1.0 Title Page

Clinical Study Protocol M16-126

A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Adults with Chronic Hepatitis C Virus (HCV) Genotype 5 or 6 Infection

Incorporating Amendment 1

AbbVie Investigational Product:	Glecaprevir/Pibrentasvir
Date:	28 July 2017
Development Phase:	3b
Study Design:	This is an open-label, multicenter study
EudraCT Number:	2016-003192-22
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc. (AbbVie)*
Sponsor/Emergency Contact:	[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	15 September 2016

The purpose of this amendment is to:

- Update Section 3.0, Introduction, GLE and PIB

  Rationale: *Updated per the AbbVie Glecaprevir/Pibrentasvir Fixed-Dose Combination Investigator's Brochure Edition 2. 06 September 2016; including Addendum 1 Edition 2 November 2016.*
- Update Section 5.2.3.3, Prohibited Therapy, Table 1, 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 G/P*
- 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: *To remove Alpha Fetoprotein from the protocol, because the protocol-required HCC screening incorporates the more sensitive and specific imaging exams (ultrasound, MRI, PET scan) and determination of Alpha Fetoprotein levels is not necessary. The HCC Screening Liver Ultrasound at Post-Treatment Week 24 was added to ascertain the subject did not develop HCC during the course of the trial.*
- Update Section 5.3.2.1, Collection of Samples for Analysis

  Rationale: *To correct the blood volume drawn for Pharmacokinetic Samples*
- Update Section 7.0, Protocol Deviations, alternative contact

  Rationale: *To reflect current study personnel.*
- Updated Section 8.1.2.1 Primary Efficacy Endpoints

Rationale: *Regulatory authority feedback requested that for high SVR_{12} rates less than 100% the Wilson score test be used for calculating the 95% confidence interval in the primary efficacy analysis, rather than using the normal approximation to the binomial distribution. To comply with this feedback, the Wilson score method will be used to calculate the confidence intervals for the primary efficacy endpoints if the number of SVR_{12} non-responders is less than 5, otherwise normal approximation to the binomial distribution will be used.*

- Appendix B, List of Protocol Signatories

  Rationale: *To reflect current study personnel.*
- Correct minor typographical and grammatical errors throughout the protocol

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-126
Name of Study Drug: Glecaprevir, Pibrentasvir	**Phase of Development:** 3b
Name of Active Ingredient: Glecaprevir Pibrentasvir	**Date of Protocol Synopsis:** 28 July 2017
Protocol Title: A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Adults with Chronic Hepatitis C Virus (HCV) Genotype 5 or 6 Infection	
Objectives: • The primary objectives of this study are to assess the efficacy (by evaluating the percentage of subjects achieving SVR_{12}) and safety of glecaprevir/pibrentasvir in adults with chronic hepatitis C virus (HCV) genotype (GT) 5 or 6 infection with or without compensated cirrhosis. The efficacy of glecaprevir/pibrentasvir will be assessed by genotypes across treatment durations (or cirrhosis status) and the safety of glecaprevir/pibrentasvir will be assessed by treatment duration (or cirrhosis status) across genotypes. • The secondary objectives are to assess efficacy of glecaprevir/pibrentasvir by hepatitis C virus (HCV) genotype (GT) 5 or 6 infection across treatment duration (or cirrhosis status) by evaluating the percentages of subjects with HCV on-treatment virologic failure and HCV virologic relapse across treatment durations (or cirrhosis status). Additional objectives are to assess pharmacokinetics and emergence and persistence of viral variants in these treatment regimens.	
Investigators: Multicenter	
Study Sites: Approximately 26	
Study Population: Chronic HCV GT5 or 6-infected male and female adults aged 18 years or older, without cirrhosis or with compensated cirrhosis, who are either HCV treatment-naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication) or treatment experienced (i.e., has failed prior interferon [IFN] or pegylated interferon [pegIFN] with or without ribavirin [RBV], or sofosbuvir [SOF] plus RBV with or without pegIFN therapy).	
Number of Subjects to be Enrolled: Approximately 80 subjects	
Methodology: This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of glecaprevir/pibrentasvir for an 8- or 12-week treatment duration in adults with chronic HCV GT5 or 6 infection, with or without compensated cirrhosis, who are either HCV treatment-naïve or treatment-experienced with IFN or pegIFN with or without RBV (defined as P/R treatment-experienced) or SOF plus RBV with or without pegIFN (defined as SOF plus RBV treatment-experienced). Approximately 80 subjects meeting the eligibility criteria will be enrolled globally. Approximately 30 GT5-infected subjects and approximately 50 GT6-infected subjects will be enrolled in the study. The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of 15 GT5 and 30 GT6 subjects and 2) up to approximately 16 subjects with compensated cirrhosis (regardless of GT). Approximately 80 eligible subjects will be enrolled into one of the following treatment arms:	

Methodology (Continued):

- Arm A: HCV GT 5 or 6 non-cirrhotic subjects will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks.
- Arm B: HCV GT 5 or 6 subjects with compensated cirrhosis will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 12 weeks.

The study will consist of two periods:

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

Scheduled visits for subjects in the Treatment Period consist of Day 1 and Weeks 1, 2, 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, adherence, concomitant medications, HCV RNA, HCV resistance, glecaprevir and pibrentasvir pharmacokinetic assays, and clinical laboratory tests, will be conducted at each visit.

Post-Treatment Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 24 weeks to monitor HCV RNA levels to evaluate efficacy and the emergence and persistence of resistant viral variants.

During the Post-Treatment Period, all subjects will have visits at Weeks 4, 12, and 24 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. Male or female, at least 18 years of age at time of Screening.
2. Screening laboratory result indicating HCV GT5 or 6 infection.
3. Subject has a positive anti-HCV Ab and plasma HCV RNA ≥ 1000 IU/mL at Screening Visit.
4. Subject must be HCV treatment-naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication) or treatment-experienced (i.e., has failed prior interferon [IFN] or pegylated interferon [pegIFN] with or without ribavirin [RBV], or sofosbuvir [SOF] plus RBV with or without pegIFN therapy). Prior HCV treatment with any other approved or investigational medications is not allowed. Previous HCV treatment must have been completed ≥ 2 months prior to screening.
5. Subject must be documented as having no cirrhosis or compensated cirrhosis (as described in Section 5.3.1.1) non-cirrhotic or cirrhotic.

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. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol in the opinion of the investigator.
3. Positive test result at Screening for hepatitis B surface antigen (HBsAg) or anti-human immunodeficiency virus antibody (HIV Ab).
4. HCV genotype performed during screening indicating co-infection with more than one HCV genotype.
5. History of severe, life-threatening or other significant sensitivity to any excipients of the study drug.

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.

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

Criteria for Evaluation:

Efficacy:

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

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 Work Productivity and Activity Impairment Questionnaire: Hepatitis C (WPAI: Hepatitis C) will assess work and activity impairment due to HCV.

Pharmacokinetic:

Individual plasma concentrations of glecaprevir and pibrentasvir will be tabulated and summarized.

Resistance:

The following information will be tabulated and summarized: 1) for all subjects with available samples, the variants at baseline 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 variants relative to baselines in available samples.

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) within each genotype (GT5 and GT6 subjects) separately across treatment arms. 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 rate for SVR_{12} is 100%, where the Wilson's score method will be used to calculate the confidence interval.

The secondary efficacy endpoints within each genotype (GT5 and GT6 subjects) separately, across treatment arms are:

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

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

Statistical Methods (Continued):

PROs:

Change from baseline to each applicable visit in the patient reported outcome summary measures will be summarized.

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) 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. Change from baseline in laboratory tests and vital signs measurements to each time point of collection will be summarized, and values that are potentially clinically significant, according to predefined criteria, will be summarized by treatment arm (i.e., cirrhosis status/study drug duration) and overall. Changes from baseline to post-baseline in the CTCAE grading of laboratory values will also be summarized.

Pharmacokinetic:

Plasma concentrations of glecaprevir and pibrentasvir will be tabulated for each subject and treatment arm. Summary statistics will be computed for each treatment arm. 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.

Resistance:

For all subjects receiving study drug, the variants at signature resistance-associated amino acid positions at baseline 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 variants in available post-baseline samples identified by NGS and comparison to the baseline sequences, 2) the amino acid variants 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 resistance by NGS.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

Ab	Antibody
ABT-267	Ombitasvir
ABT-450	Paritaprevir
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
APRI	Aminotransferase/platelet ratio index
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{24}	AUC for the 24-hour dosing interval
β	Apparent terminal phase elimination rate constant
BID	Twice Daily
BMI	Body mass index
BUN	Blood urea nitrogen
CL/F	Apparent oral plasma clearance
C_{max}	Maximum observed plasma concentration
CPK	Creatine phosphokinase
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
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture

EDTA	Edetic acid (ethylenediaminetetraacetic acid)
EOT	End of treatment
EU	European Union
GCP	Good Clinical Practice
GCSF	granulocyte colony stimulating factor
GGT	Gamma-glutamyl transferase
GT	Genotype
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
Hemoglobin A1c	Glycated hemoglobin
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon
IL28B	Interleukin 28B
IMP	Investigational Medical Product
INR	International normalized ratio
IP-10	Interferon gamma-induced protein 10
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
NS	Non-structural
NS3A	Nonstructural viral protein 3A
NS4A	Nonstructural viral protein 4A
NS5A	Nonstructural viral protein 5A
NS5B	Nonstructural viral protein 5B
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
RT-PCR	Reverse transcriptase PCR
SAD	Single Ascending Dose
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Standard Deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
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
SVR_{24}	Sustained virologic response 24 weeks post dosing
$t_{1/2}$	Terminal phase elimination half-life

T_{max}	Time to maximum observed plasma concentration (C_{max})
TN	Treatment-naïve
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 24 or Post-Treatment Discontinuation

2.0 Table of Contents

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3.0 Introduction

Hepatitis C viral (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.[5] Depending on various risk factors, between 10% and 40% of all patients with chronic HCV infection will develop cirrhosis.[6]

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.[6] Patients diagnosed with hepatocellular carcinoma have a 33% probability of death during the first year.[6] 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.[7,8]

Prior to the approval of sofosbuvir (SOF) in 2014, the recommended treatment for GT5 and GT6 HCV infection was pegINF/RBV for 48 weeks. The inclusion of SOF to pegIFN/RBV shortened the treatment to 12 weeks, and this was supported by a Phase 3 open-label study where a total of 7 treatment-naive GT5 (n = 1) and GT6 (n = 6) subjects were treated with pegINF/RBV plus SOF regimen for 12 weeks where all subjects achieved SVR_{12} (100%).[9]

AbbVie is currently developing two "next generation" DAA drugs, glecaprevir (GLE), an HCV non-structural (NS) protein 3/4A protease inhibitor (PI) and pibrentasvir (PIB), an NS5A inhibitor, for use in combination for the treatment of chronic HCV infection. The objectives of this study are to evaluate the efficacy and safety of GLE/PIB used together for the treatment of those with chronic HCV GT5 or 6 infection with or without compensated cirrhosis.

Glecaprevir (GLE)

GLE is an NS3/4A PI with potent and pangenotypic activity. Its EC_{50} values against HCV replicon stable cell lines with GT1a, 1b, 2a, 3a, 4a and 6a NS3 are 0.85, 0.94, 2.7, 1.6, 2.8 and 0.86 nM, respectively. GLE EC_{50} data for a stable replicon cell line containing NS3 from GT5a is not available, but in a transient transfection assay using a replicon containing NS3 from GT5a, GLE demonstrated an EC_{50} of ~0.15 nM, which was similar to the GLE EC_{50} values for GT1a and GT1b replicons in the same assay. GLE demonstrates a high genetic barrier to resistance and maintains activity against common variants that emerge following exposure to first generation PIs.

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.[10]

Pibrentasvir (PIB)

PIB is an NS5A inhibitor with potent and pangenotypic activity. The in vitro antiviral activity of PIB against HCV GT1a, 1b, 2a, 2b, 3a, 4a, 5a and 6a is similar, with EC_{50} values of 1.8, 4.3, 2.3, 1.9, 2.1, 1.9, 1.4 and 2.8 pM, respectively, in stable replicon cell lines. It demonstrates a high genetic barrier to resistance and maintains activity against common resistance-associated variants in NS5A in all GTs. PIB is greater than 100-fold more active than the first generation NS5A inhibitors (ombitasvir, daclatasvir, and ledipasvir) against key resistance-associated variants.

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.[10]

GLE and PIB

In general, GLE and PIB combination has been well tolerated when administered to over 800 healthy volunteers and 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. The efficacy rates were high (> 95%) among treatment-naive or pegIFN + RBV-experienced non-

cirrhotic HCV-infected GT-1 – 6 subjects treated with 8 weeks of GLE/PIB in Phase 2 studies. Among cirrhotic GT1 treatment-naïve or pegIFN + RBV-experienced treated with GLE/PIB for 12 weeks, efficacy was high (> 95%). However, longer than 12 weeks treatment may be beneficial to improve efficacy among non-cirrhotic GT3 pegIFN + RBV-experienced as efficacy rate was < 95%. Most frequently reported AEs in Phase 2 studies were mild to moderate and clinically manageable. Overall, GLE and PIB regimen has demonstrated a favorable safety profile in Phase 1 and 2 studies.

Additive or synergistic in vitro anti-HCV activity has been demonstrated with the combination of GLE and PIB.

EC_{50}s of PIB for GTs 1 – 6 are similar; EC_{50}s of GLE for GTs 1 – 6 are similar. GLE and PIB exposure are similar and increased, respectively, when administered together. Therefore, GLE and PIB are expected to demonstrate efficacy in subjects infected with these less prevalent genotypes (GT5 and 6).

When GLE was given in combination with PIB in healthy volunteers, results showed that GLE exposures were not significantly changed when co-administered with PIB (≤ 31% difference); however, the exposure of PIB increased in a GLE-dose-dependent manner (from 1.5-fold at 100 mg GLE up to 3- to 4-fold at 400 mg GLE).

Results of clinical DDI studies conducted to date have shown that as perpetrators of DDIs, GLE/PIB combination had no clinically meaningful impact on drugs that are substrates of CYP or UGT enzymes. The GLE/PIB combination increased exposure of substrates for P-gp, BCRP, OATP1B1, and OATP1B3 transporters. Except for some OATP inhibitors (e.g., high dose cyclosporine), ritonavir-boosted protease inhibitors and P-gp inducers, GLE and PIB exposures were minimally affected by co administrations of other drugs.

Phase 2 Studies (Studies M14-867 and M14-868) assessed efficacy, safety, and pharmacokinetics of the combination of GLE and PIB in HCV GT1 (Study M14-867 Part 1) or GT2- or 3-infected (Study M14-868 Part 1) in treatment-naïve (TN) and PR-experienced non-cirrhotic subjects, respectively, GT4 – 6 (Study M14-867 Part 2) or

GT2- or 3-infected (Study M14-868 Parts 1 and 2) treatment-naïve and PR-experienced subjects with and without cirrhosis.

In Part 1 of Study M14-867, 100% (40/40) of GT1-infected subjects without cirrhosis treated with GLE 200 mg QD + PIB 120 mg QD for 12 weeks and 97.4% (38/39) of subjects treated with GLE 200 mg QD + PIB 40 mg QD for 12 weeks achieved SVR_{12}. One subject in the GLE 200 mg QD + PIB 120 mg QD for 12 weeks group experienced relapse at Post-Treatment Week 4. In Part 2 of Study M14-867, 97% (33/34) of GT1-infected subjects without cirrhosis treated with GLE 300 mg QD + PIB 120 mg QD for 8 weeks achieved SVR_{12} (one subject discontinued due to metastatic cancer with HCV RNA undetectable at last visit).

In Part 1 of Study M14-868, a total of 195 subjects were enrolled and evenly distributed within the GT2 and GT3-infected groups. Two subjects discontinued due to Treatment-Emergent Adverse Events (Subjects 5904 and 9309 in Arm F), one subject discontinued due to virologic failure (Subject 9106 in Arm F), two subjects were lost to follow-up (Subjects 2005 in Arm F and Subject 2403 in Arm G), and one subject withdrew consent (Subject 4613 in Arm A). Two of these subjects (Subjects 5904 and 9309; both Arm F) achieved SVR_{12}.

The SVR_{12} rates for each of the treatment regimens were 96% (24/25) (including a subject who was lost to follow-up) of subjects treated with GLE 300 mg QD + PIB 120 mg QD for 12 weeks, 100% (24/24) of subjects treated with GLE 200 mg QD + PIB 120 mg QD for 12 weeks and 100% (25/25) of subjects treated with GLE 200 mg QD + PIB 120 mg QD + RBV for 12 weeks, and 98.1% (53/54) of subjects treated with GLE 300 mg QD + PIB 120 mg QD for 8 weeks.

In Part 1 of Study M14-868, 30 subjects with HCV GT3 infection non cirrhotic, treatment naïve and PR-experienced were treated with GLE 300 mg and PIB 120 mg without ribavirin for 12 weeks and 93.3% (28/30 subjects) achieved SVR_{12}. One subject in this arm experienced relapse at Post-Treatment Week 4 and one subject had missing SVR_{12} data.

In Part 2 of Study M14-867, 100% of subjects infected with HCV GT4, GT5 or GT6 non-cirrhotic, treatment-naïve and PR-experienced receiving treatment with GLE 300 mg QD + PIB 120 mg QD for 12 weeks achieved SVR_{12} (34/34). GT1-infected treatment-naïve and PR-experienced subjects with compensated cirrhosis were also evaluated with the same. Among the GT1 cirrhotic subjects, 96% (26/27) have achieved SVR_{12}, with one subject experiencing relapse at Post-Treatment Week 4.

In Study M14-868 Part 2, among 29 treatment-naïve non-cirrhotic subjects with GT3 infection treated for 8 weeks with GLE 300 mg QD + PIB 120 mg QD, no subject experienced on-treatment virologic failure or post-treatment relapse. One of the 29 subjects had missing SVR_{12} data. Among 24 treatment-naïve cirrhotic subjects with GT3 infection treated for 12 weeks with GLE 300 mg QD + PIB 120 mg QD, no subject experienced on-treatment virologic failure or post-treatment relapse.

To date, safety data across all arms in Part 1 of Studies M14-867 and M14-868 encompassing 276 subjects treated with GLE at doses 200 and 300 mg and PIB at doses 40 and 120 mg (with and without RBV in Study M14-868) for 12 weeks show that the most frequently reported adverse events were fatigue, nausea, and headache (occurring in > 5% of subjects). Most of them were Grade 1 in severity. There were no increases in the frequency or severity of any adverse event associated between the different regimens of GLE 200 mg plus 40 mg or 120 mg PIB, and GLE 300 mg plus 120 mg PIB.

Of the 276 subjects, there have been 4 (1.5%) treatment-emergent SAEs reported in Studies M14-867 and M14-868 combined (all assessed as not related to GLE or PIB): metastatic prostate cancer, pneumonia, atrial fibrillation, and B-cell lymphoma and one SAE that was not treatment-emergent (spontaneous abortion – also assessed as not related). Two subjects (0.7%; 2/276) had treatment-emergent adverse events leading to treatment discontinuation. Both were GT3-infected subjects in the GLE/PIB [200 mg/120 mg] QD + RBV for 12 weeks group of Study M14-868. One subject with history of irritable bowel disease discontinued for Grade 2 AE of abdominal pain assessed as having a reasonable possibility of relatedness to both the DAAs and RBV. Baseline ALT elevations for this subject normalized during treatment and there were no on-

treatment ALT elevations above baseline; subject had total bilirubin elevations that were primarily indirect. The abdominal pain for this subject resolved after discontinuation from study drug. The other subject discontinued for the aforementioned Grade 4 SAE of B-cell lymphoma for the purposes of initiating chemotherapy.

In both Studies M14-867 and M14-868, in all subjects with baseline alanine aminotransferase (ALT) elevations, the ALT levels showed a trend toward normal or became normal with DAA treatment. There have been no on-treatment ALT elevations above baseline. The ALT normalization pattern was similar across all arms (i.e., all GLE and PIB dose levels) in both studies. Other laboratory abnormalities were infrequent and primarily associated with the well-described hemolytic effect of RBV, manifesting as Grade 1 anemia in a total of 4 subjects, all occurring in Study M14 868 RBV-containing arms. Observed total bilirubin elevations were Grade 1 or 2 with predominantly indirect fraction, were mostly isolated occurrences, and normalized or stabilized with continued DAA therapy. Total bilirubin elevations were primarily observed in the RBV-containing arms.

The safety of the combination regimen of GLE and PIB in subjects with compensated cirrhosis is investigated in Study M14-867 Part 2 (GLE/PIB [200 mg/120 mg] QD for 12 weeks) and Study M14-868 Part 2 (GLE/PIB [300 mg/120 mg] QD for 12 weeks with and without ribavirin or for 16 weeks without ribavirin. Based on 82 subjects with compensated cirrhosis enrolled in these arms who have received 4 weeks or more of treatment, the GLE and PIB regimen has demonstrated a favorable safety profile in this patient population. The majority of adverse events have been Grade 1 or 2 and there have been no treatment discontinuations.

A detailed discussion of the preclinical pharmacology and toxicology, in vitro virology and metabolism, and clinical data for GLE, PIB, and the combination of GLE and PIB can be found in the GLE and PIB Fixed-Dose Combination Investigator's Brochure.[10]

3.1 Differences Statement

The current Study, M16-126, is a Phase 3b study in which the efficacy and safety of co-formulated GLE/PIB will be evaluated in treatment-naïve or treatment-experienced (i.e., has failed prior IFN or pegIFN with RBV, or SOF plus RBV with or without pegIFN therapy), chronic HCV GT5 or 6 infected adults without cirrhosis or with compensated cirrhosis for 8 or 12 weeks, respectively. The ongoing Studies M14-868 (Part 4) and M13-583 are assessing the efficacy, safety, and pharmacokinetics of GLE/PIB for 8 or 12 weeks in mono-infected HCV GT4 – 6 subjects without cirrhosis. The ongoing Phase 3 Study M14-172 is assessing the efficacy, safety, and pharmacokinetics of GLE/PIB in mono-infected HCV GT1, 2, 4 – 6 subjects with compensated cirrhosis for 12 weeks of treatment.

The current study, Study M16-126, evaluates GT5 and GT6 subjects in a wider geographic region compared with prior studies. Importantly, this study will generate additional efficacy and safety data following 8 weeks of treatment with GLE/PIB.

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 protease and NS5A inhibitors, no need for RBV, 8 or 12 weeks of treatment, and the convenience of a once daily regimen.

Adverse events that are known, and those not previously described, 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.[10]

Risks associated with PIB/GLE, including the risks of toxicity, virologic failure, and development of resistant mutations (Section 5.3.4), appear to be limited and manageable

based upon the available data. Given the potential for SVR in this population of HCV GT5 or 6 infected subjects, the risk-benefit assessment 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}) and safety of glecaprevir/pibrentasvir in adults with chronic hepatitis C virus (HCV) genotype (GT) 5 or 6 infection with or without compensated cirrhosis. The efficacy of glecaprevir/pibrentasvir will be assessed by genotypes across treatment durations (or cirrhosis status) and the safety of glecaprevir/pibrentasvir will be assessed by treatment duration (or cirrhosis status) across genotypes.

4.2 Secondary Objectives

The secondary objectives are to assess efficacy of glecaprevir/pibrentasvir by hepatitis C virus (HCV) genotype (GT) 5 or 6 infection across treatment duration (or cirrhosis status) by evaluating the following:

- The percentages of subjects with HCV on-treatment virologic failure;
- The percentages of subjects with HCV virologic relapse across treatment durations (or cirrhosis status).

Additional objectives are to assess pharmacokinetics and emergence and persistence of viral variants in these treatment regimens.

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 in HCV treatment-naïve or treatment-experienced (i.e., has failed prior IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN therapy), chronic

HCV GT5 or 6 infected subjects, without cirrhosis (F0-F3) for an 8-week treatment duration or with compensated cirrhosis (F4) for a 12-week treatment duration.

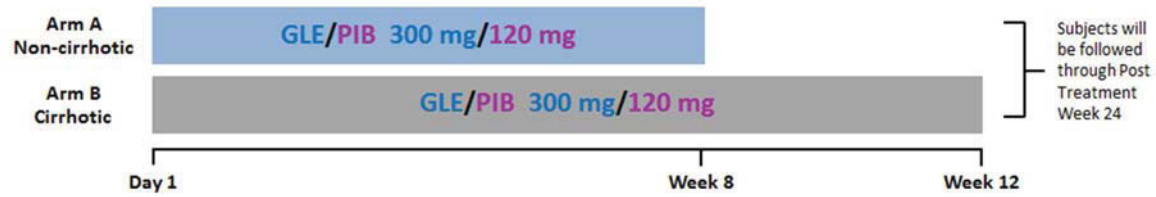
This study will consist of 2 periods as follows:

Treatment Period: Eligible subjects will be enrolled to receive GLE/PIB for an 8 or 12 week treatment duration based on cirrhotic status.

Post-Treatment Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 24 weeks after their last dose of study drug to evaluate efficacy and to monitor HCV RNA and the emergence and persistence of viral variants.

A study schematic is shown in Figure 1.

Figure 1. Study Design (Treatment Period)



* **Approximately 30 GT5-infected subjects and approximately 50 GT6-infected subjects will be enrolled in the study. The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of 15 GT5 and 30 GT6 subjects and 2) up to approximately 16 subjects with compensated cirrhosis (regardless of GT).**

Approximately 80 eligible subjects will be enrolled into one of the following treatment arms:

- Arm A: HCV GT 5 or 6 non-cirrhotic subjects will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks.
- Arm B: HCV GT 5 or 6 subjects with compensated cirrhosis will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 12 weeks.

The study was designed to enroll approximately 80 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 will not be enrolled.

5.1.1 Screening

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);
- A positive HIV test;
- HCV genotype does not meet Inclusion Criterion 4, Section 5.2.1, or meets Exclusion Criteria 4 and 5, Section 5.2.2;
- A positive serum pregnancy test (if female).

Otherwise subjects may be retested or rescreened only once.

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.

Subjects that are rescreened outside of the initial 35 day screening period must be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary.

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

5.1.2 Treatment Period

After meeting the eligibility criteria, subjects will be enrolled via IRT. Subjects will be administered study drug at the site on Study Day 1, with 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, hematology, and urinalysis as specified in Table 2. Plasma samples for pharmacokinetic analysis and HCV RNA analysis will be collected as detailed in Section 5.3.1 and Section 5.3.1.1 Blood samples for optional pharmacogenetic analysis will be collected as detailed in Appendix C.

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.

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 24 weeks following the last dose of study drug for safety, HCV RNA, and the emergence and persistence of HCV resistance-associated viral variants.

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 C 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 C.

5.2 Selection of Study Population

The study population consists of male and female adults aged 18 years or older with chronic HCV GT5 and GT6 infection, without cirrhosis or with compensated cirrhosis, who are treatment naïve (i.e., subject has never received a single dose of any approved or investigational anti-HCV medication) or treatment experienced (i.e., subject has failed prior IFN or pegIFN with or without RBV therapy, or SOF plus RBV with or without pegIFN). Subjects who meet all the 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, OR permanently surgically sterile OR for women of childbearing potential 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.

   For male subjects, no contraception is required.
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 GT5 or 6 infection.
5. Subject has positive anti-HCV Ab and plasma HCV RNA ≥ 1000 IU/mL at Screening Visit.
6. Chronic HCV infection defined as one of the following:
   - Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, or
   - A liver biopsy consistent with chronic HCV infection, or
   - Abnormal alanine aminotransferase (ALT) levels for at least 6 months before Screening.
7. Subject must be HCV treatment-naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication) or treatment-experienced (i.e., has failed prior interferon [IFN] or pegylated interferon [pegIFN] with or without ribavirin [RBV], or sofosbuvir [SOF] plus RBV with or without pegIFN therapy). Prior HCV treatment with any other approved or investigational medications is not allowed. Previous HCV treatment must have been completed ≥ 2 months prior to screening.
8. Subjects who are on stable opioid replacement must be on a therapy with methadone or buprenorphine with or without naloxone for at least 6 months prior to screening.
9. Subject must be documented as having no cirrhosis or compensated cirrhosis (as described in Section 5.3.1.1).
10. Cirrhotic Subjects Only: Compensated cirrhosis defined as Child-Pugh score of ≤ 6 at Screening and no current or past evidence of Child-Pugh B or C Classification or clinical history of liver decompensation including ascites noted on physical exam, hepatic encephalopathy or esophageal variceal bleeding.

11. Cirrhotic Subjects 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.
12. Subjects 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.
13. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.

Rationale for Inclusion Criteria

1, 4 – 7, 8 – 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
12, 13	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. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol in the opinion of the

investigator (see Section 5.6.3 for information about subjects using opioid replacement therapy).

3. Positive test result at Screening for hepatitis B surface antigen (HBsAg) or anti-human immunodeficiency virus antibody (HIV Ab).
4. HCV genotype performed during screening indicating co-infection with more than one HCV genotype.
5. Requirement for and inability or unwillingness to safely discontinue the medications or supplements listed in Table 1 at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of any study drug.
6. 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).
7. Clinically significant abnormalities, other than HCV infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile, and a 12-lead electrocardiogram (ECG) that make the subject an unsuitable candidate for this study in the opinion of the investigator, including, but not limited to:
    - Uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% at the Screening Visit.
    - Active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
    - Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric, or other medical disease or disorder, which is unrelated to the existing HCV infection.
8. Any cause of liver disease other than chronic HCV infection, including but not limited to the following:
    - Hemochromatosis.
    - Alpha-1 antitrypsin deficiency.

- Wilson's disease.
- Autoimmune hepatitis.
- Alcoholic liver disease.
- Steatohepatitis on liver biopsy considered to be the primary cause of the liver disease rather than concomitant/incidental with HCV infection.

9. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - ALT > 10 × ULN
   - AST > 10 × ULN
   - Calculated creatinine clearance (using Cockcroft-Gault method) of < 50 mL/min
   - Direct bilirubin > ULN
   - Albumin < 3.0 mg/dL for subjects with cirrhosis; < LLN for subjects without cirrhosis
   - International normalized ratio (INR) > 1.5 × ULN, unless subject has known hemophilia or is on a stable anticoagulant regimen affecting INR
   - Hemoglobin < 10 g/dL for women; < 11 g/dL for men
   - Platelets < 60,000 cells per mm^3 for subjects with cirrhosis; < 90,000 cells per mm^3 for subjects without cirrhosis
10. History of solid organ transplantation.
11. 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.
12. Receipt of any other investigational or commercially available direct acting anti-HCV agents other than sofosbuvir (e.g., telaprevir, boceprevir, simeprevir, asunaprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, or dasabuvir).
13. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive GLE/PIB.

14. History of severe, life-threatening or other significant sensitivity to any excipients of the study drug.

15. Subjects who cannot participate in the study per local law.

Rationale for Exclusion Criteria

1, 6, 9, 10, 13 – 15	In order to ensure safety of the subjects throughout the study
2, 5, 11, 12	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications
3, 4, 7 – 8	To exclude subjects with HIV and liver diseases other than chronic HCV GT5 and GT6 infection

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 interactions.

During the Post-Treatment Period, all medications taken will be recorded until 30 days following the last dose of study drug. Only medications associated with HCV or taken for a serious adverse event (SAE) will be recorded thereafter.

The AbbVie TA MD 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) or treatment-experienced (i.e., has

failed prior interferon [IFN] or pegylated interferon [pegIFN] with or without ribavirin [RBV], or sofosbuvir [SOF] plus RBV with or without pegIFN therapy). Prior HCV treatment with any other approved or investigational medications is not allowed.

Subjects will be categorized as:

- HCV Treatment-naïve: subject has never received any treatment for HCV infection.
- Subjects **with an allowed prior HCV treatment** will be categorized as:
  - **Non-responder:** HCV RNA detected at the end of a prior treatment course (except for breakthrough, which is captured separately). These subjects are further categorized as:
    - Null responder: failed to achieve a 1 $\log_{10}$ IU/mL reduction in HCV RNA by Week 4 or a 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior treatment course;
    - Partial responder: achieved at least a 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior treatment course but failed to achieve HCV RNA undetectable (or unquantifiable) at the end of treatment;
    - Unknown or unable to specify: insufficient data to categorize as null or partial responder.
  - **Breakthrough:** confirmed $\geq$ 1 $\log_{10}$ IU/mL increase from nadir or achieved HCV RNA undetectable (or unquantifiable) during a prior treatment course but HCV RNA was quantifiable during or at the end of treatment.
  - **Relapse:** achieved HCV RNA undetectable (or unquantifiable) at the end of a prior treatment course but HCV RNA was detectable following cessation of therapy.
  - **Other:** subject received a prior treatment course and reason for not achieving SVR is other than above.
  - **Unknown:** subject received a prior treatment course and reason for not achieving SVR is unknown.

Subjects must have discontinued prior HCV treatment ≥ 2 months prior to the Screening Visit in order to be eligible for the study. For subjects who had multiple HCV treatment courses, the categorization of previous response category will be based on the last prior treatment.

5.2.3.2 Concomitant Therapy

Subjects should be on a stable dose of concomitant medications for at least 2 weeks prior to initiation of study drug. The investigator should confirm that a concomitant medication/supplement can be safely administered with study drug. Some medications may require dose adjustments due to the potential for 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 drug, if applicable.

5.2.3.3 Prohibited Therapy

Subjects must be able and willing to safely discontinue any prohibited medications or supplements listed in Table 1 at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of any study drug and not use these during the entire Treatment Period and for 14 days following discontinuation of study drug.

Table 1. 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*
Ethinyl estradiol
Astemizole, cisapride, terfenadine

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

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

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).

5.2.4 Contraception Recommendations and Pregnancy Testing

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.
- 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 surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

For women of childbearing potential (WOCBP):

- 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.
  - Bilateral tubal occlusion/ligation.
  - 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).
  - 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.
  - Male or female condom with or without spermicide. Condoms without spermicide are acceptable only in countries where spermicide is not available.
  - 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, Pharmacogenetic 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 and Appendix D.

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. Waist circumference will be measured at Screening; however, if it is not measured at Screening, it can be measured on Day 1.

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 2 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)

Covance
7 rue Moise-Marcinhes
1217 Meyrin
Geneva Switzerland
(For sites in Europe, Russia and South Africa)

Covance (Asia) Pte Ltd
1 International Business Park
#01-01 The Synergy
Singapore 609917
(For sites in Asia Pacific)

Table 2. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Other Tests
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands, if detected Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable) Reticulocyte count Prothrombin Time/INR[a] Activated partial thromboplastin time (aPTT)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin[a,b] Direct and indirect bilirubin Alanine transaminase (SGPT/ALT) Aspartate transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Cholesterol Total protein Glucose Triglycerides Low Density Lipoproteins (LDL)[c,d] High Density Lipoprotein (HDL)[d] Albumin[a] Chloride Bicarbonate Magnesium Total insulin Gamma-glutamyl transferase (GGT) Creatinine clearance (Cockcroft-Gault calculation)	HBsAg[e] Anti-HCV Ab[e] HIV Ab[e] Urine and Serum Human Chorionic Gonadotropin (hCG) for females[f] HCV RNA Hepatitis B Panel[g] Hemoglobin A1C[e] IL28B[d] HCV genotype and subtype[e] Pharmacogenetic sample (optional) Alpha2-macroglobulin[b] Haptoglobin[b] Apolipoprotein A1[b]
Urinalysis		
Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocyte esterase Microscopic (reflex)		

a. Also a component of Child-Pugh Assessment.
b. Component of FibroTest and collected only if needed during the Screening Period.
c. Directly measured.
d. Performed only at Baseline.
e. Performed only at Screening.
f. Pregnancy testing is not required for females of non-childbearing potential.
g. Performed at Day 1 for all subjects and also performed for management of transaminase elevation (Section 6.1.7.1).

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

A serum pregnancy test will be performed for all female subjects of childbearing potential at Screening. Additional urine pregnancy tests will be performed every 4 weeks, starting at Day 1 (prior to enrollment) during the treatment period, including at the last Treatment Period visit and until 30 days of last study drug dose, as indicated in Appendix C and Appendix D. Determination of postmenopausal status will be made during the Screening period, based on the subject's history.

- 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.

Concomitant Medication Assessment

Please refer to Section 5.2.3.

Hepatitis B and C Virus and HIV Screen

HBsAg (hepatitis B surface antigen), 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 non-cirrhotic or cirrhotic based on the definitions below:

Non-Cirrhotic

- 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 ≤ 3, Ishak fibrosis score of ≤ 4; 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 score of ≤ 0.48 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) < 1.

Cirrhotic

- 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 ≥ 0.75 and an APRI > 2.

In the absence of a definitive diagnosis of presence or absence of cirrhosis by Fibrotest/APRI using the above criteria (indeterminate FibroTest [0.48 < result < 0.75], or conflicting FibroTest and APRI results [e.g., FibroTest ≤ 0.48, but APRI ≥ 1]), a liver biopsy or FibroScan® is required. Liver biopsy results will supersede Fibrotest/APRI or FibroScan® results and be considered definitive. At Screening, it is recommended that subjects should otherwise meet all of the 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. The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments) as shown in Table 3. Child-Pugh score will be determined at the visits indicated in Appendix C and Appendix D.

Table 3. 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)

* 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 3.

Hepatocellular Carcinoma (HCC) Screening: Liver Ultrasound

HCC screening will be required as a protocol-specified study procedure only at the Screening Visit and at Post-Treatment Week 24, 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 Post-Treatment Week 24, 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 (where allowed per local regulatory guidelines) 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

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.

Work Productivity and Activity Impairment (WPAI)-HCV Specific Instrument – Version 2

The WPAI-Hepatitis C questionnaire is an instrument to measure impairments in both paid work and unpaid work from HCV-infected people. It measures absenteeism, presenteeism, overall work productivity loss, as well as impairments in unpaid activity because of hepatitis C. The WPAI-Hepatitis C consists of 6 questions: 1 = currently employed; 2 = hours missed due to hepatitis C; 3 = hours missed other reasons; 4 = hours actually worked; 5 = degree hepatitis C affected productivity while working (using a 0 to 10 visual analog scale [VAS]); 6 = degree hepatitis C affected productivity in regular unpaid activities (VAS). The WPAI-Hepatitis C 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 and WPAI-Hepatitis C. 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.

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 5-digit numbers and will begin with 10001 with the first three 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 determined 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.

Archive Plasma Sample

Archive plasma samples will be collected at the study visits, indicated in Appendix C and Appendix D. Archive plasma samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, HCV RNA levels, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by AbbVie.

Specific instructions for preparation and storage of archive 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 each study drug taken prior to the scheduled pharmacokinetic sample collection during the Treatment Period.

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 study coordinator 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.

5.3.1.2 Collection and Handling of Pharmacogenetic Exploratory Research Samples

Specific instructions for collection, storage and shipment of pharmacogenetic samples will be provided by the central laboratory, AbbVie, or its designee.

IL28B Sample

One (required) whole blood sample for DNA isolation will be collected from each subject at Study Day 1 for Interleukin 28B (IL28B) pharmacogenetic analysis. If the IL28B pharmacogenetic sample is not collected on Day 1, it may be collected at any other visit during the study. This sample will not be used for any testing other than IL28B genotypes.

Optional Samples for Pharmacogenetic Exploratory Research

Subjects will have the option to provide samples for optional pharmacogenetic exploratory research. Subjects may still participate in the main study even if they decide not to participate in this optional exploratory research.

Optional whole blood samples for DNA and RNA isolation will be collected on Day 1, EOT Week 8 or 12, and PT Week 12 from each subject who consents to provide samples for exploratory research.

AbbVie (or people or companies working with AbbVie) will store the optional pharmacogenetic exploratory research samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on GLE/PIB (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion. The procedure for obtaining and documenting informed consent for exploratory research samples is discussed in Section 9.3.

5.3.1.3 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 and PIB will be collected by venipuncture at each study visit indicated below and in Appendix C.

- At all Treatment-Period visits: a single sample (3 mL) 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, and PIB will be provided by the central laboratory, the Sponsor, or its designee.

5.3.2.3 Disposition of Samples

The frozen plasma samples for the pharmacokinetic assays of GLE, PIB, and archive plasma samples 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 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 method by the Drug Analysis Department at AbbVie. Plasma concentrations of possible metabolites of any analytes listed above 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 Screening through 24 weeks after completion or discontinuation of treatment.

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 study drug, the variants at signature resistance-associated amino acid positions at baseline identified by next generation sequencing (NGS) will be compared to the appropriate prototypic reference sequence.

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 variants in available post-baseline samples identified by NGS and comparison to the baseline sequence, 2) the amino acid variants 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 resistance 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 and PIB will be tabulated and summarized. Values for the pharmacokinetic parameters of GLE and PIB, including apparent clearance (CL/F) and apparent volume of distribution (V/F) will be estimated using population pharmacokinetic modeling procedures. Additional parameters may be calculated if useful in the interpretation of the data.

5.3.6 Pharmacogenetic Exploratory Research Variables

IL28B status will be determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. These IL28B GT results may be analyzed as part of a multi-study assessment of IL28B and response to study drug or drugs of a similar class. The results may also be used for the development of diagnostic tests related to

IL28B and study treatment, or drugs of a similar class. The results of additional pharmacogenetic IL28B analyses may not be reported with the clinical study report.

Optional pharmacogenetic samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids, or metabolites. The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the study drug (or drugs of the same or similar class) or the development and progression of the subjects' disease or related conditions. The samples may also be used to develop new diagnostic tests, therapies, research methods, or technologies. The results from these analyses are exploratory in nature, may not be included with the study report, and may be performed by a non-GLP laboratory.

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 24 weeks for HCV RNA and the emergence and persistence of resistant viral variants.

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 resistant viral variants until 24 weeks post-treatment.

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

Glecaprevir/pibrentasvir (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 4.

Table 4. 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

All study drug will be supplied in bottles.

Each bottle will be labeled as required per country requirements.

The 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 cirrhotic 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. The number of tablets of each type of study drug returned in each bottle will be noted in the IRT system or on a drug accountability log (if appropriate). 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 current study (Study M16-126) is a Phase 3b study designed to evaluate the efficacy (percent of patients achieving SVR_{12}) and safety of combination regimen of GLE 300 mg and PIB 120 mg QD in treatment-naïve and -experienced subjects infected with chronic HCV GT5 and GT6 infection without cirrhosis or with compensated cirrhosis for 8 weeks or 12 weeks, respectively.

Treatment durations were selected based on available data (all SVR_4 and available SVR_{12} rates) from 8-week or 12-week treatment groups receiving GLE/PIB combinations in Studies M14-867 and M14-868 in HCV GT1, GT2, GT3, GT4, GT5, and GT6-infected non-cirrhotic patients with or without previous treatment experience.

The 8-week treatment duration has been evaluated in 34 GT1, 54 GT2, and 29 GT3 treatment-naïve and -experienced subjects without cirrhosis in Part 2 of Studies M14-867 and M14-868, respectively, and demonstrated robust SVR_{12} rates without virologic failures, to date. SVR_{12} rates were 97% (33/34), 98% (53/54), and 97% (28/29%) for GT1, GT2, and GT3, respectively. In addition, the GLE/PIB 300 mg/120 mg combination regimen demonstrated 100% SVR_{12} in a total of 34 GT4, GT5, and GT6-infected non-cirrhotic subjects when taken for a 12-week duration. Based on the efficacy data presented above, the 8-week treatment duration is anticipated to achieve high SVR rates in GT5 – 6-infected treatment-naïve and -experienced subjects without cirrhosis.[13,14]

The 12-week duration of the GLE/PIB combination regimen in adults with chronic HCV genotype (GT) 1, 2, 4, 5, or 6 infection with compensated cirrhosis is being evaluated in an ongoing Phase 3 (Study M14-172) study. The number of GT5 (n = 3) and GT6 (n = 7) subjects enrolled were small.

With an expected SVR rate approaching 100%, as observed in the Phase 2 Studies, the benefit of a non-inferiority design with an active-comparator is limited. This design is therefore believed to be an appropriate approach for demonstrating efficacy in these GTs of lower prevalence.

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.

5.6.3 Suitability of Subject Population

This study plans to enroll HCV GT5, or 6-infected subjects, with or without compensated cirrhosis who are HCV treatment-naïve or treatment-experienced in order to assess the safety, pharmacokinetics and antiviral activity of GLE/PIB. Subjects who are treatment-naïve as well as those who have failed prior IFN or pegIFN (with or without RBV), or SOF plus RBV (with or without pegIFN) therapy for their HCV infection are included in the study in order to evaluate the efficacy of GLE/PIB regimen in this diverse cohort of

HCV GT5 and GT6-infected subjects. There is no expectation of cross-resistance between IFN, pegIFN, RBV, or SOF with either GLE or PIB because of the differences in their mechanisms of action. Subjects who have failed treatment with a PI or NS5A inhibitor alone or in combination with interferon (with or without RBV) will not be permitted to enroll, because the results from ongoing Phase 2 study evaluating the regimen in DAA experienced patients (Study M15-410) are not available.

HCV-infected subjects with chronic HCV infection have moderate stable elevations of AST and ALT levels and are considered representative of the population who will receive anti-HCV therapy. The age range selected for this study, 18 years of age or older, is also intended to be representative of the target population. Similarly, a substantial portion of the HCV infected population has a relatively high BMI, and given the acceptable safety and pharmacokinetic profiles of GLE and PIB in previous studies, this protocol will enroll subjects without a BMI restriction.

In order to be enrolled in the study, subjects who are on stable opiate replacement must be on a therapy with methadone or buprenorphine with or without naloxone for at least 6 months prior to screening. This is based on the results from Study M13-602 that evaluated the pharmacokinetic, pharmacodynamic, safety, and tolerability effects of the co-administration of methadone or buprenorphine/naloxone and GLE/PIB in adult subjects on stable opioid therapy, which showed acceptable safety and no relevant pharmacokinetic or pharmacodynamic interactions.

5.6.4 Selection of Doses in the Study

5.6.4.1 Rationale for Dose Selections

The doses of 300 mg GLE and 120 mg PIB were selected to optimize efficacy of the combination while maintaining an acceptable safety profile, and to be consistent with the dose selection for GLE and PIB in the currently on-going AbbVie HCV Phase 3 studies.

5.6.4.1.1 GLE and PIB Dose and Treatment Duration

Based on the results from the Phase 2b studies, Studies M14-867 and M14-868, the 300 mg dose of the GLE and 120 mg dose of PIB in combination has been selected for Phase 3 studies in HCV GT1 to 6 treatment-naïve and -experienced, cirrhotic and non-cirrhotic populations. This dose has been demonstrated efficacious for the proposed Phase 3 study populations with12-week planned study duration and would reduce chances of virologic failures across genotypes and difficult-to-treat patient populations to maximize the chance for SVR. Importantly, one thousand and six HCV-infected subjects have been dosed with the combination of GLE and PIB in ongoing Phase 2b and Phase 3 studies to date. This combination has been well-tolerated and safe across all studies including cirrhotic and prior treatment experienced subjects (Data on file). The most frequently reported adverse events were fatigue, nausea and headache and were mostly Grade 1 or 2 in severity. In all subjects with baseline ALT elevations, ALT levels normalized or trended toward normal with DAA treatment, and there have been no on-treatment ALT elevations above baseline grade.

Results from GLE 300 mg QD + PIB 120 mg QD for 8-week treatment duration in HCV GT1 (n = 34) Study M14-867 Part 2) and HCV GT2 (n = 54) (Study M14-868 Part 2) showed 97.1% and 98.1% SVR_{12} respectively. In Study M14-867 Part 2, GLE 300 mg QD + PIB 120 mg QD for 12 weeks was evaluated in 34 DAA-naïve HCV GT4 (n = 22), GT5 (n = 1), and GT6 (n = 11)-infected non-cirrhotic subjects. All 34 subjects achieved SVR_{12}. Based on exposure-response analyses, simulations were conducted to predict SVR rates for GLE and PIB administered 8 weeks in HCV GT4-infected subjects and showed > 95% SVR in this population. GLE 300 mg QD + PIB 120 mg QD for 8 weeks will be used in this study for HCV genotype 5 and 6 non-cirrhotic subjects.

Efficacy results from Part 2 of Study M14-868 in GT3 treatment-naïve cirrhotic patients showed 100% SVR_{12} for GLE 300 mg + PIB 120 mg QD administered for 12 weeks. Based on simulations conducted to predict SVR rates of 300 mg/120 mg GLE/PIB for 12 and 16 weeks in HCV GT1 subjects with cirrhosis, this GLE/PIB dose could provide improved SVR rates compared to lower doses and a duration of 12 weeks could achieve

an SVR rate close to 100% in cirrhotic subjects with HCV GT1 infection. Longer duration (e.g., 16 weeks) of 300 mg/120 mg GLE/PIB QD treatment is not expected to provide a significant improvement in the SVR rate (in GT1). Similar to GT1, the predicted SVR rates for GT2 subjects with cirrhosis following 300 mg/120 mg GLE/PIB QD treatment for 12 weeks is 98%. This dose is also anticipated to yield high SVR rate following 12-week treatment duration in GT4 to GT6 infected cirrhotic population.

In summary, based on clinical trial data and exposure-response analyses, it is expected that GLE 300 mg + PIB 120 mg QD will achieve high SVR rate in both non-cirrhosis (administered for 8 weeks) and compensated cirrhosis subjects (administered for 12 weeks).

5.6.4.2 Risk of Development of Resistance Mutations During Combination DAA Trials

In subjects treated with a DAA, variants with amino acid substitution(s) in the targeted protein conferring resistance to the DAA can be selected. For example, in AbbVie HCV Phase 3 studies in which patients with GT1 infection were treated with the NS3/4A protease inhibitor paritaprevir and NS5A inhibitor ombitasvir, variants that conferred resistance to paritaprevir or ombitasvir were detected in patients experiencing virologic failure. While resistance data from patients treated with the combination of PIB and GLE are limited, it is expected that PIB, an NS5A inhibitor, will be able to suppress the appearance of virus containing resistance-associated variants in NS3 that confer resistance to GLE, because there should not be any cross-resistance in variants resistant to DAAs targeting different proteins. The converse is expected to be true as well – GLE should be able to suppress the appearance of virus containing NS5A variants conferring resistance to PIB. In addition, in vitro resistant colony selection studies in HCV replicon cells containing GT1 – 6 NS5A demonstrated that PIB had a high genetic barrier to resistance – very few colonies were selected, and most of those that were selected contained NS5A variants that conferred only modest levels of resistance to PIB. It remains to be seen whether the development of resistance in subjects treated with PIB resembles that seen in vitro. Based on accumulated clinical and in vitro data to date, the risk of development of

resistant variants during GLE and PIB combination trials is reduced when compared to treatment with first generation protease and NS5A inhibitors. For example, the combination of PIB and GLE achieved high SVR rates with few virologic failures in DAA-naïve patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection in the Phase 2 SURVEYOR-I and -II studies. These results support the prediction that the risk of development of resistance-associated variants with GLE and PIB combination treatment is low.

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 pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an 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	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

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.

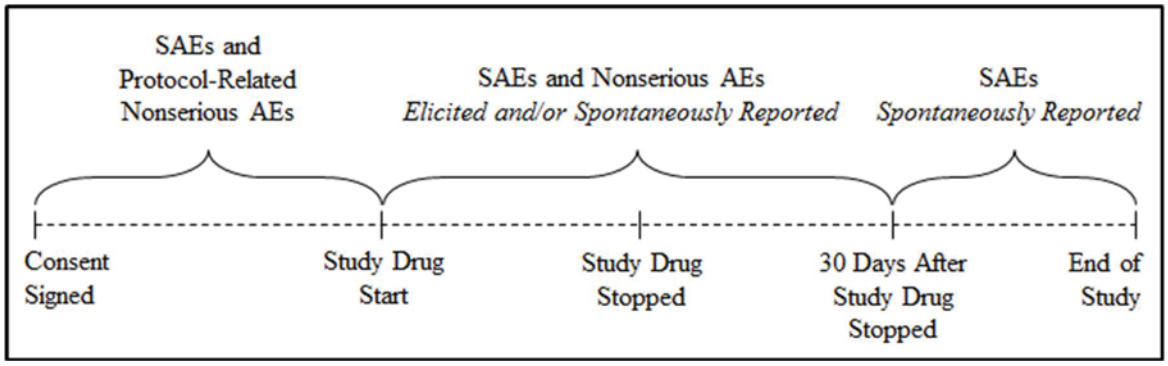
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

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	

For safety concerns, contact the Antiviral Safety Team at:

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

Office: [redacted]
Email:

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

Primary Therapeutic Area Medical Director:

[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 hepatic questionnaire.
- Evaluate for alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain additional testing as appropriate (e.g., hepatitis B panel).
- 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 hepatitis.
  - At the discretion of the investigator.

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

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]	

Such contact must be made as soon as possible to permit a review by AbbVie to Statistical Methods and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The primary analysis will occur after all subjects have completed the PT Week 12 Visit or prematurely discontinued treatment. The data for the primary analysis will be locked after data cleaning. Data after PT Week 12 will be added to a new version of the database which will be cleaned and locked at the end of the study.

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 not of GT5, 6 according to phylogenetic analyses (mITT-GT), and on the mITT-GT population further modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-GT-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, SVR_{12}, and SVR_{24}) 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 HCV GT (GT5 and 6 separately, across arms), by Arm (A and B), and overall. Demographics include age, weight, height, BMI, gender, race, and ethnicity. Baseline characteristics include HCV genotype subtype, IL28B genotype, prior HCV treatment history, baseline HCV RNA level, fibrosis stage (F0 – F1, F2, F3, F4 [if applicable]), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, former 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 all other subgroup variables defined in Section 8.1.2.4.

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.

Efficacy analyses will be performed within each genotype (GT5 and GT6 subjects) across treatment arms (representing the recommended per cirrhosis status) and in the combined treatment arms.

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.

IL28B will be reported as C/C, C/T, or T/T by the central laboratory.

8.1.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the percentage of subjects in who achieve SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) within each genotype (GT5 and GT6 subjects) across the treatment arms. The primary endpoint will be analyzed based on ITT population. The number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using the

normal approximation to the binomial distribution, unless the number of SVR_{12} non-responders is less than 5, where the Wilson's score method will be used for the confidence interval instead.

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

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints within each genotype (GT5 and GT6 subjects) separately, across treatment arms are:

- The percentage of subjects with HCV on-treatment virologic failure;
- The percentage of subjects with post-treatment HCV virologic relapse. Subjects with reinfection based on HCV NGS will be summarized separately from relapse.

The secondary endpoints of HCV on-treatment virologic failure and post-treatment HCV virologic relapse will be analyzed within each genotype (GT5 and GT6 subjects) separately, across the treatment arms.

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% confidence interval using Wilson's score method.

8.1.2.3 Sensitivity Analysis

As sensitivity analyses, the number and percentage of subjects in the mITT-GT and mITT-GT-VF populations achieving SVR_{12}, as applicable, will be summarized along with

a two-sided 95% confidence interval using the normal approximation 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 within each genotype separately. The summary statistics of subjects with SVR_{12} will be provided for the following subgroups:

- Prior HCV treatment history (naïve or experienced);
- For treatment-experienced subjects, type of previous treatment (IFN- or SOF-based);
- IL28B genotype (CC or non-CC);
- Sex (male or female);
- Age (< 65 or ≥ 65 years) and (< 75 or ≥ 75 years);
- Race (White, Black/African-American, Asian, or other) and (black or non-black);
- BMI (< 30 or ≥ 30 kg/m^2);
- Baseline HCV RNA level (< 6,000,000 or ≥ 6,000,000 IU/mL);
- Baseline fibrosis stage (F0-F1, F2, F3, or F4);
- Baseline cirrhosis Status (Yes/No)
- Baseline platelet count (< 90 or ≥ 90 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline creatinine clearance (< 60, ≥ 60 to < 90, ≥ 90 mL/min)
- Baseline eGFR (< 90 or ≥ 90 mL/min/1.73 m^2)
- History of diabetes (yes/no);
- Baseline metabolic syndrome;
- Subject on stable opiate substitution (yes/no);

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 four weeks after the last actual dose of study drug (SVR_4);
- The percentage of subjects who achieve SVR_{24} twenty-four weeks after the last actual dose of study drug (SVR_{24});
- 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.

A descriptive summary of SVR_{12} endpoints will be provided for GT5 and GT6 subjects separately and combined for all non-cirrhotic subjects who received 8 weeks of treatment and cirrhotic subjects who received 12 weeks of treatment in any of the following studies: Studies M14-868 Part 4, M14-172, or M16-126, using meta analytic methods.

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 WPAI Hepatitis C 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 (MCS) and Physical Component Summary (PCS) scores; WPAI activity impairment due to hepatitis C, overall work impairment, absenteeism, and presenteeism scores will be summarized descriptively at each visit and for change from baseline to each 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:

- Cumulative 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;
- Cumulative 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;
- Cumulative 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 Resistance Analyses

For all subjects, 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 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.

Signature resistance-associated amino acid positions are 36, 43, 54, 55, 56, 80, 155, 156, and 168 in NS3; and 24, 28, 29, 30, 31, 32, 58, 92, and 93 in NS5A.

The following definitions will be used in the resistance analyses:

- Baseline variant: a variant by NGS in a baseline sample (≥ 2% or ≥ 15% prevalence within a subject's viral population depending on variant frequency threshold utilized) that was not present in the appropriate prototypic reference amino acid sequence for a given DAA target (NS3/4A or NS5A).
- Variant at signature amino acid position: variant (relative to reference) present in a baseline or a post-baseline sample at a signature amino acid position.
- Post-baseline variant: an amino acid variant 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 variant: variant 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 variant by NGS: A post-baseline variant or an enriched variant.

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

- A listing of all baseline variants (2% detection threshold) at signature resistance-associated amino acid positions for each DAA target (NS3/4A and NS5A).
- A listing of all baseline variants (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 variants at signature amino acid positions at detection thresholds of 2% and 15%.

Analysis 2: The impact of baseline variants on treatment outcome will be assessed as follows: for each variant, the SVR_{12} rate will be calculated for subjects with and without the variant 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 variants on treatment outcome:

- For each signature amino acid position, presence of any variant at that position (vs no variant at that position), using detection thresholds of both 2% and 15%.
- Each individual variant at each signature amino acid position (vs not that variant) using detection thresholds of 2% and 15%.
- Variants 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 variants 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 variant 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 information will be presented in summaries of efficacy subgroup analyses.

8.1.5 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.

8.1.5.1 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.

8.1.5.2 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 post-baseline in the CTCAE grading of laboratory values will also be summarized.

Laboratory data values will be categorized as low, normal, or high based on reference ranges of the laboratory used in this study. The number and percentage of subjects who experience post-baseline shifts during treatment in clinical laboratory values from low/normal to high and high/normal to low based on the normal range will be summarized.

In addition, the number and percentage of subjects with post-baseline values meeting pre-specified criteria for Potentially Clinically Significant laboratory values or toxicity grades during treatment will be summarized.

8.1.5.3 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. The number and percentage of subjects with post-baseline values meeting pre-defined criteria for PCS (Potentially Clinically Significant) vital signs values during treatment will be summarized.

8.1.6 Pharmacokinetic and Exposure-Response Analyses

Plasma concentrations of GLE and PIB and possible metabolites and pharmacokinetic parameter values for GLE and PIB 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 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. The evaluation criteria described below will be used to examine the performance of different models.

- The objective function of the best model is significantly smaller than the alternative model(s).
- The observed and predicted concentrations from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) than the alternative model(s).
- Visual inspection of model fits, standard errors of model parameters and change in inter-subject and intra-subject error.

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. The relationship between these conditional estimates CL/F and V/F values with only potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic or renal function, etc.) will be explored using either stepwise forward selection method, or generalized additive method (GAM) or another suitable regression/smoothing method at a significance level of 0.05. After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the significance (at $P < 0.005$, corresponding to an increase in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

In general, all continuous covariates will be entered in the model, initially in a linear fashion, with continuous covariates centered around the median value. Linear or non-linear relationships of primary pharmacokinetic parameters with various covariates may also be explored. For example:

TVCLi = Theta(1) + Theta(2) (Comedication [1,2,…]) + Theta(3) (WTi-median value) + Theta(4) (AGEi – median value).

Where TVCLi = Typical value of clearance for an individual1, Theta(1) is the intercept and Theta(2) – (4) are regression parameters relating the fixed effects (weight and age centered on the median value) to clearance.

Relationship between exposure and clinical observations (antiviral activity) will be explored. Exposure-response relationships for primary and secondary efficacy variables and/or some safety measures of interest may also be explored.

The relationship between exposure (e.g., population pharmacokinetic model predicted concentrations over time or average concentrations or AUC or trough concentrations of the individual model-predicted pharmacokinetic profiles, or some other appropriate measure of exposure) and antiviral activity will be explored.

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 approximately a total of 80 HCV infected patients, (~30 GT5-infected subjects and ~50 GT6-infected subjects) will be enrolled in the study. A minimum of 15 GT5 and 30 GT6 subjects will be enrolled and up to approximately 16 subjects with compensated cirrhosis (regardless of GT) will be enrolled. No formal hypothesis is being tested. If the observed SVR_{12} rate in this study is 97% among 30 GT5 subjects and 50 GT6 subjects, then the half-width of 2-sided 95% normal approximation intervals are 0.061 and 0.047 for the GT5 and GT6 subjects, respectively.

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.

An informed consent, approved by an IRB/IEC, must be voluntarily signed and dated before samples are collected for optional pharmacogenetic exploratory research. The nature of the testing should be explained and the subject given an opportunity to ask questions. The informed consent must be signed before the samples are collected and any testing is performed. If the subject does not consent to provide samples for the optional pharmacogenetic exploratory research, it will not impact their participation in the study.

In the event a subject withdraws from the main study, optional pharmacogenetic exploratory research samples will continue to be stored and analyzed unless the subject specifically withdraws consent for the optional samples. If consent is withdrawn for the optional sampling, the subject must inform their study doctor, and once AbbVie is informed, the optional samples will be destroyed. However, if the subject withdraws his/her consent and the samples have already been tested, those results will still remain as part of the overall research data.

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 pharmacogenetic 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 pharmacogenetic exploratory research may be 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 Adults with Chronic Hepatitis C Virus (HCV) Genotype 5 or 6 Infection
Protocol Date:	28 July 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]		Pharmacokinetics
		Clinical
		Clinical
		Clinical
		Bioanalysis
		Statistics
		Clinical

Appendix C. Study Activities – Treatment Period

Activity	Screening	Day 1[a]	Wk 1	Wk 2	Wk 4	Wk 8	Wk 8 EOT or Wk 12 EOT* or Premature D/C from Treatment[b]
Informed Consent[c]	X						
Dispense/Review Study Drug Dosing Card		X (Dispense only)	X	X	X	X	X (Review only)
Medical History[d]	X	X					
Physical Exam	X	X					X
Vital Signs, Weight, Waist Circumference,[e] Height[e]	X	X	X	X	X	X	X
ECG	X	X					X
Hematology/Chemistry/Urinalysis/Coagulation Panel	X	X	X	X	X	X	X
Pregnancy Test (serum [s] urine [u])[f]	X (s)	X (u)			X (u)	X (u)	X (u)
HBsAg, Anti-HCV Ab, Anti-HIV Ab	X						
Hepatitis B Panel		X					
Hemoglobin A1C (HgbA1c)[g]	X						
HCV Genotype and Subgenotype	X						
FibroTest and APRI or FibroScan® or Liver Biopsy[h]	X						
IL28B Sample[i]		X					
Pharmacogenetic DNA and RNA Sample (optional)		X					X
Total Insulin		X					
Concomitant Medication Assessment	X	X	X	X	X	X	X
Adverse Event Assessment[j]	X	X	X	X	X	X	X

Activity	Screening	Day 1[a]	Wk 1	Wk 2	Wk 4	Wk 8	Wk 8 EOT or Wk 12 EOT* or Premature D/C from Treatment[b]
Study Drug Dispensed		X			X	X[k]	
HCV RNA Samples	X	X	X	X	X	X	X
Study Drug Accountability and Review of Study Drug Adherence[k]					X	X	X
HCV Resistance Sample		X	X	X	X	X	X
Archive Plasma Sample	X	X	X	X	X	X	X
Pharmacokinetic Samples[l]		X	X	X	X	X	X
Child-Pugh Score[m]	X						X
Clinical Assessment of Hepatic Decompensation[m]		X					
HCC Screening Liver ultrasound[m]	X						
Patient Reported Outcomes Instruments (PROs)[n]		X					X

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

* The EOT visit can be at Weeks 8 or 12 depending on allocated arm.

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

b. Subjects who prematurely discontinue 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) and the optional pharmacogenetic consent, if applicable.

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

e. Height will be measured at the Screening Visit only. Waist circumference will be measured at the Screening Visit, but if it is not measured at Screening, it may be measured on Day 1.

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

g. For those with history of Diabetes Mellitus.

h. For subjects who have not had a qualifying liver biopsy within the previous 24 months or a qualifying FibroScan within the previous 6 months.

i. If the IL28B sample is not collected at Study Day 1, it may be collected at any other visit during the study.

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

k 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.

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

m. 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.

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

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

Activity	PT Wk 4	PT Wk 12	PT Wk 24 or PT D/C[a]
Vital Signs and Weight	X	X	X
Hematology/Chemistry/Urinalysis/Coagulation Panel	X		X[b]
Total Insulin		X	
Pregnancy Test (urine)[c]	X (u)		X (u)[b]
Concomitant Medication Assessment	X	X[d]	X[d]
Child-Pugh Score[e]		X	X
Adverse Event Assessment	X[f]	X[g]	X[g]
HCV RNA Samples	X	X	X
HCV Resistance Sample	X	X	X
Archive Plasma Sample	X	X	X
Pharmacogenetic DNA and RNA Sample (optional)		X	
Patient Reported Outcomes Instruments (PROs)[h]		X	
HCC Screening Liver Ultrasound			X[i]

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/Urinalysis/Coagulation Panel and Pregnancy Test are not required at PT Wk 24, but only at PT D/C if subject discontinued prior to PT Wk 4.

c. Urine pregnancy testing is not required in the PT period for women that are not of childbearing potential.

d. Only medications associate with HCV treatment or taken for a serious adverse event (SAE) will be collected after 30 days post-dosing.

e. Only for subjects in Arm B (compensated cirrhosis).

f. Nonserious AEs and all SAEs will be collected until 30 days post dosing.

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. HCC Screening Liver Ultrasound performed only for subjects in Arm B (compensated cirrhotic) 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. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Delete:

sAFP Alpha fetoprotein

Section 3.0 Introduction
Subsection GLE and PIB
First paragraph, first and second sentence previously read:

In general, GLE and PIB combination has been well tolerated when administered to over 800 healthy volunteers and 500 HCV-infected subjects. The efficacy rates were high (> 95%) among treatment-naives or pegIFN + RBV-experienced noncirrhotic HCV-infected GT-1 – 6 subjects treated with 8 weeks of GLE/PIB in Phase 2 studies

Has been changed to read:

In general, GLE and PIB combination has been well tolerated when administered to over 800 healthy volunteers and 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. The efficacy rates were high (> 95%) among treatment-naive or pegIFN + RBV-experienced non-cirrhotic HCV-infected GT-1 – 6 subjects treated with 8 weeks of GLE/PIB in Phase 2 studies.

Section 3.0 Introduction
Subsection GLE and PIB
Eighth, ninth and tenth paragraph previously read:

In Part 1 of Study M14-868, no subject has experienced on treatment virologic failure or post-treatment relapse among the 74 subjects with HCV GT2 infection. Excluding

one subject who was lost to follow-up, all 73 subjects with HCV GT2 infection achieved SVR_{12}. The SVR_{12} rates for each of the treatment regimens were 96% (24/25) (including a subject who was lost to follow-up) of subjects treated with GLE 300 mg QD + PIB 120 mg QD for 12 weeks, 100% (24/24) of subjects treated with GLE 200 mg QD + PIB 120 mg QD for 12 weeks and 100% (25/25) of subjects treated with GLE 200 mg QD + PIB 120 mg QD + RBV for 12 weeks.

In Part 1of Study M14-868, 121 subjects with HCV GT3 infection were treated with GLE 300 mg and PIB 120 mg without ribavirin for 12 weeks and 93.3% (28/30 subjects) achieved SVR_{12}. One subject in this arm experienced relapse at Post-Treatment Week 4 and one subject had missing SVR_{12} data.

In Part 2 of Study M14-867, 100% of subjects infected with HCV GT4, GT5 or GT6 receiving treatment with GLE 300 mg QD + PIB 120 mg QD for 12 weeks achieved SVR_{12} (34/34). GT1-infected treatment-naïve and PR-experienced subjects with compensated cirrhosis were also evaluated with the same. Among the GT1 cirrhotic subjects, 96% (26/27) have achieved SVR_{12}, with one subject experiencing relapse at Post-Treatment Week 4.

Has been changed to read:

In Part 1 of Study M14-868, a total of 195 subjects were enrolled and evenly distributed within the GT2 and GT3-infected groups. Two subjects discontinued due to Treatment-Emergent Adverse Events (Subjects 5904 and 9309 in Arm F), one subject discontinued due to virologic failure (Subject 9106 in Arm F), two subjects were lost to follow-up (Subjects 2005 in Arm F and Subject 2403 in Arm G), and one subject withdrew consent (Subject 4613 in Arm A). Two of these subjects (Subjects 5904 and 9309; both Arm F) achieved SVR_{12}.

The SVR_{12} rates for each of the treatment regimens were 96% (24/25) (including a subject who was lost to follow-up) of subjects treated with GLE 300 mg QD + PIB 120 mg QD for 12 weeks, 100% (24/24) of subjects treated with GLE 200 mg QD + PIB 120 mg QD

for 12 weeks and 100% (25/25) of subjects treated with GLE 200 mg QD + PIB 120 mg QD + RBV for 12 weeks, and 98.1% (53/54) of subjects treated with GLE 300 mg QD + PIB 120 mg QD for 8 weeks.

In Part 1 of Study M14-868, 30 subjects with HCV GT3 infection non cirrhotic, treatment naïve and PR-experienced were treated with GLE 300 mg and PIB 120 mg without ribavirin for 12 weeks and 93.3% (28/30 subjects) achieved SVR_{12}. One subject in this arm experienced relapse at Post-Treatment Week 4 and one subject had missing SVR_{12} data.

In Part 2 of Study M14-867, 100% of subjects infected with HCV GT4, GT5 or GT6 non-cirrhotic, treatment-naïve and PR-experienced receiving treatment with GLE 300 mg QD + PIB 120 mg QD for 12 weeks achieved SVR_{12} (34/34). GT1-infected treatment-naïve and PR-experienced subjects with compensated cirrhosis were also evaluated with the same. Among the GT1 cirrhotic subjects, 96% (26/27) have achieved SVR_{12}, with one subject experiencing relapse at Post-Treatment Week 4.

Section 3.0 Introduction
Subsection <u>GLE and PIB</u>
Twelfth paragraph, first and second sentence previously read:

To date, safety data across all arms in Part 1 of Studies M14-867 and M14-868 encompassing 274 subjects treated with GLE at doses 200 and 300 mg and PIB at doses 40 and 120 mg (with and without RBV in Study M14-868) for 12 weeks show that the most frequently reported adverse events were fatigue, nausea, and headache (occurring in > 5% of subjects). Most of them were Grade 1 or 2 in severity.

Has been changed to read:

To date, safety data across all arms in Part 1 of Studies M14-867 and M14-868 encompassing 276 subjects treated with GLE at doses 200 and 300 mg and PIB at doses 40 and 120 mg (with and without RBV in Study M14-868) for 12 weeks show that the

most frequently reported adverse events were fatigue, nausea, and headache (occurring in > 5% of subjects). Most of them were Grade 1 in severity.

Section 3.0 Introduction
Subsection GLE and PIB
Thirteenth paragraph, first and second sentence previously read:

Of the 274 subjects, there have been 4 (1.5%) treatment-emergent SAEs reported in Studies M14-867 and M14-868 combined (all assessed as not related to GLE or PIB): metastatic prostate cancer, pneumonia, atrial fibrillation, and B-cell lymphoma and one SAE that was not treatment-emergent (spontaneous abortion – also assessed as not related). Two subjects (0.7%; 2/274) had treatment-emergent adverse events leading to treatment discontinuation.

Has been changed to read:

Of the 276 subjects, there have been 4 (1.5%) treatment-emergent SAEs reported in Studies M14-867 and M14-868 combined (all assessed as not related to GLE or PIB): metastatic prostate cancer, pneumonia, atrial fibrillation, and B-cell lymphoma and one SAE that was not treatment-emergent (spontaneous abortion – also assessed as not related). Two subjects (0.7%; 2/276) had treatment-emergent adverse events leading to treatment discontinuation.

Section 5.2.3.2 Concomitant Therapy
Last paragraph previously read:

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, 30 days following discontinuation of study drug, if applicable.

Has been changed to read:

During the Post-Treatment Period, investigators should reassess concomitant medications/supplements and subjects may resume previously prohibited

medications/supplements or revert to pre-study doses, 14 days following discontinuation of study drug, if applicable.

Section 5.2.3.3 Prohibited Therapy
Previously read:

Subjects must be able and willing to safely discontinue any prohibited medications or supplements listed in Table 1 at least 2 weeks 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 30 days following discontinuation of study drug.

Table 1. Prohibited Medications and Supplements

Medication or Supplement Name
Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin*
Astemizole, cisapride, terfenadine

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drug. Subjects receiving these statins should either switch to pravastatin or rosuvastatin prior to the first dose of study drug or may interrupt statin therapy throughout the treatment period and until 30 days after the last dose of study drug, based on investigator's judgment. If switching to or continuing pravastatin or rosuvastatin, it is recommended to reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drug.

Use of ethinyl estradiol containing oral contraceptives with the GLE and PIB combination was associated with ALT increases in some healthy female subjects. Hormonal contraceptives (including oral, topical [including vaginal rings], injectable, or implantable varieties) and hormonal replacement therapy containing ethinyl estradiol may not be used from 2 weeks prior to the first dose of GLE/PIB until 30 days after the end of GLE/PIB dosing. Progestin-only contraceptives and hormonal replacement therapy, such as those containing norethindrone, desogestrel, or levonorgestrel, without ethinyl estradiol, may be used with GLE/PIB. Post-menopausal hormone replacement therapy, such as with esterified or conjugated estrogens, i.e., not containing 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).

Has been changed to read:

Subjects must be able and willing to safely discontinue any prohibited medications or supplements listed in Table 1 at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of any study drug and not use these during the entire Treatment Period and for 14 days following discontinuation of study drug.

Table 1. 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*
Ethinyl estradiol
Astemizole, cisapride, terfenadine

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

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

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).

Table 2. Clinical Laboratory Tests
Column "Clinical Chemistry," test "Albumina" previously read:

Albumina

Has been changed to read:

Albumin[a]

Table 2. Clinical Laboratory Tests
Column "Other Tests"
Delete:

Alpha Fetoprotein (sAFP)[h]

Table 2. Clinical Laboratory Tests
Delete: table note "h."

Performed only for subjects in Arm B as described in Section 5.3.1.1.

Section 5.3.1.1 Study Procedures
Subsection Hepatocellular Carcinoma Screening: Liver Ultrasound and Alpha Fetoprotein
Subsection title and text previously read:

Hepatocellular Carcinoma Screening: Liver Ultrasound and Alpha Fetoprotein

Subjects with compensated cirrhosis who do not have a historical qualifying liver ultrasound, CT, or MRI 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. Subjects with compensated cirrhosis will have alpha fetoprotein assayed at the visits indicated in Appendix C and Appendix D.

Has been changed to read:

Hepatocellular Carcinoma (HCC) Screening: Liver Ultrasound

HCC screening will be required as a protocol-specified study procedure only at the Screening Visit and at Post-Treatment Week 24, 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 Post-Treatment Week 24, 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 5.3.2.1 Collection of Samples for Analysis
Bullet, first sentence previously read:

At all Treatment-Period visits: a single sample (4 mL) will be collected without regard to the time of dosing.

Has been changed to read:

At all Treatment-Period visits: a single sample (3 mL) will be collected without regard to the time of dosing.

Section 5.6.4.1.1 GLE and PIB Dose and Treatment Duration
Delete: last paragraph

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

Section 7.0 Protocol Deviations
Contact information previously read:

Primary Contact: Alternate Contact:

Has been changed to read:

Primary Contact: Alternate Contact:

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

The number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless the rate for SVR_{12} is 100%, where the Wilson's score method will be used for the confidence interval instead.

Has been changed to read:

The number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless the number of SVR_{12} non-responders is less than 5, where the Wilson's score method will be used for the confidence interval instead.

Section 15.0 Reference List
Reference 10 previously read:

AbbVie. ABT-493/ABT-530 Fixed-Dose Combination Investigator's Brochure Edition 1. 23 September 2015.

Has been changed to read:

AbbVie. Glecaprevir/Pibrentasvir Fixed-Dose Combination Investigator's Brochure Edition 2. 06 September 2016; including Addendum 1 Edition 2. November 2016.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Pharmacokinetics
		Clinical
		Clinical
		Clinical
		Bioanalysis
		Statistics
		Clinical
		Clinical Drug Supply Management

Has been changed to read:

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

Appendix C. Study Activities – Treatment Period
Header row previously read:

Activity	Screening	Day 1[a]	Wk 1	Wk 2	Wk 4	Wk 8*	Wk 8 EOT or Wk 12 EOT* or Premature D/C from Treatment[b]

Has been changed to read:

Activity	Screening	Day 1[a]	Wk 1	Wk 2	Wk 4	Wk 8	Wk 8 EOT or Wk 12 EOT* or Premature D/C from Treatment[b]

Appendix C. Study Activities – Treatment Period
Activity "Vital Signs, Weight, Waist Circumferencee, Height[e]" and "HCC Screening Liver ultrasound and Alpha Fetoprotein[m]" previously read:

Activity	Screening	Day 1[a]	Wk 1	Wk 2	Wk 4	Wk 8*	Wk 8 EOT or Wk 12 EOT* or Premature D/C from Treatment[b]
Vital Signs, Weight, Waist Circumferencee, Height[e]	X	X	X	X	X	X	X
HCC Screening Liver ultrasound and Alpha Fetoprotein[m]	X						

Has been changed to read:

Activity	Screening	Day 1[a]	Wk 1	Wk 2	Wk 4	Wk 8	Wk 8 EOT or Wk 12 EOT* or Premature D/C from Treatment[b]
Vital Signs, Weight, Waist Circumference,[e] Height[e]	X	X	X	X	X	X	X
HCC Screening Liver ultrasound[m]	X						

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

Child-Pugh Score, Clinical Assessment of Hepatic Decompensation, Liver Ultrasound, and Alpha Fetoprotein 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 (compensated cirrhotic) as described in Section 5.3.1.1.

Appendix D. Study Activities – Post-Treatment (PT) Period
Delete: Activity "Alpha Fetoprotein[e]"

Activity	PT Wk 4	PT Wk 12	PT Wk 24 or PT D/C[a]
Alpha Fetoprotein[e]		X	

Appendix D. Study Activities – Post-Treatment (PT) Period
Add: Activity "HCC Screening Liver Ultrasound"

Activity	PT Wk 4	PT Wk 12	PT Wk 24 or PT D/C[a]
HCC Screening Liver Ultrasound			X[i]

Appendix D. Study Activities – Post-Treatment (PT) Period
Add: table note "i."

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

Document Approval

Study M16126 - A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Adults with Chronic Hepatitis C Virus (HCV) Genotype 5 or 6 Infection - Amendment 1 - EudraCT 2016-003192-22 - 28Jul2017

Version: 1.0 **Date:** 03-Aug-2017 09:14:11 PM **Company ID:** 08032017-00F9F683983DB6-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	28-Jul-2017 03:05:55 PM	Approver
	28-Jul-2017 03:11:07 PM	Approver
	28-Jul-2017 03:13:53 PM	Approver
	28-Jul-2017 04:30:34 PM	Approver
	31-Jul-2017 01:10:17 PM	Approver
	31-Jul-2017 01:32:14 PM	Approver
	03-Aug-2017 09:14:10 P	Approver