

1.0

Title Page

Clinical Study Protocol M16-127

A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir/Pibrentasvir in Renally-Impaired Adults with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (EXPEDITION-5)

Incorporating Administrative Change 1 and 2 and Amendments 1 and 2 and 3

AbbVie Investigational Product:	glecaprevir/pibrentasvir
Date:	30 January 2018
Development Phase:	3b
Study Design:	This is an open-label study
EudraCT Number:	2016-004182-60
Investigators	Multicenter. Investigator information on file at AbbVie.
Sponsor:	*AbbVie

* 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.

Confidential Information

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1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	20 December 2016
Amendment 1	20 January 2017
Amendment 2	27 July 2017

The purpose of this amendment is to:

- Update to Renal Biomarker Sample and Archive Plasma Sample in Section 5.3.1.1 Study Procedures.
Rationale: *To clarify that serum samples for tumor necrosis factor-alpha (TNF- α) will not be collected and analyzed. Instead, the Archive Plasma samples collected throughout the study will analyze tumor necrosis factor-alpha (TNF- α).*
- Update Table 9, Signature Amino Acid Positions and the Key Subset of Amino Acid Positions, in Section 8.1.4, Resistance Analyses.
Rationale: *To reflect the correct analyses of the signature amino acid position of GT3.*
- Update Appendix D, Study Activities – Post-Treatment (PT) Period.
Rationale: *To further clarify that Hematology/Chemistry/Coagulation will only be performed if the subject discontinues prior to PT Wk 4 unless the patient is cirrhotic, in which labs will be collected to test INR, total bilirubin and albumin in the Post-Treatment Period.*
- Update pharmacokinetics-related text in Synopsis.
Rationale: *Removed from synopsis the text that was referring to the potential population pharmacokinetic analysis that may be performed. Details on this potential analysis are provided in Section 8.1.6.*
- Administrative and terminology changes and typographical and grammatical errors were corrected 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: M16-127
Name of Study Drug:	Phase of Development: 3b
Name of Active Ingredient: Glecaprevir, Pibrentasvir	Date of Protocol Synopsis: 30 January 2018
Protocol Title: A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir/Pibrentasvir in Renally-Impaired Adults with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (EXPEDITION-5)	
Objectives: <ul style="list-style-type: none"> The primary objectives of this study are to assess the efficacy (by evaluating the percentage of subjects achieving SVR₁₂) and safety of glecaprevir/pibrentasvir (GLE/PIB) in adults with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection with or without compensated cirrhosis and with chronic renal impairment in both HCV treatment-naïve and treatment-experienced subjects. The efficacy of GLE/PIB will be assessed based on the overall population (i.e., across treatment durations, genotypes, and cirrhosis status) and the safety of GLE/PIB will be assessed by treatment duration and cirrhosis status across genotypes. Secondary objectives are to assess the percentage of subjects with HCV on-treatment virologic failure and the percentage of subjects with HCV virologic relapse across treatment durations, genotypes, and cirrhosis status. 	
Investigators: Multicenter trial	
Study Sites: Approximately 40 sites globally	
Study Population: Chronic HCV GT1 – 6-infected adults aged 18 years or older with chronic renal impairment. Subjects with renal impairment will include Chronic Kidney Disease (CKD) Stage 3b (eGFR 30 to < 45 mL/min/1.73 m ²), Stage 4 (eGFR 15 to < 30 mL/min/1.73 m ²) and Stage 5 (eGFR < 15 mL/min/1.73 m ² or dialysis-dependent) subjects.	
Number of Subjects to be Enrolled: Approximately 120 subjects	
Methodology: <p>This is a Phase 3b, open-label, non-randomized, multicenter study to evaluate the efficacy and safety of GLE/PIB for 8, 12, or 16 weeks in chronic HCV GT1 – 6 infected subjects with chronic renal impairment, with or without compensated cirrhosis, who are either HCV treatment-naïve (TN) or prior treatment-experienced (TE) with interferon (IFN) or pegylated IFN (pegIFN) with or without ribavirin (RBV), or sofosbuvir (SOF) plus RBV with or without pegIFN.</p> <p>This study will enroll approximately 120 eligible subjects at approximately 40 sites. Subjects with renal impairment will include CKD Stage 3b (eGFR 30 to < 45 mL/min/1.73 m²), Stage 4 (eGFR 15 to < 30 mL/min/1.73 m²) and Stage 5 (eGFR < 15 mL/min/1.73 m² or dialysis-dependent) subjects. The study enrollment will be monitored to meet the following non-mutually exclusive enrollment criteria: (1) up to approximately 40 subjects with Stage 3b CKD, (2) up to approximately 75 HCV GT1-infected subjects, (3) up to approximately 30 subjects with compensated cirrhosis.</p>	

Methodology (Continued):

Subjects will be enrolled to one of the following treatment arms:

- Arm A: HCV GT1, 2, 4 – 6 subjects without cirrhosis who are TN or TE and HCV GT 3 subjects without cirrhosis who are TN will be treated for 8 weeks.
- Arm B: HCV GT1, 2, 4 – 6 subjects with cirrhosis who are TN or TE and HCV GT 3 subjects with cirrhosis who are TN will be treated for 12 weeks.
- Arm C: All HCV GT3 subjects who are TE will be treated for 16 weeks.

Note: Subjects with mixed HCV genotype infection should receive whichever duration is longer based on their genotypes, cirrhosis status and treatment experience. For subjects with an indeterminate genotype, treatment duration will default to the respective GT3 duration based upon treatment-experience and cirrhosis status.

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

Treatment Period:

Enrolled subjects will receive GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks (Arm A), 12 weeks (Arm B), or 16 weeks (Arm C). Scheduled visits in the Treatment Period consist of Day 1 and Weeks 4 and 8 for all subjects, an additional Week 12 visit for subjects in Arms B and C, and an additional Week 16 visit for subjects in Arm C. 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 in the Post-Treatment Period.

During the Post-Treatment Period, all subjects will have visits at Weeks 4, 12, and 24 following completion or premature discontinuation of the Treatment Period. Study procedures to monitor safety, clinical laboratory tests, HCV RNA, and to evaluate the efficacy and the emergence and persistence of resistant virus 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. Positive for anti-HCV antibody (Ab) at Screening and HCV RNA $\geq 1,000$ IU/mL at Screening.
3. Subject has an Estimated Glomerular Filtration Rate (eGFR) < 45 mL/min/1.73 m² as estimated by the MDRD method at screening according to the following formula:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{Serum Creatinine})^{-1.154} \times \text{Age}^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black}),$$
or is dialysis-dependent. Subjects requiring dialysis should have been receiving dialysis for at least 1 month prior to enrollment, and may be on hemodialysis or peritoneal dialysis.
4. 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.

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

Main Inclusion (Continued):

5. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.

Main Exclusion:

1. Female who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Current HBV or HIV infection on screening tests, defined as:
 - A positive HBsAg, or;
 - HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti-HBs), or;
 - A positive anti-human immunodeficiency virus antibody (HIV Ab).
3. Clinical history of acute renal failure in the 3 months prior to screening.
4. Clinically significant abnormalities or co-morbidities, or recent (within 6 months prior to study drug administration) alcohol or drug abuse that make the subject an unsuitable candidate for this study in the opinion of the investigator.
5. Receipt of any investigational or commercially available direct acting anti-HCV agents other than sofosbuvir (e.g., telaprevir, boceprevir, simeprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir or dasabuvir).

Investigational Products: glecaprevir/pibrentasvir (GLE/PIB) 100 mg/40 mg Film-coated tablet

Doses: glecaprevir/pibrentasvir (GLE/PIB) 300 mg/120 mg QD (3 tablets)

Mode of Administration: Oral with food

Reference Therapy: N/A

Doses: N/A

Mode of Administration: N/A

Duration of Treatment:

- Subjects will receive GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks (Arm A), 12 weeks (Arm B) or 16 weeks (Arm C).

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.

Criteria for Evaluation (Continued):

Patient Reported Outcomes (PROs):

The Kidney Disease Quality of Life (KDQOL-36™) will be used to assess the impact of kidney disease on a patient's quality of life.

Resistance:

The following information will be tabulated and summarized: 1) for all subjects with available samples, baseline polymorphisms at signature resistance-associated amino acid positions relative to the appropriate prototypic reference sequence; and 2) for subjects who do not achieve SVR₁₂, post-baseline substitutions relative to baseline.

Pharmacokinetic:

Individual plasma concentrations of glecaprevir and pibrentasvir, and their possible metabolites will be tabulated and summarized.

Statistical Methods:

Efficacy:

The primary efficacy endpoint is the percentage of subjects who achieve SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) based on overall population (i.e., across treatment durations, genotypes, and cirrhosis status). The primary endpoint will be analyzed based on intention-to-treat (ITT) population. The number and percentage of subjects achieving SVR₁₂ will be summarized with a two-sided 95% confidence interval based on the normal approximation of the binomial distribution unless the number of SVR₁₂ non-responders is less than 5, where the Wilson's score method will be used to calculate the confidence interval. No hypothesis will be tested.

The secondary efficacy endpoints are:

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

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.

PROs:

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

Statistical Methods (Continued):

Resistance:

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

The following resistance information will be analyzed for subjects receiving study drugs who do not achieve SVR₁₂ and who have a post-baseline sample with HCV RNA \geq 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the baseline sequence, 2) the amino acid substitutions in available post-baseline samples at signature resistance-associated positions identified by NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral substitutions by NGS.

Pharmacokinetic:

Individual plasma concentrations of glecaprevir, pibrentasvir, and their possible metabolites will be tabulated and summarized.

Safety:

Safety summaries will be provided by the treatment duration and cirrhosis status and overall. All subjects who receive at least one dose of study drug will be included in the safety analyses. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post study drug dosing) will be tabulated by MedDRA System Organ Class (SOC) and preferred term. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by grade and relationship to study drug. Change from baseline in laboratory tests and vital signs measurements to each time point of collection will be summarized, and vital sign values that are potentially clinically significant, according to predefined criteria, will be summarized by treatment duration and cirrhosis status across genotypes and overall. Changes from baseline to post-baseline in the CTCAE grading of laboratory values will also be summarized.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

Ab	Antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APRI	Aminotransferase/platelet ratio index
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
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence Interval
CL/F	Apparent oral plasma 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
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
IMP	Investigational Medical Product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention-To-Treat
IU	International units
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
KDQOL-36	Kidney Disease Quality of Life (KDQOL)-36
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT-VF	Intention-To-Treat population excluding subjects who did not achieve SVR ₁₂ for non-virologic reasons
MRI	Magnetic resonance imaging
NGS	Next generation sequence
NONMEM	Non-linear mixed-effect modeling
NS	Non-structural
NS3A	Nonstructural viral protein 3A
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
PRO	Patient reported outcome
PT	Post-Treatment
QD	Once daily
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Standard Deviation
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})
TE	Treatment-experienced
TN	Treatment-naïve
ULN	Upper limit of normal
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

1.0	Title Page	1
1.1	Protocol Amendment: Summary of Changes	2
1.2	Synopsis	4
1.3	List of Abbreviations and Definition of Terms	9
2.0	Table of Contents	12
3.0	Introduction.....	17
3.1	Differences Statement	27
3.2	Benefits and Risks	28
4.0	Study Objective	30
4.1	Primary Objective	30
4.2	Secondary Objectives	30
5.0	Investigational Plan.....	30
5.1	Overall Study Design and Plan: Description	30
5.1.1	Screening Period	33
5.1.1.1	Rescreening.....	34
5.1.2	Treatment Period (TP)	35
5.1.3	Post-Treatment (PT) Period	35
5.2	Selection of Study Population.....	36
5.2.1	Inclusion Criteria	36
5.2.2	Exclusion Criteria.....	38
5.2.3	Prior and Concomitant Therapy	40
5.2.3.1	Prior HCV Therapy	40
5.2.3.2	Concomitant Therapy	41
5.2.3.3	Prohibited Therapy.....	42
5.2.4	Contraception Recommendations	43
5.3	Efficacy Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables	44
5.3.1	Efficacy and Safety Measurements Assessed and Flow Chart	44
5.3.1.1	Study Procedures.....	44
5.3.1.2	Collection and Handling of Pharmacogenetic Exploratory Research Samples.....	56

5.3.1.3	Meals and Dietary Requirements	57
5.3.2	Drug Concentration Measurements.....	57
5.3.2.1	Collection of Samples for Analysis.....	57
5.3.2.2	Handling/Processing of Samples.....	57
5.3.2.3	Disposition of Samples	58
5.3.2.4	Measurement Methods	58
5.3.3	Efficacy Variables	58
5.3.3.1	Primary Variable	58
5.3.3.2	Secondary Variables.....	58
5.3.3.3	HCV Resistance Variables.....	59
5.3.4	Safety Variables	59
5.3.5	Pharmacokinetic Variables	59
5.3.6	Pharmacogenetic Exploratory Research Variables	59
5.4	Removal of Subjects from Therapy or Assessment	60
5.4.1	Discontinuation of Individual Subjects	60
5.4.1.1	HCV Virologic Failure Criteria	61
5.4.2	Discontinuation of Entire Study.....	61
5.5	Treatments	62
5.5.1	Treatments Administered.....	62
5.5.2	Identity of Investigational Products	62
5.5.2.1	Packaging and Labeling.....	63
5.5.2.2	Storage and Disposition of Study Drug.....	63
5.5.3	Method of Assigning Subjects to Treatment Groups	63
5.5.4	Selection and Timing of Dose for Each Subject.....	64
5.5.5	Blinding	64
5.5.6	Treatment Compliance	64
5.5.7	Drug Accountability	65
5.6	Discussion and Justification of Study Design.....	66
5.6.1	Discussion of Study Design and Choice of Control Groups	66
5.6.2	Appropriateness of Measurements.....	66
5.6.3	Suitability of Subject Population	66
5.6.4	Selection of Doses in the Study	67
5.6.4.1	Rationale for Dose Selections	67

5.6.4.2	GLE and PIB Dose and Treatment Duration	67
6.0	Complaints.....	68
6.1	Medical Complaints	68
6.1.1	Definitions	68
6.1.1.1	Adverse Event	68
6.1.1.2	Serious Adverse Events	69
6.1.2	Adverse Event Severity	70
6.1.3	Relationship to Study Drug.....	71
6.1.4	Adverse Event Collection Period	72
6.1.5	Adverse Event Reporting.....	73
6.1.6	Pregnancy.....	75
6.1.7	Toxicity Management.....	75
6.1.7.1	Management of Transaminase Elevation.....	76
6.2	Product Complaint.....	76
6.2.1	Definition	76
6.2.2	Reporting	77
7.0	Protocol Deviations	77
8.0	Statistical Methods and Determination of Sample Size	78
8.1	Statistical and Analytical Plans	78
8.1.1	Demographics and Baseline Characteristics	79
8.1.2	Efficacy	80
8.1.2.1	Primary Efficacy Endpoints.....	80
8.1.2.2	Secondary Efficacy Endpoints	81
8.1.2.3	Sensitivity Analysis	81
8.1.2.4	Subgroup Analysis	82
8.1.2.5	Additional Efficacy Endpoints.....	82
8.1.3	Patient Reported Outcomes	83
8.1.4	Resistance Analyses	84
8.1.5	Safety	88
8.1.5.1	Adverse Events.....	88
8.1.5.2	Clinical Laboratory Data	88
8.1.5.3	Vital Signs Data	89

8.1.6	Pharmacokinetic and Exposure-Response Analyses.....	89
8.2	Determination of Sample Size	90
8.3	Randomization Methods.....	90
9.0	Ethics.....	90
9.1	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)	90
9.2	Ethical Conduct of the Study	91
9.3	Subject Information and Consent.....	91
10.0	Source Documents and Case Report Form Completion	92
10.1	Source Documents.....	92
10.2	Case Report Forms	93
11.0	Data Quality Assurance	94
12.0	Use of Information	94
13.0	Completion of the Study	95
14.0	Investigator's Agreement.....	96
15.0	Reference List.....	97

List of Tables

Table 1.	Overview of Clinical Studies by Subject Population	20
Table 2.	SVR ₁₂ Rates by Treatment Experience and HCV Genotype – GT1 – 6 (ITT Population, Phase 2 and 3 Analysis Set)	22
Table 3.	Adverse Events Reported for ≥ 5.0% of Subjects (Phase 2 and 3 Analysis Set)	25
Table 4.	Definition of Chronic Kidney Disease Stages	33
Table 5.	Prohibited Medications and Supplements	42
Table 6.	Clinical Laboratory Tests	48
Table 7.	Child-Pugh Classification of Severity of Cirrhosis.....	51
Table 8.	Identity of Investigational Products	62
Table 9.	Signature Amino Acid Positions and the Key Subset of Amino Acid Positions	85

List of Figures

Figure 1.	Study Schematic	32
Figure 2.	Adverse Event Collection	73

List of Appendices

Appendix A.	Responsibilities of the Clinical Investigator	99
Appendix B.	List of Protocol Signatories	101
Appendix C.	Study Activities – Treatment Period	102
Appendix D.	Study Activities – Post-Treatment (PT) Period	105
Appendix E.	Protocol Amendment: List of Changes	107

3.0 Introduction

Hepatitis C viral (HCV) infection is a global health problem, with over 170 million individuals infected worldwide.¹ There are 7 identified HCV genotypes, with genotype 1 (GT1) being the most prevalent worldwide.² 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%).³⁻⁵ HCV GT4 is commonly found in parts of Africa and the Middle East, particularly in Egypt, GT5 is primarily found in South Africa, and GT6 is primarily found in south-east Asia, and GT7 has recently been described in Central Africa.⁶

Depending on various risk factors, between 10% and 40% of patients with chronic HCV infection will develop cirrhosis.⁷ 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.⁷ Patients diagnosed with HCC have a 33% probability of death during the first year.⁷ Successful treatment of HCV has been shown to significantly reduce the risk of disease progression and related mortality as well as the development of HCC.^{8,9}

Infection with HCV is common among patients with end stage renal disease (ESRD) undergoing dialysis in the US, EU and Japan with a prevalence of 3% to 23%, depending on the country.¹⁰ Among patients with ESRD, the presence of HCV correlates with higher rates of mortality than in the HCV-negative population.¹¹ Therefore, patients with renal disease are an important special population for study when evaluating new HCV treatments.

While a significant proportion of the HCV-infected population has renal impairment, safety and efficacy data of direct-acting antiviral agents (DAAs) in patients with severe renal impairment (i.e., creatinine clearance < 30 mL/min) is limited. Currently approved regimens to treat patients with severe renal impairment include ombitasvir/paritaprevir/ritonavir with dasabuvir with or without ribavirin (RBV) for HCV GT1 infection, ombitasvir/paritaprevir/ritonavir with RBV for HCV GT4 infection, and

elbasvir/grazoprevir with or without RBV to treat HCV GT1 and GT4 infection.¹²⁻¹⁴ The development of a safe and effective, RBV-free, pangenotypic regimen to treat HCV infected patients with severe chronic kidney disease remains an important unmet medical need.

AbbVie is currently developing two "next generation" DAAs, glecaprevir (GLE, formerly known as ABT-493), an HCV NS3/4A protease inhibitor and pibrentasvir (PIB, formerly known as ABT-530), an NS5A inhibitor, for use in combination for the treatment of chronic HCV infection. GLE and PIB each have potent in vitro antiviral activity against genotypes 1 through 6¹⁵ and a high genetic barrier to resistance, with no or little loss of potency against common resistant-associated substitutions. Additive or synergistic in vitro anti-HCV activity has been demonstrated with the combination of GLE and PIB. GLE 100 mg and PIB 40 mg are co-formulated into a fixed-dose combination tablet (hereafter referred to as GLE/PIB), which provides patients with a convenient once-daily (QD), fixed-dose combination treatment regimen of three tablets QD to maximize treatment compliance.

A detailed discussion of the preclinical pharmacology and toxicology, in vitro virology and metabolism, and clinical data can be found in the Investigator's Brochure.¹⁶

Glecaprevir/Pibrentasvir (GLE/PIB)

Overview of GLE/PIB Registrational Program and Supportive Studies

The GLE/PIB registrational program included a broad subject population including subjects with compensated liver disease and subjects with severe renal insufficiency across all genotypes using a single GLE/PIB dose of 300 mg/120 mg QD. Supportive Phase 2 studies used the Phase 2 formulation of separate GLE and PIB tablets, with each tablet containing 100 mg and 40 mg, respectively. Treatment arms from these supportive Phase 2 studies using the regimen selected for registrational studies (GLE 300 mg plus PIB 120 mg) were pooled with arms from the registrational studies for analyses of efficacy and safety. Treatment-naïve (TN) and TE subjects to any combination of pegylated IFN (pegIFN), RBV, sofosbuvir (SOF), NS5A inhibitors, or PIs were allowed

in the program. In addition, the program included subjects with human immunodeficiency virus (HIV) coinfection (Study M13-590), subjects with chronic kidney disease [CKD] Stages 4 – 5, including those on hemodialysis (Study M15-462), subjects with compensated cirrhosis (Studies M14-172, M15-462, and M14-868 Part 3), and subjects with or without cirrhosis who failed a previous regimen containing an NS5A inhibitor and/or an NS3/4A PI (Study M15-410).

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

Table 1. Overview of Clinical Studies by Subject Population

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

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

Efficacy

In TN or IFN, pegIFN, RBV, and/or SOF treatment-experienced (TE-PRS) subjects, the pooled overall SVR₁₂ rates with GLE/PIB were > 97% across GT1, 2, 4, 5 and 6 regardless of treatment experience, treatment duration, including any degree of renal impairment, presence of cirrhosis, or HIV-1 coinfection (Table 2).

Among subjects with GT3 infection, the pooled SVR₁₂ rates across durations were 95.2% among all subjects, 96.6% among cirrhotic subjects, and 100% among subjects with CKD Stages 4 – 5. The SVR₁₂ rates among subjects previously treated with a PI and/or NS5A inhibitor were $\geq 89.0\%$ for GT1 and GT4.

Table 2. SVR₁₂ Rates by Treatment Experience and HCV Genotype – GT1 – 6 (ITT Population, Phase 2 and 3 Analysis Set)

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

CI = confidence interval; CKD = chronic kidney disease; GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat; N/A = not applicable; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SVR₁₂ = sustained virologic response 12 weeks postdosing; TE = treatment-experienced; TN = treatment-naïve; TE-NS5A and/or PI = TE with NS5A inhibitor and/or PI

- CI was calculated using a stratum-weighted proportion and variance.
- CI was calculated using the normal approximation to the binomial distribution.
- Eleven subjects were classified by the central laboratory and treated as GT2 but included here as GT1 due to being identified as such by phylogenetic analysis; all 11 subjects achieved SVR₁₂.

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

Impact of Baseline Polymorphisms on Treatment Outcome

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

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

The presence of baseline polymorphisms in NS3 and/or NS5A did not have an impact on SVR₁₂ rates for GT1-, 2-, 4-, 5-, or 6-infected subjects.

Within GT3-infected subjects, baseline polymorphisms in NS3 and the NS5A polymorphisms at positions 24, 28, 31, 58, 92, or 93 did not have an impact on treatment outcome.

Amino Acid Substitutions in Subjects Experiencing Virologic Failure

Among TN and TE-PRS subjects with or without cirrhosis treated for 8, 12, or 16 weeks, 23 subjects experienced virologic failure (2 with GT1, 2 with GT2, and 19 with GT3). One GT3-infected subject experiencing virologic failure was determined to have been reinfected with GT3a virus distinct from the one present at baseline. Therefore, baseline polymorphisms and treatment-emergent substitutions were analyzed for 22 subjects experiencing virologic failure.

Among the 2 GT1-infected subjects, 1 had treatment-emergent substitutions A156V in

NS3 and Q30R/L31M/H58D in NS5A, and 1 had treatment-emergent Q30R/H58D (while Y93N was present at baseline and post-treatment) in NS5A.

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

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

Integrated Safety Results

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

As shown in [Table 3](#), the AEs occurring with a frequency $\geq 5\%$ are headache, fatigue, nausea and diarrhea. The majority of subjects experienced an AE, which were mostly considered to be mild in severity by the investigator (Grade 1). Rates of AEs that were serious, led to premature study drug discontinuation or had a severity Grade ≥ 3 were low. Including data from Study M15-462, there were 7 deaths, none of which were related to study drug, and the majority occurred several months after the last dose of study drug.

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

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

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

a. Excludes Study M15-462.

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

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

d. DAA-related AEs reported for $\geq 5.0\%$ of subjects in the Phase 2 and 3 Analysis Set.

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

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

In Study M15-462, GLE/PIB was generally well-tolerated in subjects with CKD Stage 4 and 5 as evidenced by a treatment discontinuation rate of 1.9% (2/104) due to AEs that were considered DAA-related. No subject experienced a serious AE that was assessed as DAA-related. The safety profile in subjects in Study M15-462 was consistent with

underlying ESRD and its associated comorbidities. Pruritus was the most common AE among subjects (20.2%) in this study followed by fatigue (14.4%) and nausea (11.5%). Pruritus was not an unexpected finding, as it is commonly observed in patients with severe renal impairment. Laboratory abnormalities were infrequent with no subject experiencing a Grade 3 or higher elevation in ALT or AST and 1 subject experiencing a Grade 3 elevation in total bilirubin.

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

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

A total of 6 (0.3%) subjects experienced a de novo event of HCC. In all 6 subjects, the events were considered related to subject's medical history of underlying liver disease and not to GLE/PIB.

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

Common study drug-related AEs occurring in $\geq 5\%$ of subjects were headache, fatigue, nausea and were mostly Grade 1 (mild) in severity. Serious AEs and AEs leading to premature study drug discontinuation were rare. There were no hematological or blood chemistry findings of concern or considered likely related to treatment. Unlike other protease inhibitors, no liver-related toxicities and no cases consistent with drug-induced liver injury were identified.

The objectives of this study are to evaluate the efficacy and safety of GLE/PIB in CKD Stage 3b, 4 and 5 subjects with HCV GT1 – 6 infection with or without compensated cirrhosis.

3.1 Differences Statement

The Phase 3 registration Study M15-462 evaluated GLE/PIB for a duration of 12 weeks, regardless of cirrhosis status or prior treatment experience, in HCV GT1 – 6-infected subjects with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m²) or ESRD (estimated GFR < 15 mL/min/1.73 m² or requiring dialysis). The patient population in Study M16-127 will be expanded compared to Study M15-462 to include subjects with less severe chronic renal disease by including up to 40 subjects with CKD Stage 3b (eGFR 30 to < 45 mL/min/1.73 m²) and will also include HCV GT3-infected subjects with prior treatment experience. Compared to Study M15-462 which evaluated a single treatment duration of 12 weeks, the present study will evaluate treatment durations 8, 12 and 16 weeks based on HCV genotype, cirrhosis status and prior treatment experience.

3.2 Benefits and Risks

This Phase 3b study is a three arm study in which eligible HCV GT1 – 6 infected subjects will receive GLE/PIB for 8, 12 or 16 weeks based on their genotype, cirrhosis status and prior treatment experience. The combination of GLE/PIB has been evaluated in six Phase 3 registration studies and three Phase 2b supportive studies. The results of these studies suggest that the likelihood of successfully demonstrating a high SVR₁₂ rate in HCV GT1 – 6 subjects with renal impairment is high.

The Phase 3 Study M15-462 evaluated a 12 week duration of GLE/PIB in 104 CKD Stage 4 and 5 subjects, including 85 subjects on hemodialysis, with HCV GT1 – 6 infection with and without cirrhosis. The SVR₁₂ rate of 98% (102/104) was observed based on the ITT population; no subject experienced virologic failure. In addition, the regimen was generally well-tolerated in subjects with renal impairment as evidenced by a low treatment-discontinuation rate due to AEs, no drug-related serious AEs, AEs that were mostly mild to moderate in severity and infrequent laboratory abnormalities. These results support the recommendation that adults with chronic HCV infection and severe renal impairment and ESRD follow the duration recommendations for subjects with normal renal function.

At present, no DAA regimen is approved for use in patients with HCV GT 2, 3, 5 and 6 infection with severe renal impairment (CrCl < 30 mL/min). In addition, approved DAA regimens for use in patients with HCV GT1 and 4 often include the use of RBV which is associated with toxicity in this patient population. Therefore, identification of a safe, efficacious, RBV-sparing regimen is a benefit for the CKD Stage 4 and 5 population. Moreover, an 8 week treatment duration in HCV GT1 – 6 treatment-naïve patients without cirrhosis is a benefit compared to currently available regimens which are typically 12 weeks or more in duration. Other potential benefits of treatment with GLE/PIB include a higher genetic barrier to development of drug resistance compared to first generation protease and NS5A inhibitors and the development of resistance was infrequently observed as high rates of SVR₁₂ were demonstrated across the Phase 2 and 3 studies.

In the Phase 2 and 3 studies, no significant toxicity or trends in liver chemistry abnormalities were observed and rates of study drug-related-SAEs and AEs leading to study drug discontinuation were low. Cases of potentially clinically significant ALT and total bilirubin elevations were rare in the Phase 2 and 3 analysis set with ALT elevations $> 5 \times$ upper limit of normal (ULN) occurring in $< 0.1\%$ (2/2,265) subjects and total bilirubin elevations $> 3 \times$ ULN occurring in 0.4% (8/2,265) subjects; no cases consistent with drug induced liver injury (DILI) were reported. No subject discontinued study drug due to ALT or bilirubin elevations.

Additional risks associated with GLE/PIB include the development of resistance-associated substitutions. In subjects treated with a DAA, amino acid substitution(s) in the targeted protein conferring resistance to the DAA can be selected. It is expected that PIB, an NS5A inhibitor, will be able to suppress the appearance of virus containing resistance-associated substitutions in NS3 that confer resistance to GLE, because there should not be any cross-resistance in substitutions 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 substitutions 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 substitutions that conferred only modest levels of resistance to PIB. Based on accumulated clinical and in vitro data to date, the risk of development of resistance-associated substitutions during GLE and PIB combination trials is reduced when compared to treatment with first generation protease and NS5A inhibitors. The combination of PIB and GLE achieved high SVR rates with few virologic failures in the Phase 2 and 3 studies. These results support the prediction that the risk of development of resistance-associated substitutions with GLE and PIB combination treatment is low.

Risks associated with GLE/PIB, including the risks of AEs, hepatic laboratory abnormalities, virologic failure and development of resistance-associated substitutions, appear limited and manageable based on the results from the Phase 2 and 3 studies. Given

the potential for achieving high rates of cure in renally-impaired HCV GT1 – 6 subjects, the risk-benefit balance is favorable.

4.0 Study Objective

4.1 Primary Objective

The primary objectives of this study are to assess the efficacy (by evaluating the percentage of subjects achieving SVR₁₂) and safety of GLE/PIB in adults with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection with or without compensated cirrhosis and with chronic renal impairment in both HCV treatment-naïve and treatment-experienced subjects. The efficacy of GLE/PIB will be assessed based on the overall population (i.e., across treatment durations, genotypes, and cirrhosis status) and the safety of GLE/PIB will be assessed by treatment duration and cirrhosis status across genotypes.

4.2 Secondary Objectives

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

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

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3b, open-label, non-randomized, multicenter study to evaluate the efficacy and safety of GLE/PIB for 8, 12, or 16 weeks in HCV GT1 – 6-infected subjects with chronic renal impairment, with or without compensated cirrhosis, who are either HCV treatment-naïve or prior treatment-experienced with interferon [IFN] or pegylated IFN [pegIFN] with or without RBV, or sofosbuvir [SOF] plus RBV with or without pegIFN.

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

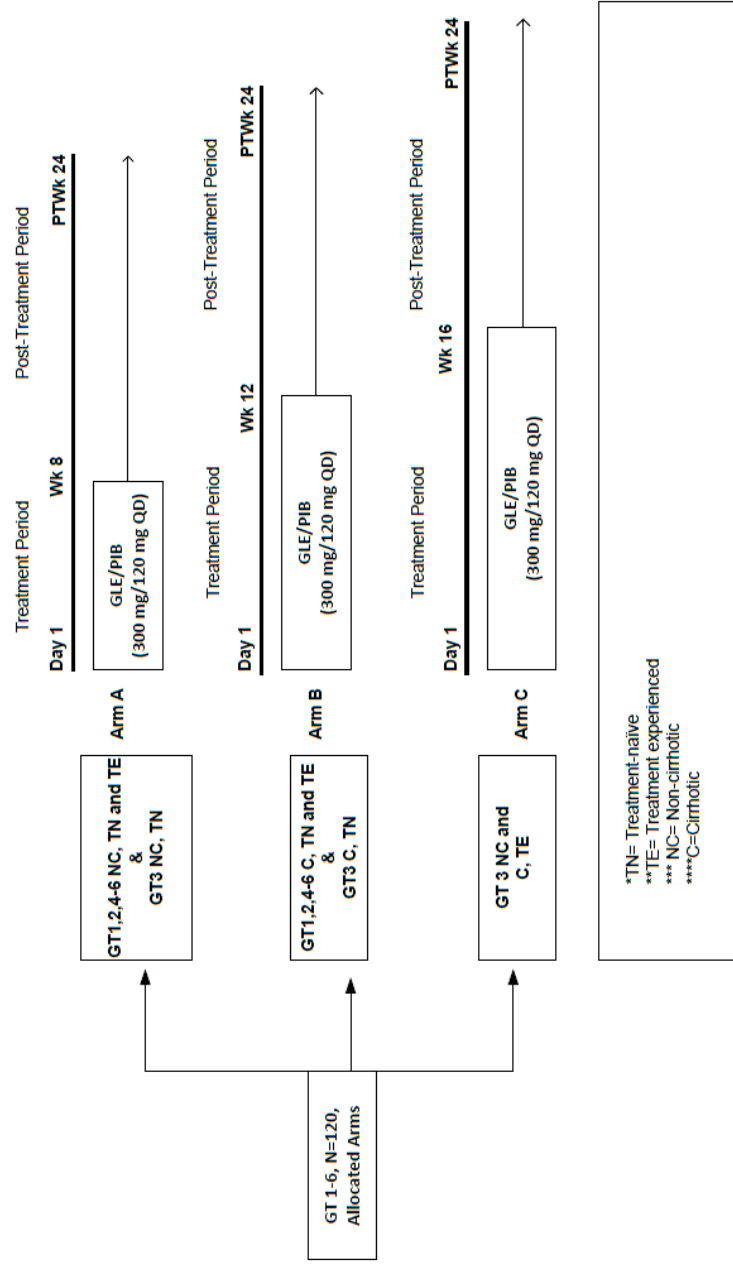
Screening Period: Subjects have up to 42 days following the Screening Visit to confirm eligibility and enroll into the study.

Treatment Period: Eligible subjects will be enrolled to receive GLE/PIB 300 mg/120 mg QD for 8 weeks (Arm A), 12 weeks (Arm B), or 16 weeks (Arm C).

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 substitutions.

A study schematic is shown below in [Figure 1](#).

Figure 1. Study Schematic



The study enrollment will be monitored to meet the following non-mutually exclusive enrollment criteria: (1) up to approximately 40 subjects with Stage 3b CKD, (2) up to approximately 75 HCV GT1-infected subjects, (3) up to approximately 30 subjects with compensated cirrhosis.

The study population will include subjects with HCV GT1 – 6; subjects with mixed HCV genotype infection should receive whichever duration is longer based on their genotypes, cirrhosis status and treatment experience. For subjects with an indeterminate genotype, treatment duration will default to the respective GT3 duration based upon treatment-experience and cirrhosis status.

Subjects with renal impairment will be categorized during screening as having CKD Stage 3b, Stage 4 or Stage 5; CKD categorization for each subject at screening will be used throughout the study. These categories are defined according to eGFR in [Table 4](#) below:

Table 4. Definition of Chronic Kidney Disease Stages

CKD Stage	eGFR (mL/min/1.73 m ²)*
3b	30 to < 45
4	15 to < 30
5	< 15 or requiring dialysis

* $\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{Serum Creatinine})^{-1.154} \times \text{Age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black}).$

The study was designed to enroll approximately 120 eligible 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 Period

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study-specific procedures will receive a unique subject number via the Interactive Response Technology (IRT) system. The investigator will evaluate whether

the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through Study Day 1 prior to dosing, and will record the results of this assessment and the details of the informed consent process in the subject's medical records. Eligible subjects have up to 42 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); or
- HBV DNA > LLOQ in subjects with isolated positive anti-HBc (i.e., negative HBsAg and Anti-HBs); or
- A confirmed positive human immunodeficiency virus (HIV) antibody test; or
- A confirmed positive pregnancy test (if female).

Subjects who meet all eligibility criteria with the exception of laboratory parameters may retest once within the 42-day screening period without prior AbbVie approval.

Subjects who have exclusionary laboratory parameter(s) are allowed to retest on the related panel(s) (e.g., exclusionary albumin 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 who fail to enroll within 42 days of Screening, regardless of the reason for falling outside of the 42-day screening window, may be allowed to rescreen only once without approval of the AbbVie Scientific Director. These subjects must be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary.

For subjects who rescreen or subjects that do not meet the study eligibility criteria including upon retest/rescreen, the site personnel must contact the IRT and identify the subject as a screen failure.

Subjects who rescreen and meet all eligibility criteria to enroll to the study will retain the same subject number, assigned at the Screening Visit, throughout the study.

5.1.2 Treatment Period (TP)

After meeting the eligibility criteria, subjects will be enrolled via IRT system. 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 and hematology as specified in [Table 6](#). 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 criterion 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 (PT) Period

All subjects who received at least one dose of study drug and either complete treatment or prematurely discontinue study drug will be monitored in the Post-Treatment Period for safety, clinical laboratory tests, HCV RNA, and the emergence and persistence of resistant viral substitutions for an additional 24 weeks following the last dose of study drug.

The Post-Treatment Period will begin the day following the last dose of study drug treatment. Study visits during the Post-Treatment Period are detailed in [Appendix D](#).

Subjects who prematurely discontinue the Post-Treatment Period should return to the site for a Post-Treatment discontinuation visit as outlined in [Appendix D](#).

5.2 Selection of Study Population

The study population is selected to address the significant unmet medical need for a safe and efficacious, RBV-sparing, pangenotypic DAA regimen to treat HCV in subjects with chronic renal impairment. The study population consists of HCV TN (i.e., patient has not received a single dose of any approved or investigational regimen for treatment of HCV) or TE (i.e., IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN) HCV GT1 – 6-infected adult male and female subjects with or without compensated cirrhosis, who have CKD Stage 3b, Stage 4 or Stage 5.

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 defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause; or
- Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L; or
- Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

OR

- A Woman of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 through at least 30 days after the last dose of study drug.
3. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine or serum pregnancy test at Study Day 1.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing.
 4. Estimated Glomerular Filtration Rate (eGFR) $< 45 \text{ mL/min/1.73 m}^2$ as estimated by the MDRD method at screening according to the following formula:
$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{Serum Creatinine})^{-1.154} \times \text{Age}^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black}),$$
or are dialysis-dependent. Subjects requiring dialysis should have been receiving dialysis for at least 1 month prior to enrollment, and may be on hemodialysis or peritoneal dialysis.
 5. Subject has positive anti-HCV antibody (Ab) at Screening and plasma HCV RNA $\geq 1000 \text{ IU/mL}$ at Screening.
 6. 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.
 7. 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.
 8. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.

Rationale for Inclusion Criteria

- | | |
|----------|---|
| 1, 4 – 6 | 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 |
| 7, 8 | In accordance with harmonized Good Clinical Practice (GCP) |

5.2.2 Exclusion Criteria

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

1. Female subject who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Current HBV or HIV infection on screening tests, defined as:
 - A positive HBsAg, or;
 - HBV DNA > LLOQ in subjects with isolated positive HBcAb (i.e., negative HBsAg and Anti-HBs), or;
 - A positive anti-human immunodeficiency virus antibody (HIV Ab).
3. Requirement for and inability to safely discontinue the medications or supplements listed in [Table 5](#) at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of any study drug.
4. Any current or historical clinical evidence of decompensated cirrhosis, including any current or past evidence of Child-Pugh B or C classification, hepatic encephalopathy or variceal bleeding; radiographic evidence of small ascites; or prior or current empiric use of lactulose/rifaximin for neurologic indications. Prophylactic use of beta blockers is not exclusionary.

5. Clinically significant abnormalities or co-morbidities, or recent (within 6 months prior to study drug administration) alcohol or drug abuse that make the subject an unsuitable candidate for this study in the opinion of the investigator.
6. Screening laboratory analyses showing any of the following abnormal laboratory results:
 - Albumin < 2.8 mg/dL
 - Hemoglobin < 9 g/dL
 - Platelets < 50,000 cells per mm³
7. History of solid organ transplantation, unless the implanted organ has since been removed, or is non-functional, and subject is no longer on immunosuppressive medication. If the organ is non-functional, the subject must be clinically stable off of immunosuppressive medication for a minimum of 6 months prior to screening.
8. Clinical history of acute renal failure in the 3 months prior to screening.
9. Receipt of any investigational or commercially available direct acting anti-HCV agents other than sofosbuvir (e.g., telaprevir, boceprevir, simeprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir or dasabuvir).
10. History of severe, life-threatening or other significant sensitivity to any excipients of the study drugs.
11. Subjects who cannot participate in the study per local law.
12. History of any suspected or confirmed hepatocellular carcinoma.

Rationale for Exclusion Criteria

1, 4 – 8, 10 – 12	In order to ensure safety of the subjects throughout the study
3, 9	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications
2, 5	To exclude subjects with HIV and liver diseases other than chronic HCV 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 drugs are 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 drugs. After 30 days post-treatment, during the Post-Treatment Period, only antiviral therapies related to the treatment of HCV and medications prescribed in association with a serious adverse event (SAE) will be recorded in EDC.

The AbbVie Scientific Director should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior HCV Therapy

Subject must be HCV treatment-naïve (i.e., patient has not received a single dose of any approved or investigational anti-HCV regimen) or treatment-experienced (i.e., has failed prior IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN therapy). Previous HCV treatment must have been completed ≥ 2 months prior to screening.

Subjects will be categorized as:

- HCV treatment-naïve: subject has never received any treatment for HCV infection.
- Subjects **with an allowed prior 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 log₁₀ IU/mL reduction in HCV RNA by Week 4 or a 2 log₁₀ IU/mL reduction in HCV RNA by Week 12 during a prior treatment course;
 - Partial responder: achieved at least a 2 log₁₀ IU/mL reduction in HCV RNA by Week 12 during a prior treatment course but failed to achieve HCV RNA undetectable at the end of treatment;
 - Unknown or unable to specify: insufficient data to categorize as null or partial responder.
- **Breakthrough:** confirmed ≥ 1 log₁₀ 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 (or quantifiable) 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.

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

The investigator should confirm that a concomitant medication/supplement can be safely administered with study drugs. Some medications may require dose adjustments due to the potential for drug-drug interactions. The investigator should refer to product labeling as needed to determine if, due to renal impairment, some medications may be contraindicated or require dose adjustment.

Management of hematopoietic growth factor therapy, if initiated by the investigator during the study, is the responsibility of the investigator; growth factors will not be provided by AbbVie, and AbbVie will not reimburse for the expense of growth factors or their use. Investigators should refer to the current package inserts of the growth factors for additional information regarding their use.

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

5.2.3.3 Prohibited Therapy

Subjects must be able to safely discontinue any prohibited medications or supplements listed in [Table 5](#) at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of GLE/PIB and not use these during the entire Treatment Period and for 14 days following discontinuation of study drugs.

Table 5. Prohibited Medications and Supplements

Medication or Supplement Name
red yeast rice (monacolin K), St. John's Wort
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin*
Astemizole, cisapride, terfenadine
Ethinyl estradiol
* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) must not be taken with the study drugs. 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 based on investigator's judgment, and either a) switch to pravastatin or rosuvastatin or b) interrupt statin therapy throughout the treatment period beginning at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drugs and until 14 days after the last dose of study drug. 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.

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.

GLE/PIB is not recommended for use in patients requiring stable cyclosporine doses > 100 mg per day. GLE/PIB may be initiated in subjects receiving cyclosporine \leq 100 mg per day.¹⁵

5.2.4 Contraception Recommendations

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

- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Male or female condom with or without spermicide.
- Cap, diaphragm or sponge with spermicide.
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier method).

- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, 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 at Screening. The subject's medical history will be updated at the Study Day 1 Visit. This updated medical history will serve as the baseline for clinical assessment.

Physical Examination

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

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

Height will be measured only at Screening.

Vital Signs and Weight

Body temperature, blood pressure, pulse and body weight will be measured at each study visit as specified in [Appendix C](#) and [Appendix D](#) or upon subject discontinuation. Blood pressure and pulse rate will 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 Screening visit as 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 6](#) 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 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, which should be taken with food. 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.

All labs collected during the study will be shipped to the central laboratory with the exception of the Day 1 serum pregnancy test in anuric women of child bearing potential which will be sent to a local lab. 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





Table 6. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Additional 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/international normalized ratio (INR) Activated partial thromboplastin time (aPTT)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Direct and indirect bilirubin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Total protein Glucose Albumin Chloride Bicarbonate Magnesium Gamma-glutamyl transferase (GGT)	Anti-HCV Ab ^a HIV Ab ^a FSH (all females) Urine and Serum Human Chorionic Gonadotropin (hCG) ^b HCV RNA HCV genotype and subtype ^a HBsAg ^c Anti-HBc IgM ^c Anti-HBc Total ^c Anti-HBs ^c HBV DNA ^d Alpha2-macroglobulin ^e Haptoglobin ^e Apolipoprotein A1 ^e Anti-HAV IgM ^f Anti-HAV IgG ^f Anti-HEV IgG ^f Anti-HEV IgM ^f HEV RNA ^f

a. Performed only at Screening.

b. Required only for females of childbearing potential.

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

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

e. Component of FibroTest and collected only if needed during the Screening Period.

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

For any laboratory test value outside the reference range that the investigator considers 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](#). Subjects who are anuric (unable to void) will have serum pregnancy tests performed instead of urine pregnancy tests. 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 the inclusion criteria) at Screening do not require pregnancy testing.

Concomitant Medication Assessment

Please refer to Section 5.2.3.2.

Hepatitis B and HIV Screen

HBsAg (hepatitis B surface antigen) will be performed at Screening, and as needed, for management of transaminase elevations. Anti-HBc IgM, Anti-HBc Total and Anti-HBs will be performed at Screening and, as needed, for management of transaminase elevations. HBV DNA will be performed at Screening for subjects who have occult HBV infection (positive Anti-HBc Total with negative HBsAg and Anti-HBs) and also performed for management of transaminase elevations.

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; 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 at any time prior to screening or during Screening period; or
- A Screening FibroTest result that is ≥ 0.75 and an APRI > 2 .

In the absence of a qualifying liver biopsy, subjects with an indeterminate FibroTest result ($0.48 < \text{result} < 0.75$), or conflicting FibroTest and APRI results (e.g., FibroTest ≤ 0.48 , but APRI ≥ 1) should be evaluated based on the investigator's clinical judgment to determine the presence or absence of cirrhosis.

If more than one method is used to determine the presence or absence of cirrhosis, the results of a liver biopsy will take precedence over FibroScan and FibroTest/APRI and the results of FibroScan will take precedence over FibroTest/APRI.

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). Child-Pugh score will be determined only for subjects with compensated cirrhosis at the visits indicated in [Appendix C](#) and [Appendix D](#).

Table 7. Child-Pugh Classification of Severity of Cirrhosis

Parameter	Points Assigned for Observed Findings		
	1	2	3
Total bilirubin, $\mu\text{mol/L}$ (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 to medication)

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

* 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.

** 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.

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 7](#).

Hepatocellular Carcinoma Screening

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

At the Screening Study Visit and at the last Post-treatment Study Visit, subjects with compensated cirrhosis will be required to have a liver ultrasound performed on them to screen for HCC, unless the subject has a historical liver ultrasound, CT or MRI performed for HCC screening within 3 months prior to those visits, in which case the result of the historical US, CT 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., MRI or CT) 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 days specified in [Appendix C](#) and [Appendix D](#). Subjects should be instructed to follow the instructions provided with the 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 the instruments may have site personnel read the questionnaires to them. Site personnel should encourage completion of the instrument at all specified visits and should ensure that a response is entered for all items.

PRO instruments should be completed prior to drug administration on Day 1 and on subsequent visits, the PRO instrument should be administered prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels.

Kidney Disease Quality of Life (KDQOL36™)

The KDQOL-36 is a disease specific Quality of Life instrument to be used in patients with chronic kidney disease. The KDQOL-36 consists of 4 subscales aimed at quantifying both general health and disease specific attributes. The subscales include: the Short Form-12 (a general health subscale SF-12), burden of kidney disease, symptoms/problems, and effects of kidney disease.

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.

Screening numbers will be unique 6 digit numbers and will begin with 100001 with the first three digits representing the investigative site, and the last three digits representing the subjects at that site. Enrolled subjects will keep their screening number as their subject number. Subjects will be enrolled on Study Day 1 as described in Section 5.5.3.

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 subgenotype determination will be collected at Screening. Genotype and subgenotype will be assessed using the Versant® HCV Genotype Inno LiPA Assay, version 2.0 or higher (LiPA; Siemens Healthcare

Diagnostics, Tarrytown, NY). If the LiPA assay is unable to genotype a sample, its genotype and subtype will be determined by a Sanger sequencing assay of 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.

Renal Biomarker Samples

Urine samples for urine total protein/creatinine ratio, urine albumin/creatinine ratio and for urine neutrophil gelatinase-associated lipocalin (NGAL) will be collected at the study visits indicated in [Appendix C](#) and [Appendix D](#). Urine samples will be collected only from subjects that are not on dialysis.

Serum samples for C-reactive protein (CRP) will be collected at the study visits indicated in [Appendix C](#) and [Appendix D](#).

The archive plasma samples will be used for tumor necrosis factor-alpha (TNF- α) collected at the study visits indicated in [Appendix C](#) and [Appendix D](#) in addition to possible analyses as indicated in the Archive Plasma Sample.

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

Archive Urine Sample

Archive urine samples will be collected at the study visits indicated in [Appendix C](#) and [Appendix D](#). Archive urine samples will be collected only from subjects that are not on dialysis. Archive urine samples are being collected for possible additional analyses, including but not limited to, safety/efficacy assessments, renal biomarkers, 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.

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, renal biomarker for tumor necrosis factor-alpha (TNF- α), study drug or metabolite measurements, viral load, 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 Investigator or designee should make sure the subject is given the dosing card at Day 1 and at every study visit until the subject completes study drug treatment.
- 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.

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, 12, or 16, 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

All study drugs should be taken with food.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

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

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

5.3.2.2 Handling/Processing of Samples

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

5.3.2.3 Disposition of Samples

The frozen plasma samples for the pharmacokinetic assays of GLE, PIB, and their possible metabolites, 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 AbbVie or the reference laboratories following separately provided instructions.

5.3.2.4 Measurement Methods

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

5.3.3 Efficacy Variables

Virologic response will be assessed by plasma HCV RNA in IU/mL at various time points from Day 1 through 24 weeks after completion of treatment or discontinuation of study.

5.3.3.1 Primary Variable

The primary efficacy variable is SVR₁₂ (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 post-treatment HCV relapse.

Additional objectives are to assess the pharmacokinetics of GLE/PIB, and the emergence and persistence of viral substitutions in the study population.

5.3.3.3 HCV Resistance Variables

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

The following resistance information will be analyzed for subjects receiving GLE/PIB who do not achieve SVR₁₂ and who have a post-baseline sample with HCV RNA ≥ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the baseline sequences, 2) the amino acid substitutions in available post-baseline samples at signature resistance-associated positions identified by NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral substitutions by NGS.

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.

5.3.6 Pharmacogenetic Exploratory Research Variables

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, the emergence and persistence of resistant viral substitutions.

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

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 DAAs may be continued at the Principal Investigator's discretion after discussion with the subject, if

the benefit of continuing DAAs is felt to outweigh the potential risk. Specific instructions regarding subject pregnancy can be found in Section 6.1.6. Subjects 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 measurements of $> 1 \log_{10}$ IU/mL above nadir) at any time point during treatment; or
- Confirmed HCV RNA ≥ 100 IU/mL (defined as 2 consecutive HCV RNA measurements ≥ 100 IU/mL) after HCV RNA $< \text{LLOQ}$ during treatment.

When confirmatory testing is required, it should be completed as soon as possible and the subject should remain on study treatment until the virologic failure criteria has been confirmed. Subjects meeting 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 substitutions 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

Each dose of study drug, GLE/PIB, will be dispensed in the form of co-formulated tablets at the visits listed in [Appendix C](#). Subjects will be instructed to take study drugs 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 GLE/PIB 100 mg/40 mg tablets. GLE/PIB will be taken orally at GLE/PIB 300 mg/120 mg (three × GLE/PIB 100 mg/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 virologic stopping criterion defined in Section 5.4.1.1 will be discontinued from treatment.

5.5.2 Identity of Investigational Products

Information about the study drugs to be used in this study is presented in [Table 8](#).

Table 8. Identity of Investigational Products

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

5.5.2.1 Packaging and Labeling

Study drugs 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	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.

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), Arm B (12 weeks of treatment) or Arm C (16 weeks of treatment) based on genotype, cirrhosis status and prior treatment experience. 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 three tablets of GLE/PIB will be dosed together QD (three tablets once daily) 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 adherence with the treatment regimen with regard to virologic response and potential development of resistance.

At each study visit during the Treatment Period denoted in [Appendix C](#), subjects will be instructed to bring all bottles of study drug (full, partial or empty) for assessment of treatment compliance. At post-baseline dispensing 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 the source and 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

This is an open-label study to evaluate the safety and efficacy of GLE/PIB administered for 8, 12 or 16 weeks in renally impaired subjects (CKD Stages 3b to 5) with HCV GT1 – 6, with or without compensated cirrhosis. The combination regimen of GLE/PIB was evaluated in non-renally impaired HCV GT1 – 6 infected subjects with and without compensated cirrhosis in the registrational studies and in CKD Stage 4 and 5 subjects with and without cirrhosis in the EXPEDITION-4 study (discussed in detail in Section 3.0). Based upon the results of these studies, AbbVie plans to evaluate the same combination regimen of GLE/PIB used in the registrational studies in an expanded population of renally-impaired subjects for durations consistent with the proposed label-recommendation. The selection of a three arm study design is appropriate in order to ensure that subjects receive the appropriate treatment duration based on their genotype, cirrhosis status and prior treatment experience.

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

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. Clonal and population sequencing methods are experimental.

5.6.3 Suitability of Subject Population

This study is planned to enroll treatment-naïve or previous treatment-experienced (IFN or pegIFN with or without RBV, pegIFN/RBV plus SOF, or SOF plus RBV) chronic HCV GT1 – 6-infected subjects, with or without compensated cirrhosis, with CKD Stages 3b to

5. With the exception of CKD Stage 3b subjects and the more inclusive eligibility criteria implemented in this study (e.g., GT3 treatment-experienced subjects, removal of specific laboratory, BMI and medical history exclusion criteria), the population enrolled in this study will be comparable to the population enrolled in the EXPEDITION-4 study. In addition, with the exception of renal impairment, the study population is comparable to that enrolled in the broader registrational Phase 2 and 3 studies in non-CKD subjects.

5.6.4 Selection of Doses in the Study

5.6.4.1 Rationale for Dose Selections

The dose of GLE/PIB 300 mg/120 mg to be used in this study is the proposed label-recommended dose. These doses have been administered to over 2,300 subjects in the registrational program, and have shown high SVR₁₂ rates with a favorable safety profile.

5.6.4.2 GLE and PIB Dose and Treatment Duration

The Phase 3 study EXPEDITION-4 evaluated a 12 week duration of GLE/PIB in 104 CKD Stage 4 and 5 subjects, including 85 subjects on hemodialysis, with HCV GT1 – 6 infection with and without cirrhosis. The SVR₁₂ rate of 98% (102/104) and no virologic failure was observed in this study support the use of GLE/PIB in renally-impaired subjects. In the registrational program, the efficacy in CKD patients was comparable to that observed for non-CKD subjects, suggesting that treatment recommendations for CKD patients should follow those for patients without renal impairment. Therefore, the current study will evaluate the proposed GLE/PIB label recommended treatment durations.

As described in Section 3.0, the high SVR₁₂ rates observed in non-CKD patients with and without cirrhosis support the proposed recommended treatment durations of 8, 12, and 16 weeks based on genotype, cirrhosis status and prior treatment experience.

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 6.1.5. 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 usually not considered to be AEs or serious adverse events (SAEs). However, laboratory abnormalities or changes in vital signs that result in study drug discontinuation or interruption, necessitate therapeutic medical intervention, meet protocol specific criteria (see Section 6.1.7 regarding toxicity management) and/or are deemed clinically significant by the investigator, should be recorded as AEs or SAEs as defined in Section 6.1.1.1 and Section 6.1.1.2.

An elective surgery/procedure scheduled to occur during a 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 CTCAE 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

Assessment of relatedness will be made with respect to the DAAs (GLE/PIB). The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

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

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

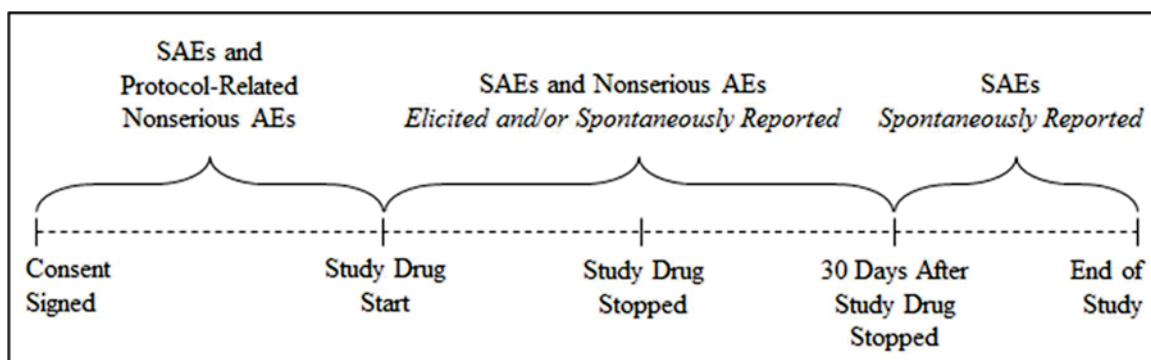
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All serious adverse events as well as protocol-related nonserious adverse events (e.g., infection at liver biopsy site) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days following discontinuation of study treatment has elapsed, all adverse events and serious 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.



For safety concerns, contact the Antiviral Safety Team at:



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



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:



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. The medical outcome for either mother or infant, meeting any serious criteria including 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 Transaminase Elevation

If a subject experiences a post-baseline increase in ALT to $> 5 \times \text{ULN}$ and also $> 2 \times$ the baseline value, the subject should have a confirmatory ALT measurement performed. If the ALT is confirmed to be $> 5 \times \text{ULN}$ and also $> 2 \times$ the baseline value, the recommendations below should be followed:

- Complete hepatic questionnaire.
- Evaluate for an alternate etiology for ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain HBsAg, Anti-HBc IgM, Anti-HBc Total, Anti-HBs, HBV DNA, Anti-HAV IgM, Anti-HAV IgG, Anti-HEV IGM, Anti-HEV IgG, and HEV RNA and other additional tests, as appropriate.
- Manage the subject as medically appropriate.
- Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and INR within 1 week. Repeat liver chemistries as indicated until resolution.
- Discontinue study drugs if any of the following is observed at any time:
 - ALT level is $\geq 20 \times \text{ULN}$ in the absence of an alternate etiology.
 - Increasing direct bilirubin or INR or onset of other symptoms/signs of liver failure.
 - At the discretion of the investigator.

Alternate management of ALT increases requires approval of the AbbVie TA MD.

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 protocol waivers, or 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), and the following AbbVie personnel:

Primary Contact:

Alternate Contact:



Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study and whether any instances of protocol non-compliance should be reported to regulatory authorities as a serious breach of GCP and the protocol.

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 study. 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 who did not achieve SVR₁₂ for reasons other than virologic failure (mITT-VF).

No data will be imputed for any efficacy or safety analysis except for analyses of SVR endpoints (HCV RNA data). HCV RNA values will be selected for the analyses of all SVR endpoints (e.g., SVR₄, SVR₁₂, and SVR₂₄) 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 subjects in the ITT population by arm (A, B and C) and overall. Demographics include age, weight, height, BMI, gender, race, and ethnicity. Baseline characteristics will be summarized as continuous variables (where appropriate) and as categorical variables, including all subgroup variables defined in Section 8.1.2.4, and including HCV genotype and subtype, prior HCV treatment history, baseline HCV RNA level, fibrosis stage (F0 – F1, F2, F3, or F4), dialysis (yes or no), CKD stage (Stage 3b, Stage 4, Stage 5), cirrhosis (yes/no), 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, history of depression or bipolar disorder, and geographic region.

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

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

8.1.2 Efficacy

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

The efficacy analyses will be performed based on overall population, i.e., across treatment durations, genotypes, and cirrhosis status.

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 that are HCV RNA detected or HCV RNA not detected. HCV RNA ≥ LLOQ are all quantifiable values.

8.1.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the percentage of subjects who achieve SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) based on overall population across treatment durations, genotypes, and cirrhosis status. The number and percentage of subjects achieving SVR₁₂ will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless the number of SVR₁₂ non-responders is less than 5, where the Wilson's score method will be used to calculate the confidence interval instead.

A summary of reason for SVR₁₂ non-response (e.g., on-treatment virologic failure, relapse, other) will be provided.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

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

For the analysis of post-treatment HCV virologic relapse, completion of treatment is defined as any subject with study drug duration of 52 days, 77 days, and 103 days or greater for subjects allocated to treatment durations of 8 weeks, 12, and 16 weeks, respectively.

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

8.1.2.3 Sensitivity Analysis

As sensitivity analyses, the number and percentage of subjects in the mITT-VF population achieving SVR₁₂, as applicable, will be summarized along with a two-sided 95% confidence interval using the normal approximation and a two-sided 95% CI 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 SVR₁₂ based on ITT population.

8.1.2.4 Subgroup Analysis

The percentage of subjects with SVR₁₂ will be calculated, as will the corresponding two sided 95% Wilson score intervals, for the following subgroups:

- HCV genotype and available subtype;
- Prior HCV treatment history (treatment-naïve or treatment-experienced);
- For treatment-experienced subjects, type of previous regimen (IFN- or SOF-based);
- Age (< 65 or ≥ 65 years) and (< 75 or ≥ 75 years);
- Race (White, Black/African-American, Asian, or other) and (black or non-black);
- Baseline HCV RNA level (< 1,000,000 or ≥ 1,000,000 IU/mL and (< 6,000,000 or ≥ 6,000,000 IU/mL);
- Baseline fibrosis stage (equivalent to Metavir F0 – F1, F2, F3, or F4);
- Baseline cirrhosis Status (Yes/No)
- Baseline platelet count (< 90 or ≥ 90 × 10⁹/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- History of diabetes (yes/no);
- Subject on stable opiate substitution;
- Hemodialysis;
- Peritoneal dialysis;
- Chronic kidney disease stage;

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

8.1.2.5 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized based on overall population:

- 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 SVR₄ (SVR 4 weeks after the last actual dose of study drug);
- The percentage of subjects who achieve SVR₂₄ (SVR 24 weeks after the last actual dose of study drug);
- The percentage of subjects who relapse after achieving SVR₁₂.

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

8.1.3 Patient Reported Outcomes

Subjects will complete the self-administered PRO instrument (where allowed per local regulatory guidelines) on the study days specified in [Appendix C](#) and [Appendix D](#). Subjects should be instructed to follow the instructions provided with the 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 the instrument may have site personnel read the questionnaire to them. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

The mean change from baseline to each applicable post-baseline timepoint in KDQOL-36 (SF-12, burden of kidney disease, symptoms and problems and effects of kidney disease on daily life) will be summarized descriptively at each visit and for change from baseline to each post baseline visit.

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

The PRO instrument should be completed prior any study procedures at each visit and prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels.

8.1.4 Resistance Analyses

For all subjects, full length NS3/4A and NS5A from baseline samples will be sequenced by NGS. For subjects who do not achieve SVR₁₂, full length NS3/4A and NS5A from the first sample after failure/discontinuation 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 SVR₁₂ due to reasons other than virologic failure but have a time point with HCV RNA ≥ 1000 IU/mL after treatment discontinuation, will have the sample at that time point sequenced.

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore, if the HCV RNA level at the time of HCV virologic failure or treatment discontinuation is < 1000 IU/mL, the sample closest in time after HCV virologic failure/treatment discontinuation with an HCV RNA level ≥ 1000 IU/mL will be used. Included time points for analyses on samples from subjects who do not achieve SVR₁₂ are 1) the sample closest in time after failure/discontinuation with an HCV RNA level of ≥ 1000 IU/mL, and 2) 24 weeks post-DAA treatment, provided that resistance-associated substitutions were detected by NGS at the time of HCV virologic failure/treatment discontinuation.

For each DAA target, signature amino acid positions and a key subset of amino acid positions are listed in [Table 9](#). Appropriate subtype specific prototypic reference sequence will be used for comparison with sequences from samples.

Table 9. Signature Amino Acid Positions and the Key Subset of Amino Acid Positions

Target	Signature Amino Acid Positions	Key Subset of Amino Acid Positions
GT1 NS3	36, 43 (GT1a only), 54, 55, 56, 80, 107, 122, 132 (GT1a only), 155, 156, 158, 168, 170, 175 (GT1b only)	155, 156, 168 (all GTs)
GT2, 3, 4, 5, 6 NS3	36, 43, 54, 55, 56, 80, 155, 156, 166 (GT3-only), 168	
GT1 NS5A	24, 28, 29, 30, 31, 32, 54 (GT1b only), 58, 62, 92, 93	24, 28, 30, 31, 58, 92, 93 (all GTs)
GT2, 3, 4, 5, 6 NS5A	24, 28, 29, 30, 31, 32, 58, 92, 93	

The following definitions will be used in the HCV resistance analyses:

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

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

- A listing of all baseline polymorphisms (2% detection threshold) at signature amino acid positions for each DAA target (NS3/4A and NS5A).
- A listing of all baseline polymorphisms (15% detection threshold) at non-signature amino acid positions for each DAA target (NS3/4A and NS5A) for subjects who experience virologic failure.
- A by subject listing of baseline polymorphisms (15% detection threshold) at signature amino acid positions in subjects with polymorphisms across both NS3 and NS5A, or those with multiple baseline polymorphisms within any one target (NS3/4A or NS5A).
- The number and percentage of subjects with baseline polymorphisms at signature amino acid positions at detection thresholds of 2% and 15%.
- Total number and percentage of subjects with baseline polymorphisms at a key subset of amino acid positions in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A, by subtype, and total (include all subtypes).

Analysis 2: The impact of baseline polymorphisms on treatment outcome will be assessed as follows: for each polymorphism, the SVR₁₂ rate will be calculated for subjects with and without the polymorphism and the 2 rates will be compared. Analysis will be grouped by HCV subtype and DAA target (NS3/4A or NS5A).

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

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

Analysis 3: In subjects with or without polymorphisms in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A at the key subset of amino acid positions at 15% detection threshold, the SVR₁₂ rate will be calculated, and the rates with or without polymorphisms will be compared using Fisher's exact test. Analysis will be separated by HCV subtype. The following tables will be provided:

- Comparison of SVR₁₂ rates by subtype, and total (include all subtypes)
- Comparison of SVR₁₂ rates by genotype, and total (include all subtypes)

Analysis 4: The following analyses will be performed for subjects who do not achieve SVR₁₂ and who have post-baseline resistance data available:

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

The persistence of post-baseline substitutions at signature amino acid positions for each target will be assessed by NGS at Post-Treatment Week 24. A listing by subject and time point of all post-baseline substitutions relative to the baseline amino acid sequence will be provided for each DAA target.

If resistance-associated substitutions are not detected in a given target for a subject at the time of failure/discontinuation, then that target may not be sequenced in subsequent samples from that subject.

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 treatment duration and cirrhosis status across genotypes 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 (PT). The tabulation of the number of subjects with treatment-emergent adverse events by severity grade and relationship to study drug (DAAs) also will 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 available 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.

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

8.1.6 Pharmacokinetic and Exposure-Response Analyses

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

Relationship between exposure (noncompartmental or population pharmacokinetic model based values of concentrations over time, AUC, C_{trough} or some other appropriate measure of exposure) and clinical observations (antiviral activity or virologic end points, such as SVR₁₂ response) will be explored, if appropriate. Exposure-response relationships for primary and secondary efficacy variables and/or some safety measures of interest may also be explored. Exposure response relationships will be explored using a logistic regression analysis and/or a semi-mechanistic viral dynamic model. Additionally, relationship between exposure and safety endpoints of interest may also be explored. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

It is anticipated that approximately 120 HCV GT1 – 6 infected subjects with chronic renal impairment, with or without compensated cirrhosis, who are either HCV TN or TE with IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN will be enrolled in the study. No formal hypothesis is being tested. If the observed SVR₁₂ rate in this study is 97% among 120 HCV GT1 – 6 renally impaired subjects, then the half-width of 2-sided 95% normal approximation interval is 0.031.

8.3 Randomization Methods

This study is not randomized. Eligible subjects will be enrolled into the study.

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 and approval by Regulatory Authority (ies), if required by local regulations, prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP and all other applicable regulatory requirements.

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

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in [Appendix A](#).

9.3 Subject Information and Consent

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

documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

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

Pharmacogenetic analysis will only be performed if the subject has voluntarily signed and dated a pharmacogenetic informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The pharmacogenetic informed consent must be signed before the pharmacogenetic testing is performed. If the subject does not consent to the pharmacogenetic testing, it will not impact the subject's 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 to the appropriate source document. The Investigator Awareness Date (SAE CRF) may serve as the source

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

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

10.2 Case Report Forms

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

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

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

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

11.0 Data Quality Assurance

To ensure data integrity and subject safety, a study monitor will continuously, throughout the study, verify that all subjects sign the informed consent prior to any study specific procedures being conducted, that the protocol procedures are being followed appropriately, and that the information provided in the eCRF is complete, accurate, and supported by information in source documents.

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 exploratory pharmacogenetic research may be provided to investigators and used in scientific publications or presented at medical conventions. Optional exploratory research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

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

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

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMA) 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/Pibrentasvir in Renally-Impaired Adults with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (EXPEDITION-5)

Protocol Date: 30 January 2018

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

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

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
		Pharmacokinetics
		Therapeutic Area
		Therapeutic Area
		Bioanalysis
		Statistics
		Clinical Program Development

Appendix C. Study Activities – Treatment Period

Activity	Screening	Day 1 ^a	Wk 4	Wk 8 ^b	Wk 12 ^b	EOT*/Premature D/C ^b
Informed Consent ^c	X					
Medical History ^d	X	X				
Physical Exam	X	X				X
Vital Signs, Weight, Height ^e	X	X	X	X	X	X
ECG	X					
Hematology/Chemistry ^f /Coagulation Panel	X	X	X	X	X	X
Pregnancy Test (serum [s] urine [u]) ^g	X (s)	X (u, s)	X (u, s)	X (u, s)	X (u, s)	X (u, s)
Hepatitis B, Hepatitis C, and HIV Testing	X					
HCV Genotype and Subgenotype	X					
Liver Biopsy or FibroTest/APRI, or FibroScan ^{®h}	X					
FSH (all females)	X					
Pharmacogenetic DNA/RNA Sample (optional) ^c		X				X
Child-Pugh Score (cirrhotic subjects only)	X					X
Concomitant Medication Assessment	X	X	X	X	X	X
Clinical Assessment of Hepatic Decompensation (cirrhotic subjects only)		X				
HCC Screening (cirrhotic subjects only) ⁱ	X					
Adverse Event Assessment ^j	X	X	X	X	X	X

Activity	Screening	Day 1 ^a	Wk 4	Wk 8 ^b	Wk 12 ^b	EOT*/Premature D/C ^b
PRO Instruments ^k		X	X		X	X
Study Drugs Dispensed		X	X	X ^l	X ^l	
Study Drug Accountability and Review of Study Drug Adherence			X	X	X	X
HCV RNA Samples	X	X	X	X	X	X
HCV Resistance Sample		X	X	X	X	X
Archive Plasma Sample	X	X	X	X	X	X
Pharmacokinetic Samples ^m			X	X	X	X
Archive Urine Sample – only for non-dialysis subjects		X				X
Urine and Serum Samples for Renal Biomarkers – urine sample only for non-dialysis subjects	X	X	X	X	X	X

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

* The EOT visit can be at Week 8 (Arm A), Week 12 (Arm B), or Week 16 (Arm C) in accordance with Section 5.1 and activities should be conducted that are located in the EOT column.

- All procedures to be performed prior to first dose.
- The Week 8 study visits apply to all subjects whose treatment duration is 12 weeks (Arm B) and 16 weeks (Arm C) in accordance with Section 5.1. The Week 12 study visits apply to all subjects whose treatment duration is 16 weeks (Arm C) in accordance with Section 5.1. 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).
- Subjects need to sign an IRB/IEC approved informed consent for the study prior to performing any screening or study-specific procedures. Subjects need to sign the IRB/IEC approved optional pharmacogenetic consent at any time during the study but prior to the collection of any pharmacogenetic samples, if applicable.
- A complete medical history will be taken at Screening and will be updated at the Study Day 1 Visit.
- Height will be measured at the Screening Visit only.

- f. Blood samples for serum chemistry tests should be collected following a minimum 8-hour fast prior to drug intake (with the exception of the Screening Visit, which may be non-fasting).
- g. Pregnancy testing is not required for females of non-childbearing potential as defined in Inclusion Criterion 2. Female subjects who are anuric (unable to void) will have serum pregnancy tests performed instead of urine pregnancy tests. Female subjects that can provide a urine sample will have a urine pregnancy test.
- h. For subjects who have not had a qualifying liver biopsy (within the previous 24 months for non-cirrhotics or at any time prior to Screening for cirrhotics) or a qualifying FibroScan[®] (within the previous 6 months for non-cirrhotics or at any time prior to Screening for cirrhotics).
- i. Required only for subjects with cirrhosis. An HCC Screening assessment is required per protocol only in the Screening Study Visit and at the Post-Treatment Period Week 24 Visit, or upon discontinuation. From Day 1 to EOT or premature D/C Study Visit, HCC screening should be performed as part of the Standard of Care for the subject. Please refer to Section 5.3.1.1, item "Hepatocellular Carcinoma Screening" for details on this study procedure.
- j. See specific information regarding adverse event collection in Section 6.1.4.
- k. PRO should be administered before any study procedures at Day 1. For all other visits, PRO should be administered prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels.
- l. The Week 8 dispensation is only required for subjects whose treatment is 12 weeks (Arm B) or 16 weeks (Arm C) and the Week 12 dispensation is only required for subjects whose treatment is 16 weeks (Arm C) in accordance with Section 5.1.
- m. Details regarding timing of PK samples are provided in Section 5.3.2.1.

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/Coagulation Panel ^g	X		X ^b
Pregnancy Test ^c	X, (u, s)		X (u, s) ^c
PRO Instruments ^d		X	X
Concomitant Medication Assessment ^e	X	X	X
Adverse Event Assessment ^f	X	X	X
HCV RNA Samples	X	X	X
HCV Resistance Sample	X	X	X
Archive Plasma Sample	X	X	X
Pharmacogenetic DNA/RNA Sample (optional)		X	
Child-Pugh Score (cirrhotic subjects only) ^g		X	X
Archive Urine Sample – only for non-dialysis subjects		X	X
HCC Screening (cirrhotic subjects only) ^h			X
Urine and Serum Samples for Renal Biomarkers – urine sample only for non-dialysis subjects	X	X	X

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

- Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C Visit procedures.
- Hematology/Chemistry/Coagulation Panel and Pregnancy Test are only required at PT D/C if subject discontinued prior to PT Wk 4 and not required at PT Wk 24.
- Women of childbearing potential do not require pregnancy testing beyond PT Wk 4. Pregnancy testing will be performed at PT D/C visit only if the subject discontinues prior to PT Wk 4. Female subjects who are anuric (unable to void) will have serum pregnancy tests performed instead of urine pregnancy tests.

- d. PROs should be administered before any study procedures, prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels at any visit.
- e. Only medications taken for SAEs and treatment of HCV will be collected after 30 days post-dosing.
- f. Nonserious AEs and all SAEs will be collected until 30 days post dosing. All spontaneously reported SAEs will be collected thereafter. See specific information regarding adverse event collection in Section 6.1.4.
- g. The Child-Pugh assessment at the PT Wk 12 and 24 visits requires that an abbreviated physical examination and lab draws are conducted. No other analytes will be resulted as part of the labs drawn at these time points. Please refer to Section 5.3.1.1 Study Procedures, 'Child-Pugh Score and Category.'
- h. Required only for subjects with cirrhosis. Please report to Section 5.3.1.1, item "Hepatocellular Carcinoma Screening" for details on this study procedure.

Appendix E. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.0 Title Page

"Sponsor/Emergency Contact:"

"Emergency Contact:" previously read:



Has been changed to read:



Section 1.2 Synopsis

Subsection Criteria for Evaluation:

Heading "Pharmacokinetic:"

Delete: last sentence

Values for the pharmacokinetic parameters including apparent clearance (CL/F) and apparent volume of distribution (V/F) will be estimated using population pharmacokinetic modeling procedures.

Section 1.2 Synopsis

Subsection Statistical Methods:

Heading "Pharmacokinetic:"

Delete: last paragraph

Pharmacokinetic data from this study may be combined with data from other studies for the population pharmacokinetic analyses. Actual sampling times relative to dosing will be used for the analyses. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software. The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies in HCV-infected subjects and healthy subjects. Apparent clearance (CL/F) and apparent volume of distribution (V/F) of glecaprevir, pibrentasvir, and their possible metabolites will be the pharmacokinetic parameters of major interest in the NONMEM analyses. Relationship between exposure and clinical observations (antiviral activity) will be explored.

Section 5.3.1.1 Study Procedures

Subsection Renal Biomarker Samples

Second paragraph previously read:

Serum samples for tumor necrosis factor-alpha (TNF- α) and C-reactive protein (CRP) will be collected at the study visits indicated in Appendix C and Appendix D.

Has been changed to read:

Serum samples for C-reactive protein (CRP) will be collected at the study visits indicated in [Appendix C](#) and [Appendix D](#).

The archive plasma samples will be used for tumor necrosis factor-alpha (TNF- α) collected at the study visits indicated in [Appendix C](#) and [Appendix D](#) in addition to possible analyses as indicated in the Archive Plasma Sample.

Section 5.3.1.1 Study Procedures

Subsection Archive Plasma Sample

First paragraph, last sentence previously read:

Archive plasma samples are being collected for possible additional analyses, including but not limited to study drug or metabolite measurements, viral load, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by AbbVie.

Has been changed to read:

Archive plasma samples are being collected for possible additional analyses, including but not limited to, renal biomarker for tumor necrosis factor-alpha (TNF- α), study drug or metabolite measurements, viral load, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by AbbVie.

Section 6.1.5 Adverse Event Reporting

"Primary Therapeutic Area Medical Director:" previously read:



Has been changed to read:



Table 9. Signature Amino Acid Positions and the Key Subset of Amino Acid Positions
Previously read:

Target	Signature Amino Acid Positions	Key Subset of Amino Acid Positions
GT1 NS3	36, 43 (GT1a only), 54, 55, 56, 80, 107, 122, 132 (GT1a only), 155, 156, 158, 168, 170, 175 (GT1b only)	155, 156, 168 (all GTs)
GT2, 4, 5, 6 NS3	36, 43, 54, 55, 56, 80, 155, 156, 168	
GT1 NS5A	24, 28, 29, 30, 31, 32, 54 (GT1b only), 58, 62, 92, 93	24, 28, 30, 31, 58, 92, 93
GT2, 4, 5, 6 NS5A	24, 28, 29, 30, 31, 32, 58, 92, 93	(all GTs)

Has been changed to read:

Target	Signature Amino Acid Positions	Key Subset of Amino Acid Positions
GT1 NS3	36, 43 (GT1a only), 54, 55, 56, 80, 107, 122, 132 (GT1a only), 155, 156, 158, 168, 170, 175 (GT1b only)	155, 156, 168 (all GTs)
GT2, 3, 4, 5, 6 NS3	36, 43, 54, 55, 56, 80, 155, 156, 166 (GT3-only), 168	
GT1 NS5A	24, 28, 29, 30, 31, 32, 54 (GT1b only), 58, 62, 92, 93	24, 28, 30, 31, 58, 92,
GT2, 3, 4, 5, 6 NS5A	24, 28, 29, 30, 31, 32, 58, 92, 93	93 (all GTs)

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
		Pharmacokinetics
		Clinical
		Clinical
		Clinical
		Bioanalysis
		Statistics
		Clinical

Has been changed to read:

	Functional Area
	Pharmacokinetics
	Therapeutic Area
	Therapeutic Area
	Bioanalysis
	Statistics
	Clinical Program Development

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

Activity	PT Wk 4	PT Wk 12	PT Wk 24 or PT D/C ^a
Vital Signs and Weight	X	X	X
Hematology/Chemistry/Coagulation Panel	X		X ^b
Pregnancy Test	X, (u, s)		X (u, s) ^b
PRO Instruments ^c		X	X
Concomitant Medication Assessment ^d	X	X	X
Adverse Event Assessment ^e	X	X	X
HCV RNA Samples	X	X	X
HCV Resistance Sample	X	X	X
Archive Plasma Sample	X	X	X
Pharmacogenetic DNA/RNA Sample (optional)		X	
Child-Pugh Score (cirrhotic subjects only) ^f		X	X
Archive Urine Sample – only for non-dialysis subjects		X	X
HCC Screening (cirrhotic subjects only) ^g			X
Urine and Serum Samples for Renal Biomarkers – urine sample only for non-dialysis subjects	X	X	X

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

- Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C Visit procedures.
- Hematology/Chemistry/Coagulation Panel and Pregnancy Test are only required at PT D/C if subject discontinued prior to PT Wk 4. Women of childbearing potential do not require pregnancy testing beyond PT Wk 4. Pregnancy testing will be performed at PT D/C visit only if the subject discontinues prior to PT Wk 4. Pregnancy testing in PT Period is not required for females of non-childbearing potential as defined in Inclusion Criterion 2. Female subjects who are anuric (unable to void) will have serum pregnancy tests performed instead of urine pregnancy tests.

- c. PROs should be administered before any study procedures, prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels at any visit.
- d. Only medications taken for SAEs and treatment of HCV will be collected after 30 days post-dosing.
- e. Nonserious AEs and all SAEs will be collected until 30 days post dosing. All spontaneously reported SAEs will be collected thereafter. See specific information regarding adverse event collection in Section 6.1.4.
- f. An abbreviated physical examination will need to be conducted for assessment of ascites and hepatic encephalopathy.
- g. Required only for subjects with cirrhosis. Please report to Section 5.3.1.1, item "Hepatocellular Carcinoma Screening" for details on this study procedure.

Has been changed to read:

Activity	PT Wk 4	PT Wk 12	PT Wk 24 or PT D/C ^a
Vital Signs and Weight	X	X	X
Hematology/Chemistry/Coagulation Panel ^g	X		X ^b
Pregnancy Test ^c	X, (u, s)		X (u, s) ^c
PRO Instruments ^d		X	X
Concomitant Medication Assessment ^e	X	X	X
Adverse Event Assessment ^f	X	X	X
HCV RNA Samples	X	X	X
HCV Resistance Sample	X	X	X
Archive Plasma Sample	X	X	X
Pharmacogenetic DNA/RNA Sample (optional)		X	
Child-Pugh Score (cirrhotic subjects only) ^g		X	X
Archive Urine Sample – only for non-dialysis subjects		X	X
HCC Screening (cirrhotic subjects only) ^h			X
Urine and Serum Samples for Renal Biomarkers – urine sample only for non-dialysis subjects	X	X	X

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

- Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C Visit procedures.
- Hematology/Chemistry/Coagulation Panel and Pregnancy Test are only required at PT D/C if subject discontinued prior to PT Wk 4 and not required at PT Wk 24.
- Women of childbearing potential do not require pregnancy testing beyond PT Wk 4. Pregnancy testing will be performed at PT D/C visit only if the subject discontinues prior to PT Wk 4. Female subjects who are anuric (unable to void) will have serum pregnancy tests performed instead of urine pregnancy tests.

- d. PROs should be administered before any study procedures, prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels at any visit.
- e. Only medications taken for SAEs and treatment of HCV will be collected after 30 days post-dosing.
- f. Nonserious AEs and all SAEs will be collected until 30 days post dosing. All spontaneously reported SAEs will be collected thereafter. See specific information regarding adverse event collection in Section 6.1.4.
- g. The Child-Pugh assessment at the PT Wk 12 and 24 visits requires that an abbreviated physical examination and lab draws are conducted. No other analytes will be resulted as part of the labs drawn at these time points. Please refer to Section 5.3.1.1 Study Procedures, 'Child-Pugh Score and Category.'
- h. Required only for subjects with cirrhosis. Please report to Section 5.3.1.1, item "Hepatocellular Carcinoma Screening" for details on this study procedure.

Document Approval

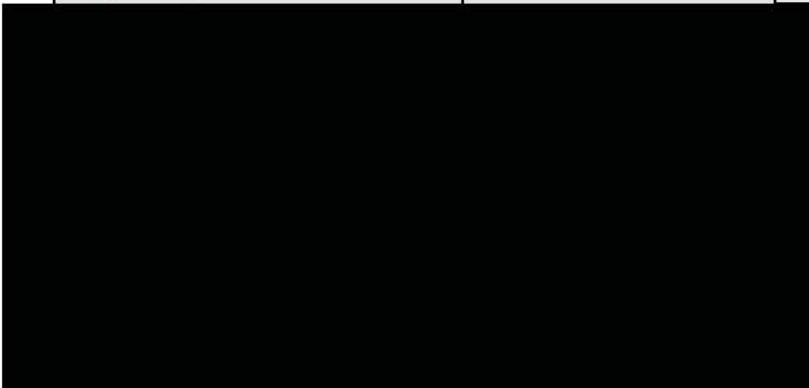
Study M16127 - A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir/Pibrentasvir
in Renally-Impaired Adults with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (EXPEDITION-5) -
Amendment 3 - EudraCT 2016-004182-60 - 30Jan2018

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Company ID: 02022018-00F9F683C0A807-00002-en

Signed by:	Date:	Meaning Of Signature:
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Approver

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Author

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