects with borderline pregnancy tests at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
- Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in the inclusion criteria) at Screening do not require pregnancy testing.

Concomitant Medication Assessment

Please refer to Section 5.2.3.2.

Hepatitis B, Hepatitis C Virus and HIV Screen

HBsAg, anti-HBc and anti-HBs, anti-HCV Ab and anti-HIV Ab will be performed at Screening. The investigator must discuss any local reporting requirements to local health

agencies with the subject. The site will report these results per local regulations, if necessary. The HIV results will not be reported by the central laboratory to the clinical database.

Liver Diagnostic Testing

Subjects will be considered to be without cirrhosis or with compensated cirrhosis based on the definitions below:

Without Cirrhosis (F2 and F3)

- A liver biopsy within 24 months prior to or during Screening demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of 2 – 3, Ishak fibrosis score of 3 or 4; or
- A FibroScan® score of 8.8 to < 12.5 kPa within ≤ 6 months of Screening or during Screening period (FibroScan® must be approved by the local regulatory agency to qualify for entrance criteria); or
- A Screening FibroTest score of 0.49 to 0.72 (inclusive).[17]

With Compensated Cirrhosis (F4)

- 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 or on a liver biopsy conducted during Screening; or
- A FibroScan® score of ≥ 12.5 kPa within ≤ 6 months of Screening or during Screening period (FibroScan® must be approved by the local regulatory agency to qualify for entrance criteria); or
- A Screening FibroTest result that is ≥ 0.73.

The result of the liver biopsy supersedes the results of FibroScan and FibroTest and result of FibroScan supersedes the results of FibroTest. At Screening, it is recommended that subjects should otherwise meet all other inclusion criteria and none of the exclusion criteria before undergoing a liver biopsy.

Child-Pugh Score and Category

Subjects with compensated cirrhosis will have Child-Pugh scores assessed, except those who are on ongoing use of anticoagulants. The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments) as shown in Table 6. Child-Pugh score will be determined at the visits indicated in Appendix C and Appendix D.

Table 6. Child-Pugh Classification of Severity of Cirrhosis

	Points Assigned for Observed Findings		
Parameter	**1**	**2**	**3**
Total bilirubin, µmol/L (mg/dL)	< 34.2 (< 2)	34.2 – 51.3 (2 – 3)	> 51.3 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28 – 35 (2.8 – 3.5)	< 28 (< 2.8)
INR	< 1.7	1.7 – 2.3	> 2.3
Ascites**	None	Slight	Moderate to severe
Hepatic encephalopathy*	None	Grade 1 or 2 (or suppressed with medication)	Grade 3 or 4 (or refractory)

Child-Pugh category A: 5 – 6 points; Child-Pugh category B: 7 – 9 points; Child-Pugh category C: 10 – 15 points.

* Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.
Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

** None.
Slight ascites = Ascites detectable only by ultrasound examination.
Moderate ascites = Ascites manifested by moderate symmetrical distension of the abdomen.
Severe ascites = Large or gross ascites with marked abdominal distension.

Clinical Assessment of Hepatic Decompensation

A clinical assessment of hepatic encephalopathy and ascites will be performed at Study Day 1 prior to dosing to confirm the subject has not progressed to hepatic decompensation since Screening for all subjects who have compensated cirrhosis. Grading system guidelines for ascites are listed above in Table 6. Subjects who present symptoms and

signs of hepatic decompensation including assessment at Day 1 prior to receiving study drug, will not be enrolled into the trial.

Hepatocellular Carcinoma Screening: Liver Ultrasound

In order to monitor for the presence of hepatocellular carcinoma (HCC), an ultrasound of the liver will be performed as indicated in Appendix C for subjects with compensated cirrhosis only. Subjects with compensated cirrhosis who do not have a historical qualifying liver ultrasound, CT, or MRI within the past 3 months will have an ultrasound performed during Screening. A positive ultrasound result suspicious for HCC will be confirmed with CT scan or MRI during Screening. Suspicious ultrasound lesions confirmed by CT or MRI are exclusionary.

Patient Reported Outcomes (PRO) Instruments (Questionnaires)

Subjects will complete the self-administered PRO instruments on the study visits specified in Appendix C and Appendix D. Subjects should be instructed to follow the instructions provided with each instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaires to them. Site personnel should encourage completion of each instrument at all specified visits and should ensure that a response is entered for all items.

Short Form 36 – Version 2 Health Survey (SF-36v2)

The SF-36v2 is a general Health Related Quality of Life (HRQoL) instrument with extensive use broad variety of health conditions and is the standard in literature for HCV. The SF-36v2 instrument comprises 36 total items (questions) targeting a subject's functional health and well-being in 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). Domain scores are also aggregated into a Physical Component Summary score and a

Mental Component Summary score. Higher SF-36v2 scores indicate a better state of health. The SF-36v2 should require approximately 10 minutes to complete.

Treatment Satisfaction Questionnaire-Medicine (TSQM)

The TSQM is a 14-item instrument and includes assessments of satisfaction with a medication's effectiveness (Effectiveness, three items), lack of side effects (Side Effects; five items), convenience (three items) and the subject's global satisfaction (Global Satisfaction; three items).

The subject should complete the questionnaire before site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response. TSQM scores range from 0 – 100 with higher scores indicating better satisfaction. The TSQM should require approximately 5 minutes to complete.

EuroQol-5 Dimensions-3 Level (EQ-5D-3L)

The EQ-5D-3L is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-3L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on 3 levels of severity. Responses to the 5 items encode a discrete health state which is mapped to a preference (utility) specific for different societies. Subjects also rate their perception of their overall health on a separate visual analogue scale (VAS). The EQ-5D-3L should require approximately 5 minutes to complete.

PRO instruments should be consistently presented so that subjects complete the questionnaires in the following order: the SF-36v2, TSQM, and EQ-5D-3L. PRO instruments should be completed prior to drug administration on Day 1 and prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels, at all study specified visits listed in Appendix C and Appendix D.

Enrollment and Assignment of Subject Numbers

All Screening activities must be completed and reviewed prior to enrollment. Subjects who meet all the Inclusion Criteria and none of the Exclusion Criteria at Screening will proceed to enrollment via the IRT system on Study Day 1.

Subject numbers will be unique 4 digit numbers and will begin with 1001 with the first two digits representing the investigative site, and the last two digits representing the subjects at that site. Enrolled subjects will keep their subject number throughout the study. Subjects will be enrolled on Study Day 1 as described in Section 5.5.4.

Study Drug Compliance for Kits

Individual bottles of GLE/PIB will be provided for subject dosing to the site. Each subject will have compliance documented by the site in the subject's source notes for GLE/PIB. At each Study Drug Accountability Visit in Appendix C, the overall number of tablets of GLE/PIB remaining in each bottle will be recorded and entered in the IRT system along with the date of reconciliation.

Additional information regarding treatment compliance can be found in Section 5.5.6.

HCV Genotype and Subgenotype

Plasma samples for HCV genotype and subtype determination will be collected at Screening. Genotype and subtype will be assessed using the Versant® HCV Genotype Inno LiPA Assay, Version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY) by the central laboratory. If the LiPA assay is unable to genotype a sample, its genotype and subtype will be evaluated by a Sanger sequencing assay of a region of the NS5B gene by the central laboratory.

HCV RNA Levels

Plasma samples for HCV RNA levels will be collected as indicated in Appendix C and Appendix D. Plasma HCV RNA levels will be determined for each sample collected by

the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan HCV Quantitative Test, v2.0. The lower limit of detection (LLOD) and lower limit of quantification (LLOQ) for this assay (regardless of genotype) are both 15 IU/mL.

HCV Resistance Testing Sample

A plasma sample for HCV resistance testing will be collected prior to dosing on Day 1 and at the study visits indicated in Appendix C and Appendix D. Specific instructions for preparation and storage of HCV RNA and HCV resistance samples will be provided by the central laboratory, AbbVie, or its designee.

Study Drug Dosing Card

Subjects will be provided with self-administration instructions and study drug dosing cards to record the exact date, time (record to the nearest minute) and number of tablets of study drug administration (GLE/PIB) for the last 2 doses of study drug taken prior to the scheduled pharmacokinetic sample collection visits during the Treatment Period as detailed in Appendix C.

The site staff will record the information about the last 2 doses taken prior to the scheduled pharmacokinetic sample collection from the study drug dosing card into the eCRF. In the event that the dosing card is not available, the site may obtain dosing information via patient interview and record this information in the source notes and the eCRF.

To facilitate proper dosing of study drug before pharmacokinetic evaluation blood samples are taken, the following procedures should be performed:

- The Investigator or designee should make sure the subject is given the dosing card at the visits listed in Appendix C.
- The Investigator or designee will contact the subject approximately 2 days before the scheduled visit date to review the importance of proper study drug administration relative to the pharmacokinetic blood collection and

documentation of dosing times on the dosing card. The date and time of the contact will be entered into the subject's source documents.

- The completed dosing card will be collected by the Investigator or designee on the day of the visit and be kept as a source record of dosage administration times documented in the eCRF.

Flow Cytometry, HIV RNA and HIV Resistance Testing Samples

For subjects with HCV/HIV coinfection, samples for plasma HIV RNA levels and flow cytometry (including but not limited to CD4+ T-cell and CD8+ T-cell counts [absolute and percent]) will be obtained at the times specified in Appendix C and Appendix D. Plasma HIV-1 RNA will be measured by the central laboratory using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, version 2.0 HIV-1 Assay. Results below the LLOD are reported as: "Not Detected." HIV treatment failure is defined as detectable HIV RNA after 6 months of highly active antiretroviral therapy (HAART) or HIV RNA detectable after a period of undetectable measurement following use of HAART.

If a HIV RNA level result of subject on stable HIV ART is ≥ 200 copies/mL, the subject's HIV RNA is to be repeated as noted in Section 5.4.1.2. At the time the repeat plasma HIV RNA is drawn, a sample should be obtained for HIV genotypic resistance testing. If the subject's repeat HIV RNA is ≥ 500 copies/mL, the sample obtained for HIV genotypic resistance testing will be analyzed.

HIV protease (PR), reverse transcriptase (RT) and integrase (IN) sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assay.

If the subject's repeat HIV RNA is < 200 copies/mL, then the subject will resume routine plasma HIV RNA assessments as shown in Appendix C and Appendix D, and described in Section 5.4.1.2.

Specific instructions for preparation and storage of flow cytometry, plasma HIV RNA, and HIV resistance samples will be provided by the central laboratory, AbbVie, or its designee.

5.3.1.2 Meals and Dietary Requirements

Study drug (GLE/PIB) tablets should be dosed together and taken with food.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic assay of GLE, PIB, and their possible metabolites will be collected by venipuncture at each study visit indicated below and in Appendix C.

- At all Treatment-Period visits, except Day 1, a single blood sample for pharmacokinetic analysis will be collected without regard to the time of dosing. The date and time of blood sample collection and the two previous doses of the study drug will be recorded to the nearest minute in the source documents. Additionally, the date and time of the two previous doses of the study drug will be recorded to the nearest minute on the eCRF.

5.3.2.2 Handling/Processing of Samples

Specific instructions for collection of blood samples and subsequent preparation and storage of plasma samples for the pharmacokinetic assays of GLE, PIB, and their possible metabolites will be provided by the central laboratory, AbbVie, or its designee.

5.3.2.3 Disposition of Samples

The frozen plasma samples for the pharmacokinetic assays of GLE, PIB, and their possible metabolites will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory.

The central laboratory will then ship the GLE and PIB samples to AbbVie or the reference laboratories following separately provided instructions.

5.3.2.4 Measurement Methods

Plasma concentrations of GLE and PIB will be determined using a validated assay methods in the Drug Analysis Department at AbbVie. Plasma concentrations of any possible GLE and PIB metabolites may also be determined using either validated or non-validated methods.

5.3.3 Efficacy Variables

Virologic response will be assessed by plasma HCV RNA levels in IU/mL at various time points from Day 1 through 24 weeks after completion or discontinuation of the study.

5.3.3.1 Primary Variable

The primary efficacy variable is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

5.3.3.2 Secondary Variables

The secondary efficacy variables are:

- The percentage of subjects with HCV on-treatment virologic failure.
- The percentage of subjects with HCV virologic relapse.

5.3.3.3 HCV Resistance Variables

For all subjects receiving GLE/PIB and with available samples, baseline polymorphisms at signature resistance associated amino acid positions identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA ≥ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the baseline sequence, 2) the amino acid substitutions in available post-baseline samples at signature resistance associated positions identified by NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of resistance-associated substitutions by NGS.

5.3.4 Safety Variables

The following safety evaluations will be performed during the study: adverse events, vital signs, physical examination, ECG, and laboratory tests assessments.

5.3.5 Pharmacokinetic Variables

Individual plasma concentrations of GLE, PIB, and their potential metabolites, if measured, will be tabulated and summarized.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.

If, during the course of study drug administration, the subject prematurely discontinues, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Appendix C and Appendix D. 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. The last dose of any study drug and reason for discontinuation will be recorded in the EDC (electronic data capture) system. 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 substitutions.

If a subject is discontinued from study drug or in 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.

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. Specific instructions regarding subject pregnancy can be found in Section 6.1.6. If a subject is discontinued, subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

5.4.1.1 HCV Virologic Failure Criteria

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.
- 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 resistance-associated viral substitutions until 12 weeks post-treatment. Alternative management will only be considered with the approval of TA MD.

5.4.1.2 Failure to Maintain HIV Virologic Suppression

HIV RNA will be assessed at each scheduled study visit during the Treatment and Post Treatment Period, as detailed in Appendix C and Appendix D.

The criteria for failure to maintain HIV virologic suppression among subjects on stable ARTs is as follows:

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

Subjects should remain on HCV study drug treatment and his/her current ART regimen while the failure to maintain HIV virologic suppression is being confirmed. A confirmatory HIV RNA and HIV genotypic resistance blood draw can be done as an unscheduled visit. However, if this blood draw falls on the date of a scheduled study visit (Appendix C and Appendix D), only a single HIV RNA and HIV genotypic resistance blood draw needs to be performed at this visit.

At the time a confirmatory HIV RNA is drawn, a sample for HIV genotypic resistance testing should also be obtained; this sample will be analyzed if the subject's repeat plasma HIV RNA is ≥ 500 copies/mL. Subjects should remain on HCV study drug treatment and his/her current ART regimen while the failure to maintain HIV virologic suppression is being confirmed. A confirmatory HIV RNA and HIV genotypic resistance blood draw can be done as an unscheduled visit. However, if this blood draw falls on the date of a scheduled study visit (Appendix C and Appendix D), only a single HIV RNA and HIV genotypic resistance blood draw needs to be performed at this visit.

During the Treatment Period, subjects with confirmed failure to maintain HIV RNA suppression should continue HCV study drug treatment unless there is a requirement for prohibited concomitant medications (Section 5.2.3.2) to construct a new HIV ART regimen.

Clinical management of failure to maintain HIV virologic suppression during the study (Treatment and Post-Treatment Period) will be handled by the Investigator according to current HIV treatment guidelines and local standard of care. Subject's change of HIV ART regimen must be discussed with the AbbVie TA MD prior to the change being made, unless the change is being made to address an immediate safety concern.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Each dose of GLE/PIB will be dispensed in the form of film-coated co-formulated tablets at the visits listed in Appendix C. Subjects will be instructed to take study drug at the same time every day with food. Please refer to Section 5.3.1.1 and Section 5.3.2.1 for more details.

GLE/PIB will be provided by AbbVie as 100 mg/40 mg film-coated tablets. GLE/PIB will be taken orally at GLE 300 mg/PIB 120 mg (three × GLE 100 mg/PIB 40 mg tablets) QD and with food.

Beginning with Study Day 1, the site will use the IRT system to obtain the study drug kit numbers to dispense at the study visits specified in Appendix C. Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. The site will also contact the IRT system to provide study drug return information for each kit at the visits specified in Appendix C. At the end of the Treatment Period or at the Premature D/C Visit from the Treatment Period, the site will contact the IRT system to provide the discontinuation visit date information and study drug return information for each kit (Section 5.5.7).

All subjects who receive at least one dose of study drug and meet the HCV virologic failure criteria defined in Section 5.4.1.1 will be discontinued from treatment.

5.5.2 Identity of Investigational Products

Information about the study drug to be used in this study is presented in Table 7.

Table 7. Identity of Investigational Products

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
Glecaprevir/Pibrentasvir	AbbVie	Oral	Film-coated tablet	100 mg/ 40 mg

5.5.2.1 Packaging and Labeling

Study drug will be supplied in bottles. Each bottle will be labeled as required per country requirements. Labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to subject.

5.5.2.2 Storage and Disposition of Study Drug

Study Drug	Storage Conditions
Glecaprevir/Pibrentasvir bottles	15° to 25°C (59° to 77°F)

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be

maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to AbbVie (or designee).

5.5.3 Method of Assigning Subjects to Treatment Groups

At the Screening Visit, all subjects will be assigned a unique subject number through the use of IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number, assigned at the Screening Visit, throughout the study. For enrollment of eligible subjects into the study, the site will utilize the IRT system in order to receive the treatment assignment. Enrolled subjects will be assigned to either Arm A (8 weeks of treatment) or Arm B (12 weeks of treatment) based on cirrhosis status. The study drug kit numbers will be assigned according to schedules computer-generated before the start of the study by the AbbVie Statistics Department.

Contact information and user guidelines for IRT use will be provided to each site. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Subjects meeting the eligibility criteria will be enrolled as described in Section 8.3.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.6.4. Study drug dosing will be initiated at the Study Day 1 Visit.

All tablets of GLE/PIB will be dosed together (three tablets once daily). All subjects should take all doses of study medications with food.

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

At the start of the study, each subject should receive counseling regarding the importance of dosing compliance with the treatment regimen with regard to HCV virologic response and potential development of resistance due to poor compliance.

At each study visit after Day 1 during the Treatment Period, subjects will be instructed to bring all bottles of study drug (full, partial, or empty) for assessment of treatment compliance. At Study Drug Accountability visits denoted in Appendix C, study site personnel will assess subject compliance by inspecting the contents of the bottles and record the status of each one, as well as the exact number of remaining tablets of GLE/PIB in IRT. Treatment compliance will be based on the number of tablets dispensed, as recorded in IRT, and the number of remaining tablets. If poor compliance is noted, the subject should be counseled and this should be documented in the subject's source.

5.5.7 Drug Accountability

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt (POR) or similar document and via recording in the IRT system. A current (running) and accurate inventory of study drug will be kept by the investigator and will include lot number, kit number, number of tablets dispensed, subject number, initials of person who dispensed study drug, and date dispensed for each subject. An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the Treatment Period. The monitor will review study drug accountability on an ongoing basis. Final accountability will be verified by the monitor at the end of study drug treatment at the site.

During the study, should an enrolled subject misplace or damage a study drug bottle of GLE/PIB the IRT system must be contacted and informed of the misplaced or damaged study drug. If the bottle is damaged, the subject will be requested to return the remaining study drug to the site. Replacement study drug may only be dispensed to the subject by contacting the IRT system. Study drug replacement(s) and an explanation of the reason for the misplaced or damaged study drug(s) will be documented within the IRT system. The study drug start date and the last dose of the regimen will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each bottle, number of tablets remaining in each one returned, and the date of reconciliation will be documented in the IRT system. The monitor will review study drug accountability on an ongoing basis.

Upon completion of or discontinuation from the Treatment Period, all original study drug bottles (containing unused study drug) will be returned to AbbVie (or designee) or destroyed on site. All destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of drug accountability procedures. Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The GLE/PIB combination regimen for 8- and 12-weeks in HCV treatment-naïve subjects without cirrhosis and with compensated cirrhosis respectively, was evaluated in HCV GT1 – 6 infected subjects in the Phase 3 studies discussed in detail in Section 3.0. A high (> 97%) efficacy and positive safety profile was demonstrated in these studies. AbbVie plans to evaluate the same combination regimen at the proposed label durations in a similar HCV GT1 – 6 infected population in Brazil. The study is designed to include subpopulations of HCV-infected patients (e.g., GT1 and GT3; severe renal disorder and HIV/HCV co-infected population) that represents the unmet clinical treatment need in Brazil. The selection of a two arm study design is appropriate so that treatment naïve

GT1 – 6 Brazilian subjects receive the proposed label treatment duration based on their cirrhosis status.

In view of the expected high SVR rate in this study and the established safety profile of GLE/PIB in patients with advanced fibrosis, a control arm would be of limited value for efficacy comparison. In this context, an open-label study is appropriate to adequately describe the efficacy and safety of this regimen administered for the proposed global label recommended durations for treatment naïve subjects.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study. HCV RNA assays are standard and validated. Next generation sequencing (NGS) methods are experimental.

5.6.3 Suitability of Subject Population

This study is intended to enroll HCV treatment-naïve adults in Brazil with chronic HCV genotype 1 – 6 without cirrhosis and with compensated cirrhosis with METAVIR equivalent fibrosis stage F2-F4. Patients with HCV/HIV co-infection and CKD Stages 1 – 5 may participate in the study. The study population includes subpopulations of HCV-infected patients (e.g., GT1 and GT3; severe CKD and HIV/HCV co-infected populations) with high unmet clinical treatment need currently in Brazil.

5.6.4 Selection of Doses in the Study

5.6.4.1 Rationale for Dose Selections

The dose GLE/PIB 300 mg/120 mg 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.

5.6.4.1.1 GLE and PIB Dose and Treatment Duration

GLE/PIB is proposed to be indicated for the treatment of chronic HCV infection in adults. In DAA-treatment naïve adults, the recommended oral dose of GLE/PIB is three 100 mg/40 mg tablets QD with food (total daily dose of 300 mg/120 mg) for 8 weeks in subjects without cirrhosis and for 12 weeks in subjects with compensated cirrhosis based on the ITT SVR_{12} rates in the registrational studies. Only HCV treatment naïve subjects will be enrolled in this study. The efficacy in subjects with CKD4 – 5 did not differ from those without CKD. Similar efficacy result was observed on HCV/HIV co-infected subjects and HCV monoinfected subjects. The recommended durations for all HCV treatment naive patients of all HCV genotypes are summarized in Table 8, and SVR_{12} is summarized by GT in Table 9. These are recommendations for all HCV-infected patients, including those co-infected with HIV and patients with any degree of renal impairment.

A favorable safety profile has been observed in HCV-infected subjects without cirrhosis or with compensated cirrhosis who received the GLE + PIB 300 mg + 120 mg dose combination. No dose response relationship was observed for adverse events, or for treatment-emergent post-nadir alanine aminotransferase elevations.

The maximum dose of ABT-493/ABT-530 will not exceed 300 mg/120 mg per day for 12 weeks.

Table 8. Recommended GLE/PIB Duration for TN Patients

	Recommended Treatment Duration	
Patient Population	**No Cirrhosis**	**Cirrhosis**
Genotype 1 – 6	8 weeks	12 weeks

GLE = glecaprevir; PIB = pibrentasvir; TN = treatment-naïve

Table 9. Summary of SVR_{12} Rates for TN and TE-PR, SOF/R or PI by Subject Population (Phase 2 and 3 Analysis Set)

	SVR_{12}%										
	GT1		GT2		GT3		GT4 – 6		GT1 – 6		
	No Cirr	Cirr	No Cirr	Cirr	No Cirr	Cirr	No Cirr	Cirr	No Cirr	Cirr	All
TN[a] + TE-P/R, SOF/R or PI[b]	99.0	97.2	98.0	100	95.2	96.6	93.1	100	97.4	97.6	97.5

cirr = cirrhosis; GT = genotype; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; P/R = regimens containing interferon, pegylated interferon, and/or ribavirin; SOF/R = regimens containing sofosbuvir and ribavirin; SVR_{12} = sustained virologic response 12 weeks postdosing; TE = treatment-experienced; TN = treatment-naive

a. Recommended treatment duration for subjects without cirrhosis is 8 weeks and with cirrhosis is 12 weeks.

b. Recommended treatment duration for GT1, 2, 4 – 6 subjects without cirrhosis is 8 weeks and with cirrhosis is 12 weeks. Recommended treatment duration for GT3 subjects is 16 weeks.

Cross reference: AbbVie. R&D16/0146. Summary of Clinical Efficacy for Glecaprevir/Pibrentasvir in HCV. 2016.

6.0 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 after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.7.1. For product complaints, please refer to Section 6.1.8.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other" cause of the event. For adverse events to be

considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (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 accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (see Section 6.1.7 regarding toxicity management) and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during the study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been 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 adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) 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.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4).

The table of clinical toxicity grades "National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4" is available from the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf and is to be used in the grading of adverse events. Below are the general grading categories. However, the investigator should always search NCI CTC AE for a given diagnostic/symptomatic AE term to identify and apply specific grading details for that AE entity.

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.

6.1.3 Relationship to Study Drug

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

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

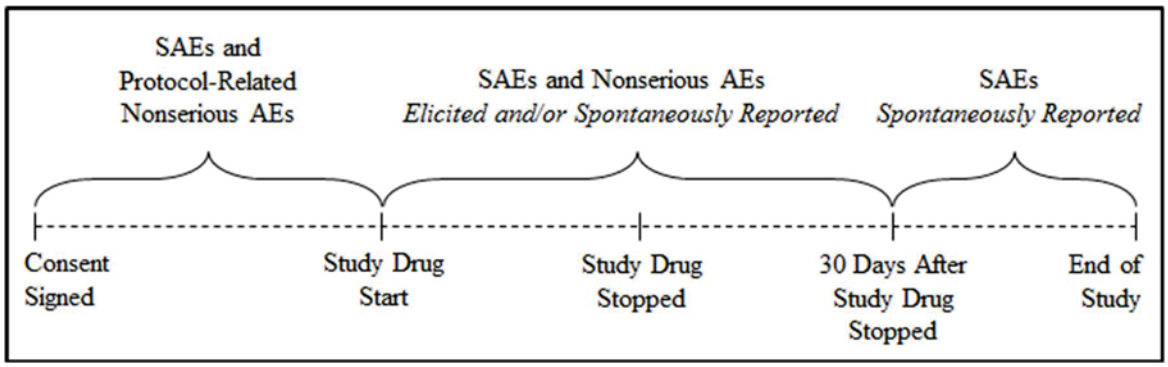
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All serious adverse events as well as protocol-related nonserious adverse events (e.g., infection at liver biopsy site) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days following discontinuation of study treatment has elapsed, all adverse events will be collected, whether solicited or spontaneously reported by the subject. After 30 days following completion of study treatment and throughout the Post-Treatment Period, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected).

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the

electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Antiviral Safety Team at:

[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office:
Email: [redacted]

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:

[redacted]
Infectious Disease Development
1500 Seaport Blvd, Suite 289H
Redwood City, CA 94063

Telephone Contact Information:
Office:
Mobile:
Email: [redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: [redacted]

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming 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 5.4.1). If a subject is discontinued, the subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

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 end of treatment.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the investigator. All adverse events 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 "National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4" is to be used in the grading of adverse events and laboratory abnormalities, which is available on the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Specific toxicity management guidelines apply to the instances of increases in ALT (Section 6.1.7.1).

6.1.7.1 Management of Increases in ALT

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 the hepatic questionnaire.
- Evaluate for an alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain Anti-HAV IgM, Anti-HAV IgG, Anti-HBc IgM, Anti-HBc Total, Anti-HBs, HBV DNA, HBsAG, Anti-HEV IgM, Anti-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 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 liver failure.
  - At the discretion of the investigator.

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

6.1.8 Collection of Data Regarding Known AIDS-Associated Opportunistic Infections

HIV infected subjects participating in clinical trials may develop infections typically associated with AIDS. A list of these known AIDS-associated opportunistic infections (OI) is presented in Appendix E. The events listed in Appendix E will be summarized as HIV-related events, not as adverse events. These OIs will be collected from the time of study drug administration until 30 days following discontinuation of study drug.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) 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.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. 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 adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitors:

Primary Contact:	Alternate Contact:
[redacted]	[redacted]
AbbVie	AbbVie
[redacted]	[redacted]
North Chicago, IL 60064	North Chicago, IL 60064
USA	USA
Office: [redacted]	Office: [redacted]
Email: [redacted]	Email: [redacted]

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

An interim data lock may occur in the study if interim study results are needed for regulatory interaction purposes. No changes to the study design or treatment of subjects would result from this interim analyses, so adjustment for multiplicity is needed.

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

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

Safety and demographic analyses will be performed on all subjects who receive at least one dose of study drug.

Efficacy analyses will be performed on the intention-to-treat (ITT) population defined as all enrolled subjects who receive at least one dose of study drug, unless otherwise specified.

Sensitivity analyses of the primary efficacy endpoint, when applicable, will be performed on the intention-to-treat population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-VF).

No data will be imputed for any efficacy or safety analysis except for analyses of SVR endpoints (HCV RNA data). HCV RNA values will be selected for the analyses of all SVR endpoints (e.g., SVR_4 and SVR_{12}) based on defined visit windows. A backward imputation method will be used to impute missing responses for SVR analyses.

8.1.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all treated subjects by Arm (A and B), and overall. Demographics include age, weight, height, body mass index (BMI), gender, race, and ethnicity. Baseline characteristics include HCV genotype subtype, prior HCV treatment history, CKD stage, baseline HCV RNA level, fibrosis stage (F2, F3, F4), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no), use of stable opiate substitution, history of diabetes, baseline metabolic syndrome, history of bleeding disorders, history of depression or bipolar disorder, history of cardiovascular disease, geographic region, and HIV coinfection status.

All the demographics and baseline characteristics will be summarized as continuous or categorical variables where appropriate. Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and BMI), and the number and percentage of subjects will be presented for categorical variables (e.g., sex and race).

Treatment compliance to study drug will be calculated based on the percentage of tablets taken relative to the total tablets expected to be taken. A subject is considered to be compliant if the percentage is between 80% and 120%. Compliance will be calculated for each subject and summarized with the mean, median, standard deviation, minimum, and maximum. The percentage of compliant subjects will be summarized.

8.1.2 Efficacy

All efficacy analyses will be performed on the ITT population, unless otherwise specified.

The efficacy analyses will be performed across all treatment durations and genotypes.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. The notation "HCV RNA < LLOQ" is used to represent all HCV RNA values

< 15 IU/mL, regardless of whether the HCV RNA is detectable or not. HCV RNA ≥ LLOQ are all quantifiable values.

8.1.2.1 Primary Efficacy Endpoints

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) within all genotypes (GT1 – 6 subjects) will be analyzed on combined treatment groups. The primary endpoint will be analyzed based on intention to treat (ITT) population. The number and percentage of subjects achieving SVR_{12} will be summarized with a two-sided 95% confidence interval. If the SVR_{12} is less than 100%, then the normal approximation of the binomial distribution will be used as a confidence interval. If the SVR_{12} rate is 100%, the Wilson's score method will be used to calculate the confidence interval.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The percentage of subjects with HCV on-treatment virologic failure (defined as confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and
- The percentage of subjects with post-treatment HCV virologic relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment; excluding subjects who have been shown to be reinfected)

For the analysis of post-treatment HCV virologic relapse, completion of treatment is defined as any subject with study drug duration of 52 days and 77 days or greater for subjects allocated to treatment durations of 8 weeks and 12 weeks, respectively.

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

8.1.2.3 Sensitivity Analysis

As sensitivity analyses, the number and percentage of subjects in the mITT-VF population achieving SVR_{12}, as applicable, will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution and a two-sided 95% confidence interval using the Wilson's score method.

The two-sided 95% confidence interval using Wilson's score method will also be calculated as a sensitivity analysis for the primary endpoint of SVR_{12} based on ITT population.

8.1.2.4 Subgroup Analysis

The subgroup analyses will be performed based on the combined treatment groups. The percentage of subjects with SVR_{12} will be calculated, as will the corresponding two sided 95% Wilson score intervals, for the following subgroups:

- HCV genotype and available subtype
- Sex
- Age
- Race
- Baseline HCV RNA level
- Baseline fibrosis stage
- Baseline cirrhosis status
- Baseline platelet count
- Baseline albumin
- Chronic Kidney Disease Stage
- HIV co-infection
- HIV ART regimen (for HIV coinfected)

- Baseline CD4+ count (for HIV coinfected)

Further details about subgroup analysis will be described in the statistical analysis plan.

8.1.2.5 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized by genotype:

- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of subjects who achieve SVR_4 4 weeks after the last actual dose of study drug (SVR_4);
- The percentage of subjects who relapse after achieving SVR_{12}.

The number and percentage of subjects meeting each additional efficacy endpoint will be summarized along with a two-sided 95% confidence interval using the Wilson's score interval.

8.1.3 Patient Reported Outcomes

The handling of missing data for patient reported outcomes (PROs) will be as follows. If a respondent answers at least 50% of the items in a multi-item scale of the SF-36v2, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing. The Mental and Physical Component Summary measures will not be computed if any domain is missing. For TSQM, if a respondent answers at least 2 items in the 3 item scales of Side Effects or Effectiveness, the missing items will be imputed with the average score of the answered items in the same scale. For EQ-5D-3L, health state index and VAS scores no imputation will be performed for missing items.

The mean change from baseline to each applicable post-baseline timepoint in the SF-36v2 Mental Component Summary (SF-36-MCS) and Physical Component Summary

(SF-36-PCS) scores; EQ5D-3L health state index and VAS score; TSQM Effectiveness, Side Effects, Convenience, and Global Satisfaction scores will be summarized descriptively at each applicable visit and for change from baseline to each applicable visit. For each of these scores, mean change from Baseline to Final Treatment Visit and from Baseline to Post-Treatment Week 12 will be summarized using an analysis of covariance (ANCOVA) model with baseline score as a covariate.

The following analyses of patient reported outcomes (PROs) also will be performed:

- Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable timepoint of greater than or equal to 3 points in the SF-36 MCS and PCS;
- Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable timepoint of greater than or equal to 5 points in the SF-36 MCS and PCS;
- Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable timepoint of greater than or equal to 5 points in the SF-36 domain scores;

Additional analyses of PROs will be performed as useful and appropriate.

8.1.4 HCV Resistance Analyses

For all subjects with an available sample, full length NS3/4A or NS5A from baseline samples will be sequenced by NGS. For subjects who experience virologic failure (on-treatment virologic failure or post-treatment relapse), full length NS3/4A and NS5A genes from the first available sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS. An appropriate subtype specific prototypic reference sequence will be used for comparison with sequences from samples. Subjects treated with study drug who do not achieve SVR_{12} due to reasons other than virologic failure but have a time point with HCV RNA ≥ 1000 IU/mL after treatment discontinuation, will have the sample at that time point sequenced.

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore, if the HCV RNA level at the time of HCV virologic failure or treatment discontinuation is < 1000 IU/mL, the sample closest in time after HCV virologic failure/treatment discontinuation with an HCV RNA level ≥ 1000 IU/mL will be used.

The following definitions will be used in the resistance analyses:

- Baseline polymorphism: a polymorphism by NGS in a baseline sample (≥ 2% or ≥ 15% prevalence within a subject's viral population depending on polymorphism frequency threshold utilized) that was not present in the appropriate prototypic reference amino acid sequence for a given DAA target (NS3/4A or NS5A).
- Polymorphism/substitution at a signature amino acid position: polymorphism (relative to reference) present in a baseline sample or substitution (relative to baseline) present in a post-baseline sample at a signature amino acid position.
- Post-baseline substitution: an amino acid substitution in a post-baseline time point sample that was not detected at baseline (< 2%) in the subject and is detectable in ≥ 2% of the sequences from the post-baseline sample.
- Enriched polymorphism: polymorphism present in both the baseline and a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post-baseline % – baseline %) ≥ 20].
- Treatment-emergent substitution by NGS: A post-baseline substitution or an enriched polymorphism detected by NGS.

Analysis 1: The following analyses will be provided for all subjects, separated by HCV subtype:

- A listing of all baseline polymorphisms (2% detection threshold) at signature resistance-associated amino acid positions for each DAA target (NS3/4A and NS5A).

- A listing of all baseline polymorphisms (15% detection threshold) at non-signature resistance-associated amino acid positions for each DAA target (NS3/4A and NS5A) for subjects who experience virologic failure.
- The number and percentage of subjects with baseline polymorphisms at signature amino acid positions at detection thresholds of 2% and 15%.

Analysis 2: The impact of baseline polymorphisms on treatment outcome will be assessed as follows: for each polymorphism, the SVR_{12} rate will be calculated for subjects with and without the polymorphism and the 2 rates will be compared. Analysis will be grouped by HCV subtype and DAA target (NS3/4A or NS5A).

The following will be included in the analyses of impact of baseline polymorphisms on treatment outcome:

- For each signature amino acid position, presence of any polymorphism at that position (vs no polymorphism at that position), using detection thresholds of both 2% and 15%.
- Each individual polymorphism at each signature amino acid position (vs not that polymorphism) using detection thresholds of 2% and 15%.
- Polymorphisms at each non-signature amino acid position at a detection threshold of 15%.

Analysis 3: The following analyses will be performed for subjects who do not achieve SVR_{12} and who have post-baseline resistance data available:

- Listings by subject of all treatment-emergent substitutions relative to the baseline amino acid sequences will be provided for each DAA target (NS3/4A and NS5A).
- Listings by subject and time point of all post-baseline substitutions at signature amino acid position relative to the baseline amino acid sequence will be provided for each DAA target (NS3/4A and NS5A).

HCV Genotype/Subtype

Phylogenetic analysis will be conducted on HCV NS3/4A and/or NS5A sequence from baseline samples from all subjects in order to accurately determine genotype/subtype. If the phylogenetic analysis is not available, then the result from Sanger sequencing of a region of NS5B by AbbVie or by the Central laboratory will be used to determine the subject's HCV genotype/subtype, if available. Finally, if neither the phylogenetic analysis result nor the Sanger sequencing assay results is available, then the Inno-LIPA assay results from the Central laboratory will be used to categorize the subject. This final HCV genotype subtype will be used in efficacy subgroup analyses.

8.1.5 HIV Resistance Analyses

If a subject develops a confirmed, plasma HIV RNA level ≥ 500 copies/mL after starting the study, the subject's HIV PR, RT, and/or IN sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assays. The number of subjects who demonstrate HIV genotypic resistance and the genotypic resistance mutations detected in the samples obtained from these subjects will be tabulated and summarized. Resistance will be defined as described by the IAS-USA Panel.[18]

8.1.6 Safety

Safety summaries will be provided by the treatment arm (i.e., study drug duration assigned by cirrhosis status) and overall. All subjects who receive at least one dose of study drug will be included in the safety analyses.

8.1.6.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term. The tabulation of the number of subjects with

treatment-emergent adverse events by severity grade (Grades 1 – 5) and relationship to each study drug will also be provided. Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe grade for the severity grade table and the most related for the relationship to study drug tables. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC.

Additional analyses will be described in the statistical analysis plan.

8.1.6.2 Clinical Laboratory Data

Clinical laboratory tests will be summarized at each visit. The baseline value will be the last non-missing measurement prior to the initial dose of study drug. Mean changes from baseline to each post-baseline visit, including Final Treatment Visit, will be summarized descriptively. Changes from baseline to maximum post-baseline CTCAE grade of laboratory values will also be summarized.

8.1.6.3 Vital Signs Data

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each post-baseline visit, including Final Treatment Visit, will be summarized descriptively. The number and percentage of subjects with post-baseline values meeting pre-defined criteria for Potentially Clinically Significant (PCS) vital signs values will be summarized.

8.1.6.4 HCV/HIV Co-Infection

The following additional safety data will be summarized and analyzed for subjects with HCV/HIV co-infection overall and in each treatment arm:

- The percentage of subjects with plasma HIV RNA suppression at the end of treatment and at Post-Treatment Week 12 using the FDA Snapshot Algorithm;
- The number and percentage of subjects with plasma HIV RNA < 20 copies/mL at each applicable time point;

- Change from baseline in CD4+ T-cell count (absolute and percent) to each applicable post-baseline time point;
- Change from baseline in lymphocytes (count and percentage) and CD8+ T-cell counts (absolute and percent) to each applicable post-baseline time point;
- The listing of subjects with a plasma HIV RNA value ≥ 200 copies/mL at any baseline or post-baseline visit during the study.

The analysis of change from baseline in CD4+ T-cell count (absolute and percent), lymphocytes (count and percentage) and CD8+ T-cell counts (absolute and percent) will report the mean and median values at baseline and at each applicable post-baseline visit, as well as N, mean, median, standard deviation (SD), minimum and maximum values for the change from baseline overall and within each treatment arm.

8.1.7 Pharmacokinetic and Exposure-Response Analyses

Plasma concentrations of GLE, PIB, and their possible metabolites, if measured, will be tabulated for each subject and group. Summary statistics will be computed for each time and visit.

Plasma concentration data from this study may be combined with data from other studies and analyzed using the following general methodology:

Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (version VII, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. Apparent oral clearance (CL/F) and apparent volume of distribution (V/F) of the PK analytes will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis. Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM.

Relationship between exposure (noncompartmental or population pharmacokinetic model based values of concentrations over time, AUC, C_{trough} or some other appropriate measure of exposure) and clinical observations (antiviral activity or virologic end points, such as SVR_{12} response) may be explored, if appropriate.

Exposure-response relationships for primary and secondary efficacy variables and/or some safety measures of interest may also be explored. Exposure response relationships will utilize a logistic regression analysis and/or a semi-mechanistic viral dynamic model. Additionally, relationship between exposure and safety endpoints of interest may also be explored. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

It is anticipated that a total of approximately 100 HCV infected treatment naïve GT1 – 6 subjects will be enrolled in this study. No formal hypothesis is being tested. If the observed SVR_{12} rate in this study is 97% among 100 HCV GT1 – 6 treatment naive subjects, then the half-width of 2-sided 95% normal approximation interval is 3.3%.

8.3 Randomization Methods

This study is not randomized. Eligible subjects will be allocated to a treatment arm according to their cirrhosis status (presence/absence).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific, and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information, and/or

advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain, and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on 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 clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

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

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will

be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

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

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

Any research that may be done using optional exploratory research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research

other than for regulatory purposes. Aggregate data from optional exploratory research may be provided to investigators and used in scientific publications or presented at medical conventions. Optional exploratory research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

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

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for GLE/PIB Fixed-Dose Combination.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection

Protocol Date: 16 February 2017

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
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., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
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 investigation and all 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. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Pharmacokinetics
		Clinical
		Clinical
		Clinical
		Statistics
		Clinical
		Clinical Drug Supply Management

Appendix C. Study Activities – Treatment Period

Activity	Screening	Day 1[a]	Wk 4	Wk 8 (Arm B Only)	EOT (Arm A and Arm B) or Premature D/C from Treatment[b]
Informed Consent[c]	X				
Dispense/Review Study Drug Dosing Card		X (Dispense only)	X	X	X (Review only)
Medical History[d]	X	X			
Physical Exam[e]	X	X			X
Vital Signs, Weight, Height[f]	X	X	X	X	X
ECG	X				
Hematology/Chemistry[g]/Coagulation Panel	X	X	X	X	X
Pregnancy Test (serum [s] urine [u])[h]	X (s)	X (u, s)	X (u)	X (u)	X (u)
Anti-HCV Ab, Anti-HIV Ab	X				
Hepatitis B Panel	X				
HCV Genotype and Subgenotype	X				
FibroTest or FibroScan® or Liver Biopsy[i]	X				
Concomitant Medication Assessment	X	X	X	X	X
Adverse Event Assessment[k]	X	X	X	X	X
Study Drug Dispensed		X	X	X[k]	
HCV RNA Samples	X	X	X	X	X
Study Drug Accountability and Review of Study Drug Adherence			X	X	X[l]
HCV Resistance Sample		X	X	X	X

Activity	Screening	Day 1[a]	Wk 4	Wk 8 (Arm B Only)	EOT (Arm A and Arm B) or Premature D/C from Treatment[b]
Pharmacokinetic Samples[m]			X	X	X
Child-Pugh Score (subjects with compensated cirrhosis only)	X	X			X
Clinical Assessment of Hepatic Decompensation (subjects with compensated cirrhosis only)		X			
HCC Screening Liver ultrasound (subjects with compensated cirrhosis only)	X				
Patient Reported Outcomes Instruments (PROs)[n]		X			X
Flow cytometry sample[o]	X	X			X
HIV RNA[o]	X	X	X	X	X

Wk = Week; EOT = End of treatment; D/C = Discontinuation

* The EOT visit can be at Week 8 or 12 in accordance with treatment duration as described in Section 5.1.

a. All procedures to be performed prior to first dose.

b. Subjects who prematurely discontinue during the Treatment Period should return to the site to complete the Premature D/C Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy).

c. Subjects need to sign an IRB/IEC approved informed consent for the study (prior to performing any Screening or study-specific procedures).

d. A complete medical history will be taken at Screening and will be updated at the Study Day 1 Visit.

e. A symptom-directed physical examination may be performed at any other visit, when necessary. Any significant physical examination findings after the first dose will be recorded as adverse events.

f. Height will be measured at the Screening Visit only.

g. Blood samples for serum chemistry tests should be collected following a minimum 8-hour fast prior to study drug intake (with the exception of the Screening Visit, which may be non-fasting).

h. Pregnancy testing is not required for women not of childbearing potential as defined in Section 5.2.4.

i. For subjects who have not had a qualifying liver biopsy within the previous 24 months for subjects without cirrhosis or at any time for subjects with compensated cirrhosis) or a qualifying FibroScan® within the previous 6 months for subjects without cirrhosis or at any time prior to Screening for subjects with compensated cirrhosis).

j. Subjects with a historical negative Liver Ultrasound, CT or MRI (within 3 months prior to screening) are not required to have a screening Liver Ultrasound performed. If additional Liver Ultrasound testing is required it should be completed as an unscheduled visit. A positive ultrasound result suspicious of HCC will be confirmed with CT scan or MRI. A liver ultrasound should be performed at the end of treatment visit if it has been 6 months or more since the historical evaluation.

k. See specific information regarding adverse event collection in Section 6.1.1.1.

l. Dispensation at Week 8 and Study Drug Accountability at Week 12 are only applicable to Arm B. Subjects should bring all study drug to every visit for the site to review adherence. However, the site will record the number of tablets returned only at the Study Drug Accountability Visits at Weeks 4, 8, 12 (if applicable) or Premature D/C.

m. PK samples will be collected at each scheduled study visit. Detail regarding timing of samples is provided in Section 5.3.2.1.

n. PROs should be administered before any study procedures in the order listed in Section 5.3.1.1.

o. For HCV/HIV co-infected subjects.

Appendix D. Study Activities – Post-Treatment (PT) Period

Activity	PT Wk 4	PT Wk 12	PT D/C[a]
Vital Signs and Weight	X	X	X
Hematology/Chemistry/Coagulation Panel	X		X[b]
Pregnancy Test (urine)[c]	X (u)		X (u)[b]
Concomitant Medication Assessment[d]	X	X[d]	X[d]
Child-Pugh Score (subjects with compensated cirrhosis only)		X	X
Adverse Event Assessment[e]	X[e]	X[f]	X[f]
HCV RNA Samples	X	X	X
HCV Resistance Sample	X	X	X
Patient Reported Outcomes Instruments (PROs)[g]		X	X
Flow cytometry sample[h]	X	X	
HIV RNA[h]	X	X	

Wk = Week; PT D/C = Post-Treatment Discontinuation

a. Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C Visit procedures.

b. Hematology/Chemistry /Coagulation Panel and Pregnancy Test are not required at PT Wk 12, but only at PT D/C if subject discontinues prior to PT Wk 4.

c. Women of childbearing potential do not require pregnancy testing beyond PTW4. Pregnancy testing will be performed at PT D/C visit only if the subject discontinues prior to PTW4. Pregnancy testing in PT Period is not required for females of non-childbearing potential as defined in Section 5.2.4.

d. Only medications taken for SAEs and treatment of HCV will be collected after 30 days post-dosing.

e. Nonserious AEs and all SAEs will be collected until 30 days post dosing. All spontaneously reported SAEs will be collected thereafter. See specific information regarding adverse event collection in Section 6.1.4.

f. Only SAEs will be collected thereafter as described in Section 6.1.4.

g. PROs should be administered before any study procedures in the order listed in Section 5.3.1.1.

h. For HCV/HIV co-infected subjects.

Note: Day 1 of the Post-Treatment Period will be defined as the day after the last dose of study drug.

Appendix E. List of AIDS-Associated Opportunistic Infections

Collection of data regarding known AIDS-associated opportunistic infections is covered in Section 6.1.8.

- Aspergillosis
- Bartonellosis
- Candidiasis (*Bronchi; *Esophagus; *Lungs; Oropharyngeal [Thrush]; *Trachea; Vulvovaginal [Persistent, Frequent, or Poorly Responsive to Therapy])
- *Coccidioidomycosis
- *Cryptococcosis
- *Cryptosporidiosis
- Cytomegalovirus (*Retinitis; *Cytomegalovirus Disease [other than liver, spleen or nodes])
- Enteric infections, Recurrent (Bacterial)
- Herpes Simplex Virus (*Bronchitis; *Esophagitis; *Pneumonitis; *Chronic Ulcer(s) [> 1 month in duration])
- *Histoplasmosis
- Human Herpesvirus-8 Disease (Kaposi Sarcoma, Primary Effusion Lymphoma, Multicentric Castleman's Disease)
- Human Papilloma Virus Infections
- *Isosporiasis (Cystoisosporiasis)
- Microsporidiosis
- *Mycobacterium avium – Complex Disease (Disseminated)
- *Mycobacterium tuberculosis – Infection and Disease
- *Pneumonia
- *Pneumonia, recurrent bacterial (and/or other respiratory infections including sinusitis, bronchitis, otitis)
- *Progressive multifocal leukoencephalopathy (JC Virus Infection)
- Syphilis

- *Toxoplasma Gondii Encephalitis
- Varicella Zoster Virus Diseases

* AIDS-defining event as described by CDC Surveillance Case Definition of 1993.

Cross reference: Guidelines for Prevention and Treatment of Opportunistic Infections in HIV Infected Adults and Adolescents. Available from: http://aidsinfo nih.gov/guidelines.

Document Approval

Study M16156 - A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection - 16Feb2017

Version: 1.0 **Date:** 17-Feb-2017 08:52:12 PM **Company ID:** 02172017-00F9F68144E8CF-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	16-Feb-2017 11:43:44 PM	Approver
	17-Feb-2017 01:48:35 AM	Approver
	17-Feb-2017 02:24:47 PM	Approver
	17-Feb-2017 02:58:43 PM	Approver
	17-Feb-2017 05:31:23 PM	Approver
	17-Feb-2017 07:52:11 PM	Approver
	17-Feb-2017 08:52:10 PM	Approver