1.0 Title Page

Clinical Study Protocol M16-135

A Single Arm, Open-label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 - 6 Infection and Compensated Cirrhosis

Incorporating Amendments 1, 2 and 3

AbbVie Investigational Product:	Glecaprevir, Pibrentasvir
Date:	11 June 2018
Development Phase:	3b
Study Design:	This is an open-label, multicenter study
EudraCT Number:	2016-004967-38
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc. (AbbVie)*
Sponsor/Emergency Contact:	[redacted], MD Medical Director Antiviral Clinical Project Team 1500 Seaport Blvd. Redwood City, CA 94063 Phone: [redacted] Fax:

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	17 January 2017
Amendment 1	25 April 2017
Amendment 2	06 September 2017

The purpose of this amendment is to:

- Update several sections of the protocol to allow for the enrollment of subjects infected with HCV Genotype 3

  Rationale: *To evaluate the efficacy and safety of an 8-week treatment regimen in a treatment-naïve cirrhotic patient population inclusive of patients with HCV GT3 infection.*
- Update Section 5.2.3.3 Prohibited Therapy

  Rationale: *To reflect most updated protocol guidance in the setting of marketing approval of GLE/PIB.*
- Update Sponsor/Emergency Contact

  Rationale: *To reflect the new physician assuming the role of Primary Therapeutic Area Medical Director.*

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:** M16-135
Name of Study Drug: Glecaprevir, Pibrentasvir	**Phase of Development:** 3b
Name of Active Ingredient: Glecaprevir, Pibrentasvir	**Date of Protocol Synopsis:** 11 June 2018
Protocol Title: A Single Arm, Open-label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 - 6 Infection and Compensated Cirrhosis	
Objectives: • To demonstrate the efficacy of the SVR_{12} rates of 8 weeks of treatment with glecaprevir/pibrentasvir compared to the historical SVR_{12} rates of 12 weeks of treatment with glecaprevir/pibrentasvir in treatment naïve adults with chronic HCV infection and compensated cirrhosis. • To assess the safety of 8 weeks of treatment with glecaprevir/pibrentasvir in treatment naïve adults with chronic HCV infection and compensated cirrhosis.	
Investigators: Multicenter	
Study Sites: Approximately 120 globally	
Study Population: Adults with chronic HCV genotype (GT) 1 - 6 infection, aged 18 years or older, with compensated cirrhosis, who are HCV treatment-naïve.	
Number of Subjects to be Enrolled: Approximately 330 subjects	
Methodology: This is a Phase 3b, single arm, open-label, multicenter study to evaluate the efficacy and safety of 8 weeks of glecaprevir/pibrentasvir in treatment-naïve subjects with chronic HCV GT 1 - 6 infection and compensated cirrhosis. The study will initially enroll subjects with HCV GT 1, 2, 4, 5, and 6 infection followed by subjects with HCV GT3 infection. Once enrollment of subjects with HCV GT3 infection begins, enrollment of subjects with HCV GT 1, 2, 4, 5 or 6 infection will be closed. The study will consist of 3 periods: <u>Screening Period:</u> Subjects have up to 42 days following the Screening Visit to confirm eligibility and enroll into the study. <u>Treatment Period:</u> Eligible subjects will be enrolled to receive glecaprevir/pibrentasvir 300 mg/120 mg once daily (QD) for 8 weeks. Scheduled visits for subjects in the Treatment Period consist of Day 1 and Weeks 1, 2, 4, and 8. Study procedures, including assessment of adverse events, vital signs, adherence, concomitant medications, HCV RNA, HCV resistance, pharmacokinetic assays, and clinical laboratory tests, will be conducted at each visit.	

Methodology (Continued):

Because subjects with GT 1, 2, 4, 5 or 6 infection will be enrolled first, separate treatment extension criteria will apply to subjects with GT 1, 2, 4, 5 or 6 infection versus subjects with GT3 infection, as described below. However, if treatment is extended for all or a particular subgroup of subjects with GT 1, 2, 4, 5 or 6 infection, then enrollment of subjects with GT3 infection will be terminated and all GT3-infected subjects who are on treatment or have completed treatment within the previous 7 days will have their treatment extended to 12 weeks.

In subjects with HCV GT 1, 2, 4, 5, and 6 infection, an efficacy assessment will evaluate the post-treatment relapse rate after the first 30 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to 12 weeks is needed for all GT 1, 2, 4, 5, and 6-infected subjects or for a particular subgroup of GT 1, 2, 4, 5, and 6-infected subjects who are on treatment or have completed treatment within the previous 7 days.

In subjects with HCV GT3 infection, an efficacy assessment will evaluate the post-treatment relapse rate after the first 20 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to 12 weeks is needed for all GT3-infected subjects or for a particular subgroup of GT3-infected subjects who are on treatment or have completed treatment within the previous 7 days.

Post-Treatment Period:

Subjects who complete or prematurely discontinue the Treatment Period will be followed for 24 weeks to monitor safety, HCV RNA levels and to evaluate efficacy and the emergence and persistence of resistance associated substitutions.

During the Post-Treatment Period, all subjects will have visits at Weeks 4, 12, and 24 following completion of the Treatment Period. Study procedures to monitor safety, HCV RNA, and the emergence and persistence of resistant 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. Screening laboratory result indicating HCV GT 1 - 6 infection;
3. Positive plasma HCV antibody and HCV RNA viral load ≥ 1000 IU/mL at Screening;
4. Treatment-naïve to any approved or investigational anti-HCV medication;
5. Subject must be documented as cirrhotic, with a Child-Pugh score of ≤ 6.

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

Main Exclusion:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study, or for approximately 30 days after the last dose of study drug;
2. 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 empiric use of lactulose/rifaximin for neurologic indications. The use of beta blockers is not exclusionary;
3. 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).
4. HCV genotype performed by the central laboratory during screening indicating co-infection with more than one HCV genotype;
5. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - Alanine aminotransferase ALT > 10 × ULN
   - Aspartate aminotransferase AST > 10 × ULN
   - Total Bilirubin > 3.0 mg/dL
   - Calculated creatinine clearance (CrCl, Cockcroft-Gault method) of < 50 mL/min
   - Albumin < 2.8 mg/dL
   - Hemoglobin < 10 g/dL
   - Platelets < 50,000 cells/mm^3

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

Duration of Treatment: Subjects will receive glecaprevir/pibrentasvir for 8 weeks.

Criteria for Evaluation:

Efficacy:

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

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests, 12-Lead ECGs and vital signs.

Criteria for Evaluation (Continued):

Patient Reported Outcomes (PROs):

The Treatment Satisfaction Questionnaire-Medication (TSQM) will be used to assess subjects' satisfaction with the treatments efficacy and side effects. The Short Form 36 Version 2 Health Status Survey (SF-36v2) will be used to assess the functional health and well-being of subjects. The Fatigue Severity Scale (FSS) will be used to measure the severity of fatigue and its effect on lifestyle and activities.

Pharmacokinetic:

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

Resistance:

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

Statistical Methods:

Efficacy:

The Intention-to-Treat (ITT) population includes all enrolled subjects who receive at least one dose of study drug. The Per-Protocol (PP) population includes all enrolled subjects who receive at least one dose of study drug, with the exception of subjects who experience breakthrough, or prematurely discontinue treatment prior to Week 8, or have no HCV RNA value in the SVR_{12} visit window or later.

The primary efficacy endpoint is SVR_{12}. The following primary and key secondary efficacy analyses are the comparisons of the SVR_{12} rate of the 8-week treatment duration to a historical SVR_{12} rate for 12 weeks in the Per-Protocol (PP) population and in the Intention-to-Treat (ITT) population. The primary efficacy analyses will be conducted among HCV GT1, 2, 4, 5, and 6-infected subjects, and the two key secondary efficacy analyses will be conducted among all (HCV GT1 - 6) subjects. The primary efficacy analyses are listed below and will be tested through a fixed-sequence testing procedure:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 94% in the PP population.
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 93% in the ITT population.

Statistical Methods (Continued):

Efficacy (Continued):

The two key secondary efficacy analyses included in the fixed-sequence testing procedure are:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 3, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 94% in the PP population.
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 3, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 93% in the ITT population.

The primary and key secondary efficacy analyses will be tested using the hierarchical order outlined above to control the Type I error rate. Only if success has been demonstrated for the first primary efficacy analysis of SVR_{12} based on the PP population in HCV GT1, 2, 4, 5, and 6-infected subjects will the testing proceed to the second primary efficacy analysis of SVR_{12} based on the ITT population in HCV GT1, 2, 4, 5, and 6-infected subjects. And only if success has been demonstrated for the second primary efficacy analysis will the testing proceed to the first key secondary efficacy analysis of SVR_{12} based on the PP population in HCV GT1, 2, 3, 4, 5, and 6-infected subjects, and so on. For all primary and key secondary efficacy analyses, the percentage of subjects achieving SVR_{12} and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial distribution, unless the number of subjects who failed to achieve SVR_{12} is less than 5, then the Wilson's score method will be used for the confidence interval instead.

The other secondary efficacy analyses are listed below and are not included in the fixed-sequence testing:

- The percentage of HCV GT3-infected subjects in the PP population who achieve SVR_{12};
- The percentage of HCV GT3-infected subjects in the ITT population who achieve SVR_{12};
- The percentage of subjects with on-treatment virologic failure (OTVF) across genotypes, within HCV GT 1, 2, 4, 5, and 6-infected subjects combined, and within HCV GT3-infected subjects (based on ITT population);
- The percentage of subjects with post-treatment relapse across genotypes, within HCV GT 1, 2, 4, 5, and 6-infected subjects combined, and within HCV GT3-infected subjects (based on ITT population).

The number and percentage of subjects will be summarized along with a two-sided 95% confidence interval using Wilson's score method.

For the analysis of OTVF and post-treatment relapse, separate summaries will be provided for all subjects across genotypes, within HCV GT1, 2, 4, 5, and 6-infected subjects combined, and within HCV GT3-infected subjects.

Statistical Methods (Continued):

Safety:

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 severity grade (Grades 1 – 5) and relationship to study drug. Mean changes in clinical laboratory and vital sign data from baseline to each post-baseline visit will be summarized. The number and percentage of subjects with post-baseline laboratory values meeting toxicity grades and meeting pre-defined criteria for laboratory parameters of interest during treatment will be summarized. The number and percentage of subjects with post-baseline vital sign values during the Treatment Period meeting pre-specified criteria for potentially clinically significant vital sign values will be summarized.

Patient Reported Outcomes (PROs):

The mean change from baseline to each applicable post-baseline timepoint in the FSS total score and the SF-36v2 Mental Component Summary (SF-36-MCS) and Physical Component Summary SF-36-PCS scores will be summarized descriptively at each visit. The TSQM subscales (global satisfaction, convenience, effectiveness, side effects) will be summarized descriptively at Weeks 2, 4, and 8 and the change from the baseline visit will be summarized at all on treatment timepoints.

Pharmacokinetic:

Plasma concentration of glecaprevir and pibrentasvir will be tabulated for each subject. Plasma concentrations of glecaprevir and pibrentasvir will be summarized based on last dosing time, sampling time and time since last dose. Summary statistics will be computed for glecaprevir and pibrentasvir plasma concentrations binned by time since last dose.

Resistance:

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

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the corresponding 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.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

Ab	Antibody
ADR	Study drug related AE
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APRI	Aminotransferase/platelet ratio index
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area Under the Concentration Curve
BMI	Body Mass Index
BUN	Blood urea nitrogen
CL/F	Apparent Oral Clearance
CrCl	Creatinine clearance
CRF	Case report form
CT	Computed Tomography
CTEP	Cancer Therapy Evaluation Program
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMEA	European Agency for the Evaluation of Medicinal Products
EOT	End of treatment
EU	European Union
FSS	Fatigue Severity Scale
GAM	Generalized additive method
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLE	Glecaprevir

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
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
HRQoL	Health Related Quality of Life
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon
IL28B	Interleukin 28B
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
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria
NGS	Next generation sequence
NONMEM	Non-linear mixed-effect modeling
NS3A	Nonstructural viral protein 3A
NS4A	Nonstructural viral protein 4A
NS5A	Nonstructural viral protein 5A
NS5B	Nonstructural viral protein 5B
OTVF	On-treatment virologic failure
PCS	Potentially clinically significant

PegIFN	Pegylated-interferon alfa-2a or alfa-2b
PegIFN/RBV	Combination of pegylated-interferon alfa-2a or alfa-2b and ribavirin
PI	Protease Inhibitor
PIB	Pibrentasvir
PK	Pharmacokinetic
POR	Proof of receipt
PP	Per-protocol
PRO	Patient Reported Outcome
PR	pegIFN/RBV
PT	Post-Treatment
QD	Once daily
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
RTV or r	Ritonavir
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Standard Deviation
SF-36v2	Short Form 36 – Version 2 Health Survey
SF-36-MCS	Mental Component Summary
SF-36-PCS	Physical Component Summary
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
TA MD	Therapeutic Area Medical Director
TN	Treatment naïve
TSQM	Treatment Satisfaction Questionnaire – Medication
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 (GLE/PIB)
Study Day 1	First day of study drug dosing
Treatment Period	Day 1 through last dose of study drug
Post-Treatment Period	Day after the last dose of study drug through Post-Treatment Week 24 or Post-Treatment Discontinuation

2.0 Table of Contents

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3.0 Introduction

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

Depending on various risk factors, between 10% and 40% of all patients with chronic HCV infection will develop cirrhosis.[6] Deaths related to the complications of cirrhosis may occur at an incidence of approximately 4% per year; hepatocellular carcinoma (HCC) occurs in this population at an estimated incidence of 1% to 5% per year.[6] Patients diagnosed with hepatocellular carcinoma have a 33% probability of death during the first year.[6] Successful treatment of HCV has been shown to significantly reduce the risk of disease progression and related mortality as well as the development of hepatocellular carcinoma.[7,8]

At the time of initiation of this study, therapy for HCV had improved considerably with the approval of several interferon (IFN)-free direct-acting antiviral agent (DAA) regimens (ledipasvir [LDV]/sofosbuvir [SOF], SOF, simeprevir [SMV], daclatasvir [DCV], ombitasvir [OBV]/paritaprevir [PTV]/ritonavir [r] + dasabuvir [DSV], elbasvir [ELB]/grazoprevir [GZV], and SOF/velpatasvir [VEL]).[9,10] However, the approved and recommended regimens are not equally potent across all HCV genotypes and subpopulations. Additional limitations of several current regimens include the requirement of ribavirin (RBV) for certain populations, significant drug to drug interactions, limited options for subjects with renal insufficiency, reduced efficacy in patients with baseline amino acid variants associated with reduced susceptibility to the

HCV nonstructural 5A (NS5A) inhibitors or NS3/NS4A protease inhibitors (PIs), and limited options for patients who have failed IFN-free treatment regimens.

AbbVie has developed two next generation DAAs for use in combination for the treatment of HCV infection. These next generation DAAs are glecaprevir (GLE, formerly known as ABT-493), an HCV NS3/4A PI and pibrentasvir (PIB, formerly known as ABT-530), an NS5A inhibitor. Co-formulated GLE/PIB is now an approved treatment for infection with all six major HCV genotypes in patients without cirrhosis and with compensated cirrhosis.[13,14] GLE and PIB each have potent in vitro antiviral activity against genotypes 1 through 6,[11] 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 100 mg/40 mg 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.[12]

GLE/PIB

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

The GLE/PIB registrational program included a broad subject population without cirrhosis or with compensated cirrhosis (defined by a Child Pugh A [CPA] score) 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 treatment-experienced (TE) subjects to any combination of pegylated IFN (pegIFN), RBV, SOF, NS5A inhibitors, or PIs were

allowed in the program. In addition, studies allowed subjects with human immunodeficiency virus (HIV) coinfection (Study M13-590), subjects with chronic kidney disease [CKD] Stages 4 and 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 take GLE 300 mg QD and PIB 120 mg QD without RBV. 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)

Table 1. Overview of Clinical Studies by Subject Population (Continued)

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

Overall Efficacy on the GLE/PIB Registrational Program and Among TN GT 1 - 6-Infected Subjects with Compensated Cirrhosis

In treatment-naïve (TN) or interferon, pegylated interferon, ribavirin, and/or sofosbuvir treatment experienced (TE-PRS) subjects, the pooled overall SVR_{12} rates with GLE/PIB were > 97% across GT1, 2, 4, 5 and 6 regardless of treatment experience, treatment duration, including any degree of renal impairment, presence of cirrhosis, or HIV-1 coinfection (Table 2).

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

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

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

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

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

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

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

The rate of non-virologic failures in the GLE/PIB registrational program was 1.2% (29/2369).

In the GLE/PIB registrational program, 117 treatment naïve subjects with compensated cirrhosis infected with GTs 1, 2, 4, 5, or 6 were treated with GLE/PIB for 12 weeks. Of those, 2 subjects did not achieve SVR_{12} (one discontinued treatment early and the other had missing SVR_{12} data). No virologic failure was observed. Therefore, the SVR_{12} rate in a Per-Protocol population (PP), defined as subjects who receive at least one dose of study drug, with the exception of subjects who experience breakthrough, or prematurely discontinue treatment prior to Week 8, or have no HCV RNA value in the SVR_{12} visit window or later) was 100%.

In the registrational program, the SVR_{12} rate (ITT) was 98.5% (64/65) in HCV GT3-infected, treatment-naïve subjects with compensated cirrhosis treated for 12 weeks. No virologic failure was observed. Therefore, the PP SVR_{12} rate in this population was 100%.

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 SVR_{12} rates for GT1-, 2-, 4-, 5-, or 6-infected subjects. Baseline polymorphisms in NS3

did not have an impact on SVR_{12} in GT3-infected subjects. Among baseline polymorphisms in NS5A in GT3-infected subjects, Y93H did not have an impact on SVR_{12} rates except in treatment-experienced non-cirrhotic subjects receiving 12 weeks of treatment. A30K in NS5A at baseline was associated with lower SVR_{12} rates among non-cirrhotic treatment-naïve subjects receiving 8 weeks of treatment and treatment-experienced subjects receiving 12 weeks of treatment, but had no impact on SVR_{12} rates in treatment-naïve non-cirrhotic subjects receiving 12 weeks of treatment. The SVR_{12} rates in subjects with A30K at baseline were 77.8% (14/18), 25.0% (1/4), and 92.9% (13/14) among treatment-naïve subjects receiving 8 weeks, treatment-experienced subjects receiving 12 weeks, and treatment-naïve subjects receiving 12 weeks of treatment, respectively. Given the A30K prevalence of 6.3% among GT3-infected subjects, the difference in SVR_{12} attributable to the impact of A30K between the 8 and 12 weeks treatment duration is < 1%. Among treatment-experienced non-cirrhotic or cirrhotic subjects receiving 16 weeks of treatment, the impact of A30K is unclear due to the low prevalence of the polymorphism in this arm of the study.

Integrated Safety Results

The clinical program enrolled a broad HCV population (n = 2,369), including subjects with and without cirrhosis, subjects with advanced renal disease, HIV coinfected subjects, and subjects who previously failed DAA-based regimens, including NS5A-experienced subjects.

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.

The adverse events occurring with a frequency ≥ 5.0% of subjects were headache, fatigue, nausea and diarrhea (Table 3). 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. Adverse events in subjects without cirrhosis (n = 1,977) were similar in type, frequency, and severity compared with subjects with cirrhosis (n = 288).

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

	Phase 2 and 3 Analysis Set[a] (N = 2,265) n (%)	
	All Adverse Events	DAA-Related Adverse Events[b]
Any AE	1,529 (67.5)	929 (41.0)
An AE Grade ≥ 3	65 (2.9)	4 (0.2)
Any SAE	48 (2.1)	1 (< 0.1)
Discontinuation of study drug due to any AE	8 (0.4)	3 (0.1)
All deaths[c]	6 (0.3)	0
Preferred Term[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.

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

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 ≥ 2 × ULN. None of these subjects prematurely discontinued study drug due to an ALT or bilirubin increase.
  - ALT abnormalities in 3 of these 4 subjects were not clinically significant
  - One subject experienced concurrent ALT > 3 × ULN (increased from nadir grade) and total bilirubin ≥ 2 × ULN in the context of multiple gallstones 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 (ADRs) occurring in ≥ 5% of subjects were headache, fatigue, nausea. ADRs 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.

Glecaprevir/Pibrentasvir (GLE/PIB) Viral Dynamic Modeling for Study M16-135

To determine the likelihood of success for Study M16-135, HCV modeling simulations were conducted using a viral dynamic model, including dynamics of hepatocytes, infected cells, wild type virus and mutants. In vitro efficacy and resistance data was incorporated. Viral load and SVR data from GLE/PIB Phase 2 and 3 studies in non-cirrhotic and cirrhotic subjects receiving 8 to 16 week treatment durations were included in the modeling. Additional internal and external efficacy data from treatments with different durations (4 to 24 weeks) were also taken into considerations in the modeling and simulations.

For this analysis, HCV virus in treatment-naïve GT 1, 2, 4, 5 or 6 cirrhotic subjects were assumed to have comparable responses to the GLE/PIB combination and non-virologic failures were not accounted in the simulations. The clinical trial simulation scenarios for an 8-week treatment duration in treatment-naïve subjects with compensated cirrhosis resulted in an SVR_{12} rate of approximately 98% in GT 1-, 2-, 4-, 5-, or 6-infected subjects and approximately 92% for GT3-infected subjects.

The objectives of this study are to evaluate the efficacy and safety of 8 weeks of GLE/PIB for the treatment of treatment-naïve subjects with chronic HCV GT 1 - 6 infection and compensated cirrhosis.

3.1 Differences Statement

The current Phase 3b Study M16-135 is the first study to evaluate the efficacy and safety of GLE/PIB in treatment-naïve adult subjects with chronic HCV GT 1 - 6 infection with compensated cirrhosis for 8 weeks. In the registrational program, treatment naïve subjects with compensated cirrhosis were treated with GLE/PIB for 12 weeks and the observed SVR_{12} rates were high across genotypes.

3.2 Benefits and Risks

This Phase 3b study is a single arm study in which eligible HCV GT 1 - 6 infected subjects with compensated cirrhosis will receive GLE/PIB for 8 weeks. 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, together with PK modeling based on the registrational data, suggest that the likelihood of demonstrating a high SVR_{12} rate with an 8 week regimen in subjects with HCV GT 1 - 6 infection with compensated cirrhosis is high.

As demonstrated in the registration studies, the benefits of treatment with GLE/PIB include: pangenotypic antiviral activity, higher genetic barrier to development of drug resistance across genotypes compared to first generation HCV protease and NS5A inhibitors, no need for RBV, 8 or 12 weeks of treatment, and the convenience of a once daily regimen. In a compensated cirrhotic population at risk for clinical events, a short duration DAA regimen with high SVR rates can be a favored option. The GLE/PIB regimen is potent; according to a Phase 2 and 3 analysis, SVR_{12} rates in treatment naïve cirrhotics treated for 12 weeks were 97.2% (69/71) for GT 1 and 100% (46/46) for GT 2, 4 – 6. Overall, the SVR_{12} rate was 98.3% (115/117) for GT 1, 2, 4, 5, or 6. The SVR_{12} rate in treatment naïve cirrhotics with GT3 infection treated for 12 weeks was 98.5% (64/65).

Risk of hepatic decompensation with jaundice, ascites, encephalopathy and/or variceal bleeding are possible, but are likely to occur as a result of the natural history of advanced liver disease rather than a DAA class effect. No safety signals with respect to hepatic decompensation were observed on the Phase 2 and 3 studies of GLE/PIB in the compensated cirrhotic population.

Based on safety data from the registrational and supportive clinical trials where over 2369 HCV-infected subjects were treated, the fixed-dose combination of GLE/PIB demonstrated a favorable safety profile. The most frequent GLE/PIB AEs include headache, fatigue, nausea and diarrhea these were mostly Grade 1 in severity. Serious

AEs and AEs leading to premature study drug discontinuation were rare. Adverse events that are known, and those that may potentially occur with GLE/PIB are described in the informed consent form for this study. In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures. Additional safety data for each DAA alone and the combination of GLE/PIB are detailed in Section 3.0 and in the Investigator's Brochure.[12]

No significant trends in liver chemistry abnormalities have been observed in Phase 2 and 3 studies, including patients with compensated cirrhosis.

The overall rates of virologic failure for the GLE/PIB regimen in Phase 2 and 3 studies were low. With the shortened duration of treatment in this study, higher rates of virologic failure may be observed. In patients who experience virologic failure, amino acid substitution(s) in NS3 and/or NS5A conferring resistance to GLE and/or PIB, respectively, may emerge. NS3 substitutions tend to revert back to wild type, while NS5A substitutions have been reported to persist for years. Retreatment of subjects who experience virologic failure with the GLE/PIB regimen for 8 weeks will be offered in the AbbVie Study M15-942.

An assessment of the post-treatment relapse rate occurring in this study in the non-GT3 and in the GT3 population will be performed on a periodic basis in order to minimize exposure to a potentially suboptimal duration (see Section 5.4.1.2).

Based on results of Phase 1 pharmacokinetic studies clinically significant DDI's with GLE/PIB have been identified. Monitoring of subjects, with dose adjustment of concomitant medications, as well as exclusion of subjects requiring the use of prohibited medications is expected to mitigate this risk. Hepatitis B virus reactivation has been reported as a pharmacological class risk for DAAs. This risk will be mitigated by proper screening and surveillance for HBV as described in the protocol.

Risks associated with GLE/PIB including the risks of toxicity, virologic failure, and development of resistant mutations substitutions (Section 5.6.4.3) appear to be limited and manageable based upon the available data.

Overall, given the potential for achieving SVR_{12} with 8 weeks of treatment in this population of HCV GT 1 - 6 infected subjects with compensated cirrhosis, the risk-benefit assessment is considered favorable.

4.0 Study Objective

4.1 Primary Objective

The primary objectives of this study are:

- To demonstrate the efficacy of the SVR_{12} rates of 8 weeks of treatment with glecaprevir/pibrentasvir compared to the historical SVR_{12} rates of 12 weeks of treatment with glecaprevir/pibrentasvir in treatment naïve adults with chronic HCV infection and compensated cirrhosis.
- To assess the safety of 8 weeks of treatment with glecaprevir/pibrentasvir in treatment naïve adults with chronic HCV infection and compensated cirrhosis.

4.2 Secondary Objectives

The secondary objectives are:

- To assess the percentage of subjects with on-treatment virologic failure (OTVF).
- To assess the percentage of subjects with post-treatment relapse.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of 8 weeks of GLE/PIB in HCV treatment-naïve adult subjects with chronic HCV GT 1 - 6

infection and compensated cirrhosis. The study will initially enroll subjects with HCV GT 1, 2, 4, 5 and 6 infection followed by subjects with HCV GT3 infection. Once enrollment of subjects with HCV GT3 infection begins, enrollment of subjects with HCV GT 1, 2, 4, 5 or 6 infection will be closed.

This study will consist of 3 periods as follows:

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 once daily (QD) for 8 weeks.

Scheduled visits for subjects in the Treatment Period consist of Day 1 and Weeks 1, 2, 4, and 8. Study procedures, including assessment of adverse events, vital signs, adherence, concomitant medications, HCV RNA, HCV resistance, pharmacokinetic assays, and clinical laboratory tests, will be conducted at each visit.

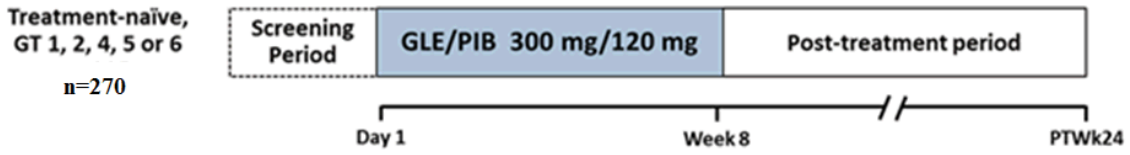
An assessment of the post-treatment relapse rate occurring in this study in the non-GT3 and in the GT3 population will be performed on a periodic basis in order to minimize exposure to a potentially suboptimal duration (see Section 5.4.1.2).

Post-Treatment Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 24 weeks to monitor safety, HCV RNA levels and to evaluate efficacy and the emergence and persistence of resistance associated substitutions.

During the Post-Treatment Period, all subjects will have visits at Weeks 4, 12, and 24 following completion of the Treatment Period. Study procedures to monitor safety, HCV RNA, and the emergence and persistence of resistant virus will be conducted during these visits.

A study schematic is shown in Figure 1.

Figure 1. Study Schematic



The study is designed to enroll approximately 330 subjects (approximately 270 with GT1, 2, 4, 5, or 6 infection and approximately 60 with GT3 infection) 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.

Analyses will occur after subjects have completed the Post-Treatment Week 12 Visit or prematurely discontinued from the study, starting with HCV GT1, 2, 4, 5, and 6-infected subjects.

5.1.1 Screening

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

- A quantifiable HBV DNA;
- A positive HIV test;
- An exclusionary HCV genotype(s);
- A positive serum pregnancy test (if female of childbearing potential);
- Development of decompensated liver disease during the screening period, as defined in the Exclusion Criteria.

Otherwise, subjects may be retested or rescreened only once without approval of the AbbVie Therapeutic Area Medical Director (TA MD), as follows.

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

Subjects who fail to enroll within the initial 42-day screening period, regardless of the reason for falling outside the 42-day screening window, may rescreen only once and must be rescreened for all laboratory and eligibility criteria (except for HBV, HIV, HCV genotype and subtype, and FibroScan/liver biopsy, which do not need to be retested), not just those that were exclusionary.

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

5.1.2 Treatment Period

After meeting the eligibility criteria, subjects will be enrolled via IRT. Subjects will be administered study drugs 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 5. Plasma samples for pharmacokinetic analysis and HCV RNA analysis will be collected as detailed in Section 5.3.1. 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 the study visits. Subjects who cannot complete their study visit per the visit schedule should ensure that they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

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

Subjects who prematurely discontinue from the Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined in Appendix C and as described in Section 5.4.1.

5.1.3 Post-Treatment Period

All subjects who received at least one dose of study drug, and either completed or prematurely discontinued treatment will be monitored in the Post-Treatment Period for 24 weeks following the last dose of study drug for safety, HCV RNA, and the emergence and persistence of HCV resistance-associated viral substitutions. The Post-Treatment Period will begin the day following the last dose of study drug. Study visits during the Post-Treatment period are detailed in Appendix D and Section 5.3.1.1.

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

5.2 Selection of Study Population

The study population consists of treatment-naïve male and female adults aged 18 years or older with chronic HCV GT 1 - 6 infection, with compensated cirrhosis. 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.
     - 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
   - Women 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 stopping study drug.
3. WOCBP must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.

   Women of non-childbearing potential (either postmenopausal or permanently surgically sterile (as defined in the Inclusion Criteria) are not required to do pregnancy testing.
4. Screening central laboratory result indicating HCV GT1 - 6-infection.
5. Subject has positive plasma HCV antibody and HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.

6. Subject must be HCV treatment-naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication).
7. Subject must be documented as cirrhotic, as specified in Section 5.3.1.1, with a Child-Pugh score of ≤ 6.
8. Subject must have absence of hepatocellular carcinoma (HCC) as indicated by a negative ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or a negative ultrasound at Screening. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.
9. Subject must voluntarily sign and date an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to the initiation of any Screening or study specific procedures.
10. Subject must be able to understand and adhere to the study visit schedule and all other protocol requirements.

Rationale for Inclusion Criteria

1, 4 – 8	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
9, 10	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

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

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. HCV genotype performed by the central laboratory during screening indicating co-infection with more than one HCV genotype.
3. 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).
4. Requirement for and inability to safely discontinue the medications or supplements listed in Table 4 at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of any study drug.
5. Clinically significant abnormalities or co-morbidities, or recent (within 1 year prior to study drug administration) alcohol or drug abuse that make the subject an unsuitable candidate for this study in the opinion of the investigator.
6. Any current or 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 empiric use of lactulose/rifaximin for neurologic indications. The use of beta blockers is not exclusionary.
7. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - Alanine aminotransferase (ALT) > 10 × ULN
   - Aspartate aminotransferase (AST) > 10 × ULN
   - Total Bililirubin > 3.0 mg/dL
   - Calculated creatinine clearance (CrCl, Cockcroft-Gault method) < 50 mL/min
   - Albumin < 2.8 mg/dL
   - Hemoglobin < 10 g/dL

- Platelets < 50,000 cells/mm^3

8. Receipt of any investigational or commercially available anti-HCV agents, including direct acting antivirals (e.g., interferon, ribavirin, sofosbuvir, telaprevir, boceprevir, simeprevir, paritaprevir, grazoprevir, voxilaprevir daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir, or dasabuvir).
9. History of severe, life-threatening or other significant sensitivity to any excipients of the study drug.
10. Subject who cannot participate in the study per local law.
11. 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.
12. History of suspected or confirmed hepatocellular carcinoma.

Rationale for Exclusion Criteria

1 – 4, 6 – 7, 9 – 12	In order to ensure safety of the subjects throughout the study
5, 8	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving from the time of signing the consent through the Treatment Period and 30 days after the last dose of study drugs, 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 Primary Therapeutic Area Medical Director (TA MD) should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior HCV Therapy

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

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.

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

5.2.3.3 Prohibited Therapy

Medications or supplements prohibited to be administered with GLE/PIB are listed in Table 4. For subjects in the study in countries where GLE/PIB has received marketing authorization, any medications in the local label that are contraindicated to be administered with GLE/PIB are also considered to be prohibited medications. Subjects must be able to safely discontinue any prohibited medications or supplements at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of GLE/PIB and not use these during the entire Treatment Period and for 14 days following discontinuation of

study drug. The Informed Consent Form must be signed and dated prior to discontinuing any prohibited medications or supplements.

Table 4. Prohibited Medications and Supplements

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

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drug. After signing the consent form, subjects receiving these statins should either (a) switch to pravastatin or rosuvastatin at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug or (b) may interrupt statin therapy throughout the treatment period beginning at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug and until 14 days after the last dose of study drug, based on investigator's judgment. If switching to or continuing pravastatin or rosuvastatin, it is recommended to either 1) reduce the pravastatin or rosuvastatin dose in accordance with the GLE/PIB approved local product label (if approved in the country); or 2) reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drug if GLE/PIB is not yet approved in the respective location.

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

5.2.4 Contraception Recommendations

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of each) OR a Women 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), initiated at least 1 month prior to Study Day 1.

- Bilateral tubal occlusion/ligation (if via hysteroscopy [i.e., Essure], provided that 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 from each subject at Screening Visit. The subject's medical history will be updated at the Study Day 1 Visit. This update 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. The subject will not wear shoes.

Vital Signs and Weight

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

12-Lead Electrocardiogram

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

The ECG will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign, and date all ECG tracings and will

provide his/her global interpretation as a written comment on the tracing using the following categories:

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

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

Clinical Laboratory Tests

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

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

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

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

Covance
8211 SciCor Drive
Indianapolis, IN 46214 USA (For sites in North America)

Covance
7 rue Moise-Marcinhes
1217 Geneva
Meyrin Switzerland
(For sites in Europe)

Covance (Asia) Pte Ltd
1 International Business Park
No. 01-01 The Synergy
Singapore 609917
(For sites in Asia Pacific)

Table 5. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Other Tests
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands, if detected Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable) Reticulocyte count Prothrombin Time/INR[a] Activated partial thromboplastin time (aPTT)	Blood Urea Nitrogen (BUN) Creatinine Creatinine clearance (Cockcroft-Gault calculation) eGFR (MDRD method) Total bilirubin[a,b] Direct and indirect bilirubin Alanine aminotransferase (ALT)[b] Aspartate aminotransferase (AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Cholesterol Total protein Glucose Triglycerides Albumin[a] Chloride Bicarbonate Magnesium Gamma-glutamyl transferase (GGT)[b]	Anti-HCV Ab[c] HIV Ab[c] Urine and Serum Human Chorionic Gonadotropin (hCG)[d] FSH (females only) HCV RNA Hepatitis B Panel (Anti-HBc Total, Anti-HBs and HBsAg)[e] Anti-HAV IgM[f] Anti_ HAV Total[f] Anti-HEV IgG[f] Anti-HEV IgM[f] HEV RNA[f] Anti-HBc IgM[f] HBV DNA[g] IL28B[h] HCV genotype and subtype[c] Pharmacogenetic sample (optional) Alpha2-macroglobulin[b] Haptoglobin[b] Apolipoprotein A1[b]
Urine Drug/Alcohol Screen[c]		
Opiates Barbiturates Amphetamines Cocaine Benzodiazepines Phencyclidine Propoxyphene Alcohol		

a. Also a component of Child-Pugh Assessment.

b. Also a component of FibroTest.

c. Performed only at Screening.

d. Required only for females of childbearing potential.

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

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

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

h. Performed only at Baseline.

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

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

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

Pregnancy Testing

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

Concomitant Medication Assessment

Please refer to Section 5.2.3.

Hepatitis B and C Virus and HIV Screen

HBsAg, anti-HBc and anti-HBs, anti-HCV Ab and anti-HIV Ab will be performed at Screening. The investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report these results per local regulations, if

necessary. The HIV results will not be reported by the central laboratory to the clinical database.

Urine Screens for Drugs of Abuse and Alcohol

Urine specimens will be tested at the Screening Visit for the presence of drugs of abuse and alcohol. The panel for drugs of abuse will minimally include the drugs listed in Table 5. The results of these tests will be available to the Investigator to help determine the suitability of the subject for participation in this study.

These analyses will be performed by the certified central laboratory chosen for the study.

Liver Diagnostic Testing

Subject must be documented as having cirrhosis at any time previous to or at Screening, by meeting one of the following criteria:

- Histologic diagnosis of cirrhosis on a liver biopsy e.g., a METAVIR, Batts Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of > 3 or Ishak fibrosis score of > 4; or
- A screening FibroTest score of ≥ 0.75 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) > 2;
    - Subjects with discordant FibroTest and APRI results (e.g., FibroTest ≥ 0.75, but APRI ≤ 2) must have a qualifying FibroScan® or liver biopsy
- FibroScan score ≥ 14.6 kPa.

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

FibroTest will also be conducted at Day 1 and PT Week 12 and 24 for all subjects.

Child-Pugh Score and Category

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

Table 6. Child-Pugh Classification of Severity of Cirrhosis

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

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

* None.
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 decompensation, as defined in the Exclusion Criteria, will be performed in all subjects at Study Day 1 prior to dosing, to confirm that the subject has not progressed to hepatic decompensation during Screening.

Hepatocellular Carcinoma Screening Liver Ultrasound

Hepatocellular carcinoma (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 all enrolled subjects. 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 will be required to perform a liver ultrasound to screen for HCC, unless the subject has a historical liver ultrasound (US), 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 visits specified in Appendix C and Appendix D. Subjects should be instructed to follow the instructions provided with each instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaires to them. Site personnel should encourage completion of each instrument at all specified visits and should ensure that a response is entered for all items.

Treatment Satisfaction Questionnaire – Medication (TSQM)

Subjects will complete the TSQM questionnaire at the designated study visits listed in Appendix C. The TSQM is a 14-item instrument and includes assessments of satisfaction with a medication's effectiveness (Effectiveness, three items), lack of

side effects (Side Effects; five items), convenience (three items) and the subject's global satisfaction (Global Satisfaction; three items).

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

Short Form 36 – Version 2 Health Survey

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

Fatigue Severity Scale (FSS)

The FSS measures the impact of fatigue over the past week on specific types of functioning (e.g., motivation, exercise, physical functioning, carrying out duties, interfering with work, family, or social life). The survey consists of 9 questions using a 7-point Likert scale. A total score is calculated as the average of the individual item responses. The scale's psychometric properties have been confirmed in chronic hepatitis C and other diseases. The FSS should require approximately 5 minutes to complete.

PRO instruments should be consistently presented prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels at each visit

where PROs are required throughout the study and in the following order: the TSQM (when applicable), the SF-36v2 and FSS. The Day 1 SF-36v2 and FSS questionnaires should be completed prior to drug administration on Day 1.

Enrollment and Assignment of Subject Numbers

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

Subject numbers will be unique 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 subject number throughout the study. Subject 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 Subtype

Plasma samples for HCV genotype and subtype determination will be collected at Screening. Genotype and subtype will be assessed using the Versant® HCV Genotype Inno LiPA Assay, Version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY) by the central laboratory. If the LiPA assay is unable to genotype a sample, its genotype and subtype will be determined by a Sanger sequencing assay of a region of the NS5B gene by the central laboratory.

HCV RNA Levels

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

HCV Resistance Testing Sample

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

Archive Serum and Plasma Samples

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

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

Study Drug Dosing Card

Subjects will be provided with self-administration instructions and study drug dosing cards to record the exact date, time (record to the nearest minute) and number of tablets of study drug administration (GLE/PIB) for the last 2 doses 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 the visits listed in Appendix C.
- The completed dosing card will be collected by the Investigator or designee on the day of the visit and be kept as a source record of dosage administration times documented in the eCRF.

5.3.1.2 Collection and Handling of Pharmacogenetic Exploratory Research Samples

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

IL28B Sample

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

Optional Samples for Pharmacogenetic Exploratory Research

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

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

5.3.1.3 Meals and Dietary Requirements

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

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

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

- At all Treatment-Period visits, except for Study Day 1: a single sample (3 mL) will be collected without regard to the time of dosing. The date and time of blood sample collection and the two previous doses of the study drug will be recorded to the nearest minute in the source documents. Additionally, the date and time of the two previous doses of the study drug will be recorded to the nearest minute on the eCRF.

5.3.2.2 Handling/Processing of Samples

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

5.3.2.3 Disposition of Samples

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

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

5.3.2.4 Measurement Methods

Plasma concentrations of GLE and PIB will be determined using a validated method by the Bioanalysis Department at AbbVie. Plasma concentrations of possible metabolites of any analytes listed above may also be determined using either validated or non-validated methods.

5.3.3 Efficacy Variables

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

5.3.3.1 Primary Variables

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

5.3.3.2 Secondary Variable

The secondary efficacy variables are:

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

5.3.3.3 HCV Resistance Variables

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

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the corresponding 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.

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

Plasma concentration of glecaprevir and pibrentasvir will be tabulated for each subject. Plasma concentrations of glecaprevir and pibrentasvir will be summarized based on last dosing time, sampling time and time since last dose. Summary statistics will be computed for glecaprevir and pibrentasvir plasma concentrations binned by time since last dose. Values for the pharmacokinetic parameters of GLE and PIB, including apparent oral clearance (CL/F) and apparent volume of distribution (V/F) will be estimated using population pharmacokinetic modeling procedures if population pharmacokinetic analysis is conducted. Additional parameters may be calculated if useful in the interpretation of the data.

5.3.6 Pharmacogenetic Exploratory Research Variables

IL28B status will be determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. These IL28B GT results may be analyzed as part of a multi-study assessment of IL28B and response to study drug or drugs of a similar class. The results may also be used for the development of diagnostic tests related to IL28B and study treatment, or drugs of a similar class. The results of additional pharmacogenetic IL28B analyses may not be reported with the clinical study report. Optional pharmacogenetic samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids, or metabolites. The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the study drug (or drugs of the same or similar class) or the development and progression of the subjects' disease or related conditions. The samples may also be used to develop new diagnostic tests, therapies, research methods, or technologies. The results from these analyses are exploratory in nature, may not be included with the study report, and may be performed by a non-GLP laboratory.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

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

If, during the course of study drug administration, the subject prematurely discontinues, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Appendix C and Appendix D. Ideally this should occur on the day of study drug discontinuation, but no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the

investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment. The last dose of any study drug and reason for discontinuation will be recorded in the EDC (electronic data capture) system. The subject should then begin the Post-Treatment Period where the subject will be monitored for 24 weeks for HCV RNA and the emergence and persistence of resistant viral substitutions.

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

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the Treatment Period, the administration of study drug may be continued at the Principal Investigator's discretion after discussion with the subject, if the benefit of continuing study drug is felt to outweigh the potential risk. Specific instructions regarding subject pregnancy can be found in Section 6.1.6. If a subject is discontinued, subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

5.4.1.1 HCV Virologic Failure Criteria

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

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurement of > 1 $\log_{10}$ IU/mL above nadir) at any time point during study drug treatment; or
- Confirmed HCV RNA ≥ 100 IU/mL (defined as 2 consecutive HCV RNA measurements ≥ 100 IU/mL) after HCV RNA < LLOQ during study drug treatment.

Confirmatory testing should be completed as soon as possible and the subject should remain on study drug treatment until the OTVF criterion has been confirmed. Subjects with confirmed OTVF will be discontinued from study drug and will continue to be followed in the Post-Treatment Period for the emergence and persistence of resistant viral substitutions until 24 weeks post-treatment.

Post-treatment relapse is defined as confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) between end of treatment and 12 weeks after the last dose of study drug (up to and including the SVR_{12} assessment time point), for a subject who completed treatment (defined as study drug duration ≥ 52 days for subjects assigned to 8 weeks of treatment) and had HCV RNA < LLOQ at final treatment visit, excluding cases of reinfection.

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

5.4.1.2 Treatment Extension Criteria

Because subjects with GT 1, 2, 4, 5 or 6 infection will be enrolled first, separate treatment extension criteria will apply to subjects with GT 1, 2, 4, 5 or 6 infection versus subjects with GT3 infection, as described below. However, if treatment is extended for all or a particular subgroup of subjects with GT 1, 2, 4, 5 or 6 infection, then enrollment of subjects with GT3 infection will be terminated and all GT3-infected subjects who are on treatment or have completed treatment within the previous 7 days will have their treatment extended to 12 weeks.

In subjects with GT 1, 2, 4, 5, or 6 infection, an efficacy assessment will evaluate the post-treatment relapse rate when the first 30 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to

12 weeks is needed for all GT 1, 2, 4, 5, and 6-infected subjects or for a particular subgroup of GT 1, 2, 4, 5, and 6-infected subjects who are on treatment or have completed treatment within the previous 7 days.

The enrollment of additional GT 1, 2, 4, 5, or 6-infected subjects in this study will be terminated if extension of treatment is needed for all GT 1, 2, 4, 5, or 6-infected subjects. If the extension is needed for a particular subgroup of GT 1, 2, 4, 5, or 6-infected subjects, then the enrollment will be terminated for this particular subgroup but other subgroups will continue to be allowed to enroll in the study with 8 weeks treatment duration.

In subjects with GT3 infection, an efficacy assessment will evaluate the post-treatment relapse rate after the first 20 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to 12 weeks is needed for all GT3-infected subjects or for a particular subgroup of GT3-infected subjects who are on treatment or have completed treatment within the previous 7 days.

The enrollment of additional GT3-infected subjects in this study will be terminated if extension of treatment is needed for all GT3-infected subjects. If the extension is needed for a particular subgroup of GT3-infected subjects, then the enrollment will be terminated for this particular subgroup but other subgroups will continue to be allowed to enroll in the study with 8 weeks treatment duration. Retreatment of subjects who experience virologic failure with the GLE/PIB regimen for 8 weeks will be offered retreatment in the AbbVie Study M15-942.

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

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

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

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

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

5.5.2 Identity of Investigational Products

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

Table 7. Identity of Investigational Products

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

5.5.2.1 Packaging and Labeling

All study drug will be supplied in bottles.

Each bottle will be labeled as required per country requirements.

The labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to subject.

5.5.2.2 Storage and Disposition of Study Drugs

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

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to AbbVie (or designee).

5.5.3 Method of Assigning Subjects to Treatment Groups

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

Subjects who are enrolled will retain their subject number, assigned at the Screening Visit, throughout the study. For enrollment of eligible subjects into the study, the site will utilize the IRT system in order to receive unique study drug kit numbers. 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.

5.5.4 Selection and Timing of Dose for Each Subject

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

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

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

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

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

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

5.5.7 Drug Accountability

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

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

Upon completion of or discontinuation from the Treatment Period, all original study drug bottles (containing unused study drug) will be returned to AbbVie (or designee) or destroyed on site. All destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of drug accountability procedures. The number of tablets of each type of study drug returned in each bottle will be noted in the IRT system or on a drug accountability log (if appropriate). Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The current study (Study M16-135) is a multicenter, single-arm, open-label, Phase 3b study evaluating the efficacy and safety of the co-formulated combination regimen of GLE 300 mg and PIB 120 mg QD administered for 8 weeks in treatment-naïve subjects with chronic HCV GT 1 - 6 infection and compensated cirrhosis.

The 12-week regimen of GLE/PIB was studied in adults with chronic HCV GT 1, 2, 4, 5, or 6 infection and compensated cirrhosis in Study M14-172 and studied in adults with chronic HCV GT3 infection and compensated cirrhosis in Study M14-868. Other Phase 3 studies also enrolled a few cirrhotic subjects. The integrated analysis of the registrational studies will serve as the historical control and reference point for the design of the current trial.

In the registrational program, 117 treatment naïve subjects with compensated cirrhosis infected with GTs 1, 2, 4, 5, or 6 were treated with GLE/PIB for a 12 weeks. Of those, 2 subjects did not achieve SVR_{12} (one discontinued treatment early and the other had missing SVR_{12} data). No virologic failure was observed. Hence, the historical SVR_{12} rate based on PP population is 100% for GT1, 2, 4, 5, and 6-infected subjects. Similarly, the historical SVR_{12} rate based on a PP population is 100% for GT1-6-infected subjects, as 65 treatment naïve subjects with compensated cirrhosis infected with GT3 were treated with GLE/PIB for 12 weeks. Of those, 1 subject did not achieve SVR_{12} due to missing SVR_{12} data. No virologic failure was observed.

The observed rate of non-virologic failure in the overall GLE/PIB registrational program was 1.2% (29/2369). For this reason, this study assumes that the historical SVR_{12} rate for the ITT population for GT1, 2, 4, 5, and 6-infected and for GT1-6-infected subjects will be 99% (assuming 1% of non-virologic failures). The observed SVR rates for the GLE/PIB 12 weeks duration in the Phase 2/3 development program is very high (> 97%) for the treatment naïve GT 1, 2, 3, 4, 5, or 6-infected cirrhotic subjects. Given such a high SVR rate, an active control arm does not provide value in establishing the efficacy of the

new regimen. That is, the efficacy of the new regimen can be established via an absolute criterion (comparison to a threshold) rather than a relative criterion (non-inferiority to an active control). Hence, the observed SVR rate from Phase 2/3 program will be used as historical control to provide a comparator for assessment of efficacy for the 8-week arm in this study for the treatment naïve cirrhotic patients.

A threshold for the primary and key secondary efficacy analyses of the 8 weeks GLE/PIB regimen to the historical control is determined by subtracting a margin of 6% from the historical SVR_{12} rate of 100% or 99% (for PP or ITT population, respectively) for GLE/PIB for 12 weeks.

A margin of 6% is selected to be used in this study to ensure a minimal loss of efficacy of the 8-week arm relative to the historical SVR_{12} rate for 12-week arm, and is in alignment with the GLE/PIB registrational program.

Thus, to establish efficacy of 8 weeks GLE/PIB to the 12 weeks GLE/PIB in treatment naïve cirrhotic subjects, the lower bound of the 95% CI for the SVR_{12} rate in the 8-week arm must exceed 94% or 93% for the PP and ITT populations, respectively.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical and laboratory procedures will be utilized in this study. HCV RNA assays are standard and validated.

5.6.3 Suitability of Subject Population

HCV GT3-infected patients are known to be a more difficult to treat population for DAA-based regimens. Therefore, subjects infected with HCV GT1, 2, 4, 5 and 6 were enrolled first in this trial, while subjects infected with HCV GT3 were initially excluded. The protocol was later amended to include GT3-infected subjects based on the following registrational clinical data:

- SVR_{12} rate (ITT) of 98.5% (64/65) in treatment-naïve GT3-infected subjects with compensated cirrhosis treated for 12 weeks of GLE/PIB, with no virologic failures observed; the PP SVR_{12} rate was 100% (64/64).
- SVR_{12} rate (ITT) of 95.2% (177/186) and 95.6% (258/270) in treatment-naïve GT3-infected subjects without cirrhosis treated for 8 and 12 weeks of GLE/PIB, respectively; PP SVR_{12} rates were 97.3% (177/182) and 98.9% (258/261) for 8 and 12 weeks of GLE/PIB, respectively.[15]
- GLE/PIB for 8 weeks in treatment-naïve GT3-infected subjects without cirrhosis was determined to be non-inferior to GLE/PIB for 12 weeks in Study M13-594 (ENDURANCE-3).[16]

This subject population will include treatment-naïve subjects only. While high SVR_{12} rates with 8 weeks of GLE/PIB are expected, the ultrashort nature of this study risks an increase of post-treatment relapse or EOT failure in treatment-experienced patients.

This study will exclude subjects with HIV/HCV coinfection, as this sub-population is currently being evaluated in Study M14-730 (EXPEDITION-2).[17]

Child Pugh B and C patients are also excluded from Study M16-135, since GLE/PIB has not been studied in this patient population.

The pharmacokinetics of GLE/PIB has been evaluated in subjects with hepatic impairment. In non-HCV infected subjects with mild hepatic impairment, exposures were higher for GLE (increase of 33%) compared to healthy subjects (Study M13-604). GLE exposures are higher (increase to ~2-fold) in HCV-infected subjects with compensated cirrhosis than in subjects without cirrhosis (R&D/16/0234). PIB exposures were comparable across populations. No GLE/PIB dose adjustment is recommended in patients with compensated cirrhosis (Module 2, Section 2.7.2.3.4.4).

HCV-infected subjects with chronic HCV infection have moderate stable elevations of AST and ALT levels and are considered representative of the population who will receive anti-HCV therapy. The age range selected for this study, 18 years of age or older, is also intended to be representative of the target population. Similarly, a substantial portion of

the HCV infected population has a relatively high BMI, and given the acceptable safety and pharmacokinetic profiles of GLE and PIB in previous studies, this protocol will enroll subjects without a BMI restriction.

5.6.4 Selection of Doses in the Study

5.6.4.1 Rationale for Dose Selections

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

5.6.4.2 GLE and PIB Dose and Treatment Duration

GLE/PIB 300 mg/120 mg QD regimens with 8-week and 12-week durations were evaluated in non-cirrhotic subjects in registrational trials. Efficacy of 8-week treatment duration is established for GT1-, GT2- and GT3- infected non-cirrhotic subjects [R&D/16/0144, R&D/15/1230]. Fifty-two non-cirrhotic GTs 4, 5, or 6-infected subjects received 8-weeks of GLE/PIB and no virologic failure was observed. Overall, these results conclude that 8-weeks of GLE/PIB 300 mg/120 mg dose is efficacious for non-cirrhotic GT 1 - 6-infected subjects.

Based on modeling and simulations, assuming no subjects experience non-virologic failures, following 8 weeks of GLE/PIB in treatment-naïve HCV-infected subjects with compensated cirrhosis, the predicted SVR_{12} rate is approximately 98% for GT1, 2, 4, 5, and 6-infected subjects, and approximately 92% for GT3-infected subjects.

5.6.4.3 Risk of Development of Resistance Mutations During Combination DAA Trials

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 resistant 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 subjects with HCV GT1 – 6 infection in 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.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

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

6.1 Medical Complaints

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

investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (see Section 6.1.7 regarding toxicity management) and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during 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 4.03" is available from the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf and is to be used in the grading of adverse events. Below are the general grading categories. However, the investigator should always search NCI CTC AE for a given diagnostic/symptomatic AE term to identify and apply specific grading details for that AE entity.

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

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

ADL = Activities of Daily Living

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

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

6.1.3 Relationship to Study Drug

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

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

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

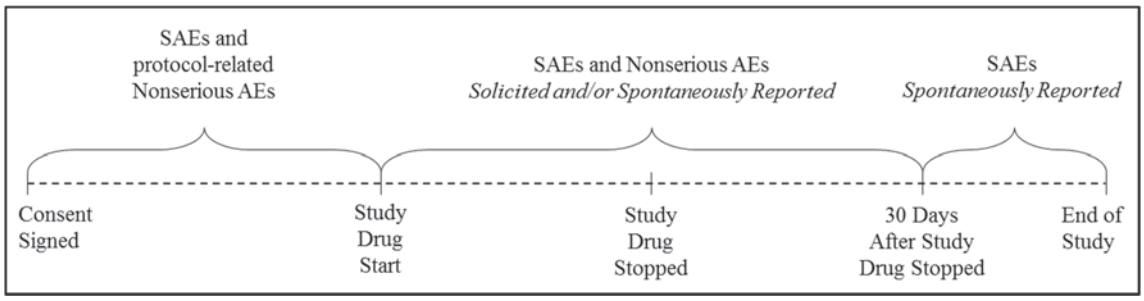
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

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

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

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site

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

Email:	[redacted]
FAX to	

For safety concerns, con Antiviral Safety Team at:

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

Office:
Email: [redacted]

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

Primary Therapeutic Area Medical Director:

[redacted] MD
Medical Director
1500 Seaport Blvd.
Redwood City, CA 94063

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

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

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

Phone: [redacted]

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

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Administration of study drug may be continued at the investigator's discretion after discussion with the subject, if the benefit of continuing therapy is felt to outweigh the risk (Section 5.4.1). If a subject is discontinued, the subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

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

Pregnancy in a study subject is not considered an adverse event. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, 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 4.03" 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 Elevations

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

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

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

Alternate management of ALT increases is permitted with approval of the AbbVie Therapeutic Area Medical Director (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 Clinical Monitors:

Primary Contact:

[redacted]
1 North Waukegan Rd.
North Chicago, IL 60064

Office: [redacted]
Fax:

Alternate Contact:

[redacted]
41-45 Marinou Antypa Street
14121 N. Irakleio
Athens, Greece

Office: [redacted]
Fax:

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

Analyses will occur after subjects have completed the PT Week 12 Visit or prematurely discontinued study. The first analysis will occur after all HCV GT1, 2, 4, 5, and 6-infected subjects have completed the PT Week 12 Visit or prematurely discontinued study; the second analysis will occur after all HCV GT3-infected subjects have completed the PT Week 12 Visit or prematurely discontinued study; the third and final analysis will occur after all subjects have completed or prematurely discontinued from 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 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. The Per-Protocol (PP) population includes all enrolled subjects who receive at least one dose of study drug, with the exception of subjects who experience breakthrough, or prematurely discontinue treatment prior to Week 8, or have no HCV RNA value in the SVR_{12} visit window or later.

The primary and key secondary efficacy analyses will be performed on the PP and ITT populations, as specified. The other secondary efficacy analyses will be performed on the ITT population, unless otherwise specified.

Sensitivity analyses of SVR_{12}, when applicable, will be performed on the intention-to-treat population modified to exclude subjects who were enrolled with ineligible genotypes (e.g., GT3 according to phylogenetic analyses for the group of non-GT3-infected subjects) (mITT-GT), and on the mITT-GT population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-GT-VF).

No data will be imputed for any efficacy or safety analysis except for analyses of SVR endpoints (HCV RNA data) and PRO questionnaires. HCV RNA values will be selected for the analyses of all SVR endpoints (e.g., SVR_4, SVR_{12}, and SVR_{24}) based on defined visit windows. A backward imputation method will be used to impute missing responses for SVR analyses. Imputation of missing responses on PRO questionnaires is described in Section 8.1.3.

8.1.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all subjects in the ITT population across genotypes. Demographics include age, weight, height, BMI, sex, race, geographic region, 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, in addition to HCV genotype and subtype, baseline Child-Pugh score, tobacco and alcohol use status.

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

The primary and key secondary efficacy analyses will be performed on both the PP and ITT populations, as specified. The other secondary efficacy analyses will be analyzed based on ITT population, unless otherwise specified.

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

IL28B rs12979860 will be resulted as C/C, C/T, or T/T by the central laboratory.

8.1.2.1 Primary Efficacy Endpoints

The two primary efficacy analyses are:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 94% in the PP population.
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 93% in the ITT population.

The two primary and two key secondary (defined in Section 8.1.2.2.1) efficacy analyses will be performed following a fixed-sequence testing procedure which is described in Section 8.1.2.6.

Only if success has been demonstrated for the first primary efficacy analysis of SVR_{12} based on the PP population in HCV GT1, 2, 4, 5, and 6-infected subjects will the testing proceed to the second primary efficacy analysis of SVR_{12} based on the ITT population in HCV GT1, 2, 4, 5, and 6-infected subjects. And only if success has been demonstrated for the second primary efficacy analysis will the testing proceed to the key secondary efficacy analyses described in Section 8.1.2.2.1.

For the first primary efficacy analysis, the PP population will be used. The PP analysis is used to reduce the risk of bias toward no treatment difference that can occur due to dropouts or other measurement problems, since the subjects excluded in the PP population experience SVR failure for reasons that do not help in discriminating between treatment durations.

For both primary efficacy analyses, the percentage of subjects achieving SVR_{12} and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial distribution, unless the number of subjects who failed to achieve SVR_{12} is less than 5, then the Wilson's score method will be used for the confidence interval instead.

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

8.1.2.2 Secondary Efficacy Endpoints

8.1.2.2.1 Key Secondary Efficacy Endpoints

The two key secondary efficacy analyses included in the fixed-sequence are listed below:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 3, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 94% in the PP population;

2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 3, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 93% in the ITT population.

Only if success was demonstrated for both primary efficacy analyses will testing proceed to the two key secondary efficacy analyses in the order listed above. If success has been demonstrated for the first key secondary efficacy analysis of SVR_{12} based on the PP population in HCV GT1-6-infected subjects, then testing will proceed to the second key secondary efficacy analysis of SVR_{12} based on the ITT population in HCV GT1-6-infected subjects.

8.1.2.2.2 Other Secondary Efficacy Endpoints

The other secondary efficacy analyses, which are not included in the fixed sequence, are listed below:

- The percentage of HCV GT3-infected subjects in the PP population who achieve SVR_{12};
- The percentage of HCV GT3-infected subjects in the ITT population who achieve SVR_{12};
- The percentage of subjects with OTVF (defined as confirmed increase of > 1 log10 IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and
- The percentage of subjects with post-treatment relapse ($Relapse_{12}$: defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug [up to and including the SVR_{12} assessment time point] among subjects who completed treatment as planned [defined as study drug duration ≥ 52 days for subjects assigned to 8 weeks of treatment] with HCV RNA < LLOQ at the end of treatment; excluding subjects who have been shown to be reinfected).

For the analyses of SVR_{12} among HCV GT3-infected subjects, the number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using Wilson's score method.

For the analysis of OTVF and post-treatment relapse, the number and percentage of subjects in the ITT population will be summarized along with a two-sided 95% confidence interval using Wilson's score method. Separate summaries will be provided for all subjects across genotypes, within HCV GT1, 2, 4, 5, and 6-infected subjects combined, and within HCV GT3-infected subjects.

8.1.2.3 Sensitivity Analysis

As a sensitivity analysis, the percentage of subjects in the mITT-GT and mITT-GT-VF populations achieving SVR_{12}, as applicable, will be summarized.

The two-sided 95% confidence interval using Wilson's score method will also be calculated if applicable, as a sensitivity analysis for the primary and key secondary efficacy analyses of SVR_{12} based on the PP and ITT populations.

8.1.2.4 Subgroup Analysis

The subgroup analyses will be performed across genotypes based on ITT population. The summary statistics of subjects with SVR_{12} will be provided for the following subgroups:

- HCV genotype and subtype;
- Sex;
- Age;
- Race;
- BMI;
- Baseline HCV RNA level;
- Baseline platelet count;
- Baseline albumin;

- Baseline APRI;
- Baseline FibroTest;
- Baseline FIB-4;
- Baseline AST/ALT ratio;
- Geographic region;
- Baseline creatinine clearance;
- Baseline eGFR;
- History of diabetes;
- Subject on stable opiate substitution.

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

8.1.2.5 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized across genotypes in the ITT 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 SVR_4 (HCV RNA < LLOQ 4 weeks after the last actual dose of study drug);
- The percentage of subjects who achieve SVR_{24} (HCV RNA < LLOQ 24 weeks after the last actual dose of study drug);
- The percentage of subjects who experience post-treatment relapse after achieving SVR_{12}.

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

8.1.2.6 Multiplicity

In order to control family-wise Type I error rate, a fixed-sequence testing procedure will be used for the two primary and two key secondary efficacy analyses of SVR_{12} as listed below. The fixed-sequence testing procedure will utilize the endpoint sequence of the first primary analysis followed by the second primary analysis, then the first key secondary analysis, and lastly the second key secondary analysis. For example, only if success has been demonstrated for the first primary efficacy analysis of SVR_{12} based on the PP population, will the testing proceed to the second primary efficacy analysis of SVR_{12} based on the ITT population, and so on.

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

1. Primary 1: Efficacy of the SVR_{12} rate of 8-week treatment duration compared to the historical 12 week treatment duration based on the PP population in HCV GT1, 2, 4, 5, and 6-infected subjects: If this endpoint is statistically significant, then proceed to the following efficacy endpoint. If this endpoint is not statistically significant, then stop the testing procedure and declare that no endpoints in the study met statistical significance.
3. Primary 2: Efficacy of the SVR_{12} rate of 8-week treatment duration compared to the historical 12 week treatment duration based on the ITT population in HCV GT1, 2, 4, 5, and 6-infected subjects: If this endpoint is statistically significant, then declare the SVR_{12} endpoint is statistically significant on both the PP and ITT populations in HCV GT1, 2, 4, 5, and 6-infected subjects. If not, then announce that SVR_{12} endpoint is statistically significant based on only the PP population in HCV GT1, 2, 4, 5, and 6-infected subjects and stop testing.
4. Key Secondary 1: Efficacy of the SVR_{12} rate of 8-week treatment duration compared to the historical 12 week treatment duration based on the PP population in HCV GT1, 2, 3, 4, 5, and 6-infected subjects: If this endpoint is statistically significant, then declare the SVR_{12} endpoint is statistically significant on both the

PP and ITT populations in HCV GT1, 2, 4, 5, and 6-infected subjects and on the PP population in HCV GT1-6-infected subjects. If not, then announce that SVR_{12} endpoint is statistically significant based on only the preceding populations and stop testing.

5. Key Secondary 2: Efficacy of the SVR_{12} rate of 8-week treatment duration compared to the historical 12 week treatment duration based on the ITT population in HCV GT1, 2, 3, 4, 5, and 6-infected subjects: If this endpoint is statistically significant, then declare the SVR_{12} endpoint is statistically significant on both the PP and ITT populations in HCV GT1, 2, 4, 5, and 6-infected subjects and on both the PP and ITT populations in HCV GT1-6-infected subjects. If not, then announce that SVR_{12} endpoint is statistically significant based on only the preceding populations and stop testing.

8.1.3 Patient Reported Outcomes

The handling of missing data for patient reported outcomes (PROs) will be as follows. If a respondent answers at least 50% of the items in a multi-item scale of the SF-36v2, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing. The missing item of the FSS questionnaire will be imputed with the average score of the answered items as long as more than 50% of the items on the FSS are answered.

The mean change from baseline to each applicable post-baseline timepoint in the FSS total score and the SF-36v2 Mental Component Summary (SF-36-MCS) and Physical Component Summary SF-36-PCS scores will be summarized descriptively at each visit. The TSQM subscales (global satisfaction, convenience, effectiveness, side effects) will be summarized descriptively at Weeks 2, 4, and 8.

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

- Number and percentage of subjects who have experienced an increase from baseline at each applicable timepoint of greater than or equal to 3 points in the SF-36-MCS and SF-36-PCS;
- Number and percentage of subjects who have experienced an increase from baseline at each applicable timepoint of greater than or equal to 5 points in the SF-36-MCS and SF-36-PCS;
- Number and percentage of subjects who have experienced an increase from baseline at each applicable timepoint of greater than or equal to 5 points in the SF-36 domain scores;
- Number and percentage of subjects who have experienced an increase from baseline at each applicable timepoint of greater than or equal to 0.7 in the FSS total score;
- Number and percentage of subjects who have experienced an increase from baseline at each applicable timepoint of greater than or equal to 1 in the FSS total score.

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

8.1.4 Resistance Analyses

For all subjects, full length NS3/4A or NS5A from baseline samples will be sequenced by NGS. For subjects who experience virologic failure (OTVF or post-treatment relapse), full length NS3/4A and NS5A genes from the first sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS. An appropriate subtype specific prototypic reference sequence will be used for comparison with sequences from samples. Subjects treated with study drug who do not achieve SVR_{12} due to reasons other than virologic failure but have a time point with HCV RNA ≥ 1000 IU/mL after treatment discontinuation will have the sample at that time point sequenced.

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 SVR_{12} 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 8. Appropriate subtype specific prototypic reference sequence will be used for comparison with sequences from samples.

Table 8. 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, 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, and 93	

The following definitions will be used in the resistance analyses:

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

- Post-baseline substitution: an amino acid substitution in a post-baseline time point sample that was not detected at baseline (< 2%) in the subject and is detectable in ≥ 2% of the sequences from the post-baseline sample.
- Enriched polymorphism: polymorphism present in both the baseline and a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post-baseline % – baseline %) ≥ 20].
- Treatment-emergent substitution by NGS: A post-baseline substitution or an enriched polymorphism.

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 SVR_{12} rate will be calculated for subjects with and without the polymorphism and the 2 rates will be compared. Analysis will be grouped by HCV subtype and DAA target (NS3/4A or NS5A).

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

- For each signature amino acid position, presence of any polymorphism at that position (vs no polymorphism at that position), using detection thresholds of both 2% and 15%.
- Each individual polymorphism at each signature amino acid position (vs not that polymorphism) using detection thresholds of 2% and 15%.
- Polymorphism 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 SVR_{12} rate will be calculated, and the rates with or without polymorphisms will be compared using Fisher's exact test. Analysis will be separated by HCV subtype. The following tables will be provided:

- Comparison of SVR_{12} rates by subtype, and total (include all subtypes)
- Comparison of SVR_{12} rates by genotype, and total (include all subtypes)

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

- Listings by subject of all treatment-emergent substitutions relative to the baseline amino acid 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).

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 and resistance analyses.

8.1.5 Safety

Safety summaries will be provided across genotypes. All subjects who receive at least one dose of study drug will be included in the safety analyses.

8.1.5.1 Adverse Events

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

Additional analyses will be described in the statistical analysis plan.

8.1.5.2 Clinical Laboratory Data

Clinical laboratory tests will be summarized at each visit. The baseline value will be the last non-missing measurement prior to the initial dose of study drug. Mean changes from baseline to each post-baseline visit, including Final Treatment Visit, will be summarized descriptively. Summary of Child-Pugh score from baseline to each post-baseline visit, including applicable post treatment visits, will be provided.

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

The number and percentage of subjects with post-baseline values meeting pre-specified criteria for toxicity grades and meeting pre-defined criteria for laboratory parameters of interest during treatment will be summarized.

8.1.5.3 Vital Signs Data

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each post-baseline visit, including Final Treatment Visit, will be summarized descriptively. The number and percentage of subjects with post-baseline values meeting pre-defined criteria for Potentially Clinically Significant (PCS) vital signs values during treatment will be summarized.

8.1.6 Pharmacokinetic and Exposure-Response Analyses

Plasma concentration of GLE and PIB will be tabulated for each subject. Plasma concentrations of GLE and PIB will be summarized based on last dosing time, sampling time and time since last dose. Summary statistics will be computed for GLE and PIB plasma concentrations binned by time since last dose.

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

Population pharmacokinetic analysis will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (version VII, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. Apparent oral clearance (CL/F) and apparent volume of distribution (V/F) of the analytes will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis. The evaluation criteria described below will be used to examine the performance of different models.

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

Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM. The relationship between these conditional estimates CL/F and V/F values with only potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic or renal function, etc.) will be explored using either stepwise forward selection method, or generalized additive method (GAM) or another suitable regression/smoothing method at a significance level of 0.05. After identification of all relevant covariates, a stepwise

backward elimination of covariates from the full model will be employed to evaluate the significance (at $P < 0.005$, corresponding to an increase in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

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

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

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

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

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

Additionally, relationship between exposure and safety endpoints of interest may also be explored. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

It is planned to enroll approximately 330 adult subjects with chronic HCV GT 1 - 6 infection with compensated cirrhosis who are HCV treatment-naïve in the study.

The study was initially designed to enroll about 270 non-GT3-infected subjects and amended to include GT3-infected subjects for a total of 330 GT1 - 6-infected (270 non-GT3 and 60 GT3) subjects.

With approximately 270 subjects with HCV GT1, 2, 4, 5, or 6 infection, this study has approximately 91% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 94%) based on Per-Protocol (PP) population, assuming that 98% of the GT1, 2, 4, 5, and 6-infected subjects receiving 8 weeks of treatment in PP population achieve SVR_{12}.

With approximately 270 subjects with HCV GT1, 2, 4, 5, or 6 infection, this study has approximately 82% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 93%) based on Intention-to-Treat (ITT) population, assuming that 97% of the GT1, 2, 4, 5, and 6-infected subjects receiving 8 weeks of treatment in ITT population achieve SVR_{12}.

With approximately 330 subjects with HCV GT1 - 6 infection, this study has approximately 90% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 94%) based on the PP population, assuming that 98% of the GT1 - 6-infected subjects receiving 8 weeks of treatment in the PP population achieve SVR_{12}.

With approximately 330 subjects with HCV GT1-6 infection, this study has approximately 81% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 93%) based on the ITT population, assuming that 97% of the GT1 - 6-infected subjects receiving 8 weeks of treatment in the ITT population achieve SVR_{12}.

8.2.1 Justification of Success Criteria for SVR_{12}

Efficacy for the 8-week regimen in this study is established by comparing the SVR_{12} rate from this study to the historical control regimen of GLE/PIB administered for 12 weeks.

The SVR_{12} rate of the historical control regimen is calculated, and a threshold is determined by subtracting a margin of 6% from the historical SVR_{12} rate. Efficacy is established if the lower 95% confidence bound of the SVR_{12} rate in the 8-week regimen is greater than the threshold.

In the registrational program, 117 treatment naïve, compensated cirrhotic subjects, GT 1, 2, 4, 5, or 6 subjects and 65 treatment naïve, GT3-infected subjects with compensated cirrhosis were treated with GLE/PIB for 12 weeks duration. Three subjects did not achieve SVR_{12}, one discontinued treatment early and two had missing SVR_{12} data. No virologic failure was observed among these subjects which means SVR_{12} rate based on PP population is 100%. Hence, for this study it assumed that the historical SVR_{12} rate for GT1 - 6-infected cirrhotic patients is 100%. To establish efficacy to the historical control, a margin of 6% is applied to the historical control rate of 100%, resulting in a threshold of 94%.

Historical SVR rate based on ITT population depends on the non-virologic failure in a study. Study-to-study variability has been observed in non-virologic failure rates, and is typically around 1%. The observed rate of non-virologic failure in the registrational program is 1.2% (29/2369). For this reason, this study assumes that the historical SVR_{12} rate based on ITT population for cirrhotic patients is 99% (with 1% non virologic failure). To establish efficacy to the historical control, a margin of 6% is applied to the historical control rate of 99%, resulting in a threshold of 93%.

A margin of 6% is selected to be used in this study to ensure a minimal loss of efficacy of the 8-week arm relative to the historical SVR_{12} rate for 12-week arm.

8.3 Randomization Methods

This study is not randomized. Eligible subjects will be enrolled into a single arm.

9.0 Ethics

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

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

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

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

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

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

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

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

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded 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

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

12.0 Use of Information

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

medical conventions. Optional exploratory research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

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

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

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

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

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for Glecaprevir (GLE)/Pibrentasvir (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 Single Arm, Open-label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 - 6 Infection and Compensated Cirrhosis

Protocol Date: 11 June 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:

6. 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.
7. Personally conducting or supervising the described investigation(s).
8. 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.
9. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
10. 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).
11. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
12. 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.
13. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

14. 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.

15. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

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

Appendix C. Study Activities – Treatment Period

Activity	Screening	Day 1[a]	Wk 1	Wk 2	Wk 4	EOT* or Premature D/C from Treatment[b,c]
Informed Consent[d]	X					
Medical History[e]	X	X				
Concomitant Medication Assessment	X	X	X	X	X	X
Adverse Event Assessment[f]	X	X	X	X	X	X
12 Lead ECG	X	X				X
Physical Exam	X	X				X
Vital Signs, Weight, Height[g]	X	X	X	X	X	X
Hematology/Chemistry/Coagulation Panel	X	X	X	X	X	X
Pregnancy Test (serum [s] urine [u])[h]	X (s)	X (u, s)			X (u)	X (u)
Anti-HCV Ab, Anti-HIV Ab	X					
Hepatitis B Panel	X					
Drug/Alcohol Screen	X					
FSH (all females)	X					
HCV Genotype and Subgenotype	X					
Pharmacogenetic DNA and RNA Sample (optional)[i]		X				X
IL28B Sample[i]		X				
FibroTest and APRI, FibroScan® or Liver Biopsy[j]	X	X[k]				
HCV RNA Samples	X	X	X	X	X	X
HCV Resistance Sample		X	X	X	X	X

Activity	Screening	Day 1[a]	Wk 1	Wk 2	Wk 4	EOT* or Premature D/C from Treatment[b,c]
Archive Plasma and Serum Sample	X	X	X	X	X	X
Pharmacokinetic Samples[l]			X	X	X	X
Child-Pugh Score	X					X
HCC Screening Liver Ultrasound[m]	X					
Clinical Assessment of Hepatic Decompensation		X				
Patient Reported Outcomes Instruments (PROs)[n]		X		X[o]	X	X
Study Drugs Dispensed		X			X	
Dispense/Review Study Drug Dosing Card		X (Dispense only)	X	X	X	X (Review only)
Perform Study Drug Accountability and Review of Study Drug Adherence[p]					X	X

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

* The EOT visit will be at either Week 8 or Week 12 depending on if Treatment Extension Criteria has been met.

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

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

c. If Treatment Extension Criteria has been met, subjects will receive treatment for 12 weeks and will have an additional visit at Week 8 which will include all procedures performed at Week 4.

d. Subjects need to sign an IRB/IEC approved informed consent for the study (prior to performing any screening or study-specific procedures) and the optional pharmacogenetic sample(s), if applicable.

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

f. See specific information regarding adverse event collection in Section 6.1.1.

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

h. Pregnancy testing is not required for females of non-childbearing potential as defined in the inclusion criteria.

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

j. For subjects who have not had a historical qualifying liver biopsy or a historical qualifying FibroScan®.

k. On Day 1, only FibroTest will be conducted for all subjects. Biopsy and FibroScan will not be conducted on Day 1.

l. Detail regarding timing of samples is provided in Section 5.3.2.1.

m. An HCC Screening assessment is required per protocol in the Screening Study Visit and at the PT Wk 24 or PT D/C Visit. 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.

n. PROs should be administered before any study procedures in the order listed in Section 5.3.1.1. TSQM is not administered at Day 1, only the FSS and SF-36 are collected at Day 1.

o. TSQM is the only PRO that should be administered at Week 2.

p. Subjects should bring all study drug to every visit for the site to review adherence. However, the site will record the number of tablets returned only at the Study Drug Accountability Visits at Weeks 4, 8, (Week 12 due to Treatment Extension Criteria) or Premature D/C.

Appendix D. Study Activities – Post-Treatment 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	X	X[b]	X[b]
Pregnancy Test (urine [u])[c]	X (u)		X (u)[a]
Concomitant Medication Assessment[d]	X	X[d]	X[d]
Adverse Event Assessment[e]	X	X[e]	X[e]
HCV RNA Samples	X	X	X
HCV Resistance Sample	X	X	X
Pharmacogenetic DNA and RNA Sample (optional)		X	
Archive Plasma and Serum Sample	X	X	X
FibroTest and APRI		X	X
Child-Pugh Score		X	X
Physical Exam[h]		X	X
HCC Screening Liver Ultrasound			X[i]
Patient Reported Outcomes Instruments (PROs)[f,g]		X	X

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

a. Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C Visit procedures. Hematology/Chemistry/Coagulation Panel and Pregnancy Test are not required at PT Wk 24 but at PT D/C only if subject discontinues prior to PT Wk 4.

b. Hematology/Chemistry/Coagulation Panel drawn at PT Wk 12 and PT Wk 24 are only conducted to support Child-Pugh assessment and/or FibroTest and APRI determination. No other analytes will be resulted as part of the labs drawn at these timepoints.

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

d. Only medications taken for SAEs and for 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; nonserious AEs will not be collected (see Section 6.1.4).

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

g. TSQM should not be collected in the post-treatment period.

h. An abbreviated Physical Exam should be conducted to assess Ascites, and potential hepatic encephalopathy required for the Child Pugh assessment score.

i. Please refer to Section 5.3.1.1 item "Hepatocellular Carcinoma Screening Liver Ultrasound" for details on this study procedure.

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

Appendix E. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.0 Title Page
Protocol title previously read:

A Single Arm, Open-label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis

Has been changed to read:

A Single Arm, Open-label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 - 6 Infection and Compensated Cirrhosis

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

Sponsor/Emergency Contact:	[redacted] MD Associate Medical Director Antiviral Clinical Project Team 1 North Waukegan Road North Chicago, IL 60064	Phone: Fax: [redacted]

Has been changed to read:

Sponsor/Emergency Contact:	[redacted] MD Medical Director Antiviral Clinical Project Team 1500 Seaport Blvd. Redwood City, CA 94063	Phone: Fax: [redacted]

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M16-135
Name of Study Drug: Glecaprevir, Pibrentasvir	**Phase of Development:** 3b
Name of Active Ingredient: Glecaprevir, Pibrentasvir	**Date of Protocol Synopsis:** 06 September 2017
Protocol Title: A Single Arm, Open-label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis	
Objectives: • To demonstrate the efficacy of the SVR_{12} rate of 8 weeks of treatment with glecaprevir/pibrentasvir compared to the historical SVR_{12} rate of 12 weeks of treatment with glecaprevir/pibrentasvir in treatment naïve adults with chronic HCV GT 1, 2, 4, 5 or 6 infection and compensated cirrhosis. • To assess the safety of 8 weeks of treatment with glecaprevir/pibrentasvir in treatment naïve adults with chronic HCV GT 1, 2, 4, 5 or 6 infection and compensated cirrhosis.	
Investigators: Multicenter	
Study Sites: Approximately 135 globally	
Study Population: Adults with chronic HCV genotype (GT) 1, 2, 4, 5 or 6 infection, aged 18 years or older, with compensated cirrhosis, who are HCV treatment-naïve.	
Number of Subjects to be Enrolled: Approximately 270 subjects	
Methodology: This is a Phase 3b, single arm, open-label, multicenter study to evaluate the efficacy and safety of 8 weeks of glecaprevir/pibrentasvir in treatment-naïve subjects with chronic HCV GT 1, 2, 4, 5 or 6 infection and compensated cirrhosis. The study will consist of 3 periods: <u>Screening Period:</u> Subjects have up to 42 days following the Screening Visit to confirm eligibility and enroll into the study. <u>Treatment Period:</u> Eligible subjects will be enrolled to receive glecaprevir/pibrentasvir 300 mg/120 mg once daily (QD) for 8 weeks. Scheduled visits for subjects in the Treatment Period consist of Day 1 and Weeks 1, 2, 4, and 8. Study procedures, including assessment of adverse events, vital signs, adherence, concomitant medications, HCV RNA, HCV resistance, pharmacokinetic assays, and clinical laboratory tests, will be conducted at each visit.	

Methodology (Continued):

An efficacy assessment will evaluate the post-treatment relapse rate after the first 30 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to 12 weeks is needed for all subjects or for a particular subgroup of subjects who are on treatment or have completed treatment within the previous 7 days.

Post-Treatment Period:

Subjects who complete or prematurely discontinue the Treatment Period will be followed for 24 weeks to monitor safety, HCV RNA levels and to evaluate efficacy and the emergence and persistence of resistance associated substitutions.

During the Post-Treatment Period, all subjects will have visits at Weeks 4, 12, and 24 following completion of the Treatment Period. Study procedures to monitor safety, HCV RNA, and the emergence and persistence of resistant 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. Screening laboratory result indicating HCV GT 1, 2, 4, 5 or 6 infection;
3. Positive plasma HCV antibody and HCV RNA viral load ≥ 1000 IU/mL at Screening;
4. Treatment-naïve to any approved or investigational anti-HCV medication;
5. Subject must be documented as cirrhotic, with a Child-Pugh score of ≤ 6.

Main Exclusion:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study, or for approximately 30 days after the last dose of study drug;
2. 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 empiric use of lactulose/rifaximin for neurologic indications. The use of beta blockers is not exclusionary;
3. 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).
4. HCV genotype performed by the central laboratory during screening indicating genotype 3 infection or co-infection with more than one HCV genotype;

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

Main Exclusion (Continued):

5. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - Alanine aminotransferase ALT > 10 × ULN
   - Aspartate aminotransferase AST > 10 × ULN
   - Total Bilirubin > 3.0 mg/dL
   - Calculated creatinine clearance (CrCl, Cockcroft-Gault method) of < 50 mL/min
   - Albumin < 2.8 mg/dL
   - Hemoglobin < 10 g/dL
   - Platelets < 50,000 cells/mm^3

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

Duration of Treatment: Subjects will receive glecaprevir/pibrentasvir for 8 weeks.

Criteria for Evaluation:

Efficacy:

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

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests, 12-Lead ECGs and vital signs.

Patient Reported Outcomes (PROs):

The Treatment Satisfaction Questionnaire-Medication (TSQM) will be used to assess subjects' satisfaction with the treatments efficacy and side effects. The Short Form 36 Version 2 Health Status Survey (SF-36v2) will be used to assess the functional health and well-being of subjects. The Fatigue Severity Scale (FSS) will be used to measure the severity of fatigue and its effect on lifestyle and activities.

Pharmacokinetic:

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

Resistance:

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

Statistical Methods:

Efficacy:

The Intention-to-Treat (ITT) population includes all enrolled subjects who receive at least one dose of study drug. The Per-Protocol (PP) population includes all enrolled subjects who receive at least one dose of study drug, with the exception of subjects who experience breakthrough, or prematurely discontinue treatment prior to Week 8, or have no HCV RNA value in the SVR_{12} visit window or later.

The two primary efficacy endpoints are the comparisons of the SVR_{12} rate of the 8-week treatment duration to a historical SVR_{12} rate for 12 weeks in the Per-Protocol (PP) population and in the Intention-to-Treat (ITT) population. The primary efficacy analyses will be performed across genotypes following a fixed-sequence testing procedure:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of subjects in the 8-week treatment duration achieving SVR_{12} is greater than 94% in the PP population.
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of subjects in the 8-week treatment duration achieving SVR_{12} is greater than 93% in the ITT population.

The primary efficacy endpoints will be tested using the hierarchical order outlined above to control the Type I error rate. Only if success has been demonstrated for the first primary efficacy endpoint of SVR_{12} based on the PP population will the testing proceed to the second primary efficacy endpoint of SVR_{12} based on the ITT population. For both primary efficacy endpoints, the percentage of subjects achieving SVR_{12} and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial distribution, unless the number of subjects who failed to achieve SVR_{12} is less than 5, then the Wilson's score method will be used for the confidence interval instead.

The secondary efficacy endpoints are:

- The percentage of subjects with on-treatment virologic failure (OTVF) across genotypes (based on ITT population).
- The percentage of subjects with post-treatment relapse across genotypes (based on ITT population).

The number and percentage of subjects will be summarized along with a two-sided 95% confidence interval using Wilson's score method.

Statistical Methods (Continued):

Safety:

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 severity grade (Grades 1 – 5) and relationship to study drug. Mean changes in clinical laboratory and vital sign data from baseline to each post-baseline visit will be summarized. The number and percentage of subjects with post-baseline laboratory values meeting toxicity grades and meeting pre-defined criteria for laboratory parameters of interest during treatment will be summarized. The number and percentage of subjects with post-baseline vital sign values during the Treatment Period meeting pre-specified criteria for potentially clinically significant vital sign values will be summarized.

Patient Reported Outcomes (PROs):

The mean change from baseline to each applicable post-baseline timepoint in the FSS total score and the SF-36v2 Mental Component Summary (SF-36-MCS) and Physical Component Summary SF-36-PCS scores will be summarized descriptively at each visit. The TSQM subscales (global satisfaction, convenience, effectiveness, side effects) will be summarized descriptively at Weeks 2, 4, and 8 and the change from the baseline visit will be summarized at all on treatment timepoints.

Pharmacokinetic:

Plasma concentration of glecaprevir and pibrentasvir will be tabulated for each subject. Plasma concentrations of glecaprevir and pibrentasvir will be summarized based on last dosing time, sampling time and time since last dose. Summary statistics will be computed for glecaprevir and pibrentasvir plasma concentrations binned by time since last dose.

Resistance:

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

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the corresponding 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.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M16-135
Name of Study Drug: Glecaprevir, Pibrentasvir	**Phase of Development:** 3b
Name of Active Ingredient: Glecaprevir, Pibrentasvir	**Date of Protocol Synopsis:** 11 June 2018
Protocol Title: A Single Arm, Open-label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 - 6 Infection and Compensated Cirrhosis	
Objectives: • To demonstrate the efficacy of the SVR_{12} rates of 8 weeks of treatment with glecaprevir/pibrentasvir compared to the historical SVR_{12} rates of 12 weeks of treatment with glecaprevir/pibrentasvir in treatment naïve adults with chronic HCV infection and compensated cirrhosis. • To assess the safety of 8 weeks of treatment with glecaprevir/pibrentasvir in treatment naïve adults with chronic HCV infection and compensated cirrhosis.	
Investigators: Multicenter	
Study Sites: Approximately 120 globally	
Study Population: Adults with chronic HCV genotype (GT) 1 - 6 infection, aged 18 years or older, with compensated cirrhosis, who are HCV treatment-naïve.	
Number of Subjects to be Enrolled: Approximately 330 subjects	
Methodology: This is a Phase 3b, single arm, open-label, multicenter study to evaluate the efficacy and safety of 8 weeks of glecaprevir/pibrentasvir in treatment-naïve subjects with chronic HCV GT 1 - 6 infection and compensated cirrhosis. The study will initially enroll subjects with HCV GT 1, 2, 4, 5, and 6 infection followed by subjects with HCV GT3 infection. Once enrollment of subjects with HCV GT3 infection begins, enrollment of subjects with HCV GT 1, 2, 4, 5 or 6 infection will be closed. The study will consist of 3 periods: <u>Screening Period:</u> Subjects have up to 42 days following the Screening Visit to confirm eligibility and enroll into the study. <u>Treatment Period:</u> Eligible subjects will be enrolled to receive glecaprevir/pibrentasvir 300 mg/120 mg once daily (QD) for 8 weeks. Scheduled visits for subjects in the Treatment Period consist of Day 1 and Weeks 1, 2, 4, and 8. Study procedures, including assessment of adverse events, vital signs, adherence, concomitant medications, HCV RNA, HCV resistance, pharmacokinetic assays, and clinical laboratory tests, will be conducted at each visit.	

Methodology (Continued):

Because subjects with GT 1, 2, 4, 5 or 6 infection will be enrolled first, separate treatment extension criteria will apply to subjects with GT 1, 2, 4, 5 or 6 infection versus subjects with GT3 infection, as described below. However, if treatment is extended for all or a particular subgroup of subjects with GT 1, 2, 4, 5 or 6 infection, then enrollment of subjects with GT3 infection will be terminated and all GT3-infected subjects who are on treatment or have completed treatment within the previous 7 days will have their treatment extended to 12 weeks.

In subjects with HCV GT 1, 2, 4, 5, and 6 infection, an efficacy assessment will evaluate the post-treatment relapse rate after the first 30 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to 12 weeks is needed for all GT 1, 2, 4, 5, and 6-infected subjects or for a particular subgroup of GT 1, 2, 4, 5, and 6-infected subjects who are on treatment or have completed treatment within the previous 7 days.

In subjects with HCV GT3 infection, an efficacy assessment will evaluate the post-treatment relapse rate after the first 20 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to 12 weeks is needed for all GT3-infected subjects or for a particular subgroup of GT3-infected subjects who are on treatment or have completed treatment within the previous 7 days.

Post-Treatment Period:

Subjects who complete or prematurely discontinue the Treatment Period will be followed for 24 weeks to monitor safety, HCV RNA levels and to evaluate efficacy and the emergence and persistence of resistance associated substitutions.

During the Post-Treatment Period, all subjects will have visits at Weeks 4, 12, and 24 following completion of the Treatment Period. Study procedures to monitor safety, HCV RNA, and the emergence and persistence of resistant 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. Screening laboratory result indicating HCV GT 1 - 6 infection;
3. Positive plasma HCV antibody and HCV RNA viral load ≥ 1000 IU/mL at Screening;
4. Treatment-naïve to any approved or investigational anti-HCV medication;
5. Subject must be documented as cirrhotic, with a Child-Pugh score of ≤ 6.

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

Main Exclusion:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study, or for approximately 30 days after the last dose of study drug;
2. 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 empiric use of lactulose/rifaximin for neurologic indications. The use of beta blockers is not exclusionary;
3. 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).
4. HCV genotype performed by the central laboratory during screening indicating co-infection with more than one HCV genotype;
5. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - Alanine aminotransferase ALT > 10 × ULN
   - Aspartate aminotransferase AST > 10 × ULN
   - Total Bilirubin > 3.0 mg/dL
   - Calculated creatinine clearance (CrCl, Cockcroft-Gault method) of < 50 mL/min
   - Albumin < 2.8 mg/dL
   - Hemoglobin < 10 g/dL
   - Platelets < 50,000 cells/mm^3

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

Duration of Treatment: Subjects will receive glecaprevir/pibrentasvir for 8 weeks.

Criteria for Evaluation:

Efficacy:

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

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests, 12-Lead ECGs and vital signs.

Criteria for Evaluation (Continued):

Patient Reported Outcomes (PROs):

The Treatment Satisfaction Questionnaire-Medication (TSQM) will be used to assess subjects' satisfaction with the treatments efficacy and side effects. The Short Form 36 Version 2 Health Status Survey (SF-36v2) will be used to assess the functional health and well-being of subjects. The Fatigue Severity Scale (FSS) will be used to measure the severity of fatigue and its effect on lifestyle and activities.

Pharmacokinetic:

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

Resistance:

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

Statistical Methods:

Efficacy:

The Intention-to-Treat (ITT) population includes all enrolled subjects who receive at least one dose of study drug. The Per-Protocol (PP) population includes all enrolled subjects who receive at least one dose of study drug, with the exception of subjects who experience breakthrough, or prematurely discontinue treatment prior to Week 8, or have no HCV RNA value in the SVR_{12} visit window or later.

The primary efficacy endpoint is SVR_{12}. The following primary and key secondary efficacy analyses are the comparisons of the SVR_{12} rate of the 8-week treatment duration to a historical SVR_{12} rate for 12 weeks in the Per-Protocol (PP) population and in the Intention-to-Treat (ITT) population. The primary efficacy analyses will be conducted among HCV GT1, 2, 4, 5, and 6-infected subjects, and the two key secondary efficacy analyses will be conducted among all (HCV GT1 - 6) subjects. The primary efficacy analyses are listed below and will be tested through a fixed-sequence testing procedure:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 94% in the PP population.
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 93% in the ITT population.

Statistical Methods (Continued):

Efficacy (Continued):

The two key secondary efficacy analyses included in the fixed-sequence testing procedure are:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 3, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 94% in the PP population.
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 3, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 93% in the ITT population.

The primary and key secondary efficacy analyses will be tested using the hierarchical order outlined above to control the Type I error rate. Only if success has been demonstrated for the first primary efficacy analysis of SVR_{12} based on the PP population in HCV GT1, 2, 4, 5, and 6-infected subjects will the testing proceed to the second primary efficacy analysis of SVR_{12} based on the ITT population in HCV GT1, 2, 4, 5, and 6-infected subjects. And only if success has been demonstrated for the second primary efficacy analysis will the testing proceed to the first key secondary efficacy analysis of SVR_{12} based on the PP population in HCV GT1, 2, 3, 4, 5, and 6-infected subjects, and so on. For all primary and key secondary efficacy analyses, the percentage of subjects achieving SVR_{12} and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial distribution, unless the number of subjects who failed to achieve SVR_{12} is less than 5, then the Wilson's score method will be used for the confidence interval instead.

The other secondary efficacy analyses are listed below and are not included in the fixed-sequence testing:

- The percentage of HCV GT3-infected subjects in the PP population who achieve SVR_{12};
- The percentage of HCV GT3-infected subjects in the ITT population who achieve SVR_{12};
- The percentage of subjects with on-treatment virologic failure (OTVF) across genotypes, within HCV GT 1, 2, 4, 5, and 6-infected subjects combined, and within HCV GT3-infected subjects (based on ITT population);
- The percentage of subjects with post-treatment relapse across genotypes, within HCV GT 1, 2, 4, 5, and 6-infected subjects combined, and within HCV GT3-infected subjects (based on ITT population).

The number and percentage of subjects will be summarized along with a two-sided 95% confidence interval using Wilson's score method.

For the analysis of OTVF and post-treatment relapse, separate summaries will be provided for all subjects across genotypes, within HCV GT1, 2, 4, 5, and 6-infected subjects combined, and within HCV GT3-infected subjects.

Statistical Methods (Continued):

Safety:

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 severity grade (Grades 1 – 5) and relationship to study drug. Mean changes in clinical laboratory and vital sign data from baseline to each post-baseline visit will be summarized. The number and percentage of subjects with post-baseline laboratory values meeting toxicity grades and meeting pre-defined criteria for laboratory parameters of interest during treatment will be summarized. The number and percentage of subjects with post-baseline vital sign values during the Treatment Period meeting pre-specified criteria for potentially clinically significant vital sign values will be summarized.

Patient Reported Outcomes (PROs):

The mean change from baseline to each applicable post-baseline timepoint in the FSS total score and the SF-36v2 Mental Component Summary (SF-36-MCS) and Physical Component Summary SF-36-PCS scores will be summarized descriptively at each visit. The TSQM subscales (global satisfaction, convenience, effectiveness, side effects) will be summarized descriptively at Weeks 2, 4, and 8 and the change from the baseline visit will be summarized at all on treatment timepoints.

Pharmacokinetic:

Plasma concentration of glecaprevir and pibrentasvir will be tabulated for each subject. Plasma concentrations of glecaprevir and pibrentasvir will be summarized based on last dosing time, sampling time and time since last dose. Summary statistics will be computed for glecaprevir and pibrentasvir plasma concentrations binned by time since last dose.

Resistance:

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

The following resistance information will be analyzed for subjects receiving study drug who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the corresponding 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.

Section 3.0 Introduction

Fourth paragraph, first, second and third sentence previously read:

AbbVie has developed two next generation DAAs for use in combination for the treatment of HCV. These next generation DAAs are glecaprevir (GLE, formerly known as ABT-493), an HCV NS3/4A PI and pibrentasvir (PIB, formerly known as ABT-530),

an NS5A inhibitor. GLE and PIB each have potent in vitro antiviral activity against genotypes 1 through 6,[11] and a high genetic barrier to resistance with no or little loss of potency against common resistant-associated substitutions.

Has been changed to read:

AbbVie has developed two next generation DAAs for use in combination for the treatment of HCV infection. These next generation DAAs are glecaprevir (GLE, formerly known as ABT-493), an HCV NS3/4A PI and pibrentasvir (PIB, formerly known as ABT-530), an NS5A inhibitor. Co-formulated GLE/PIB is now an approved treatment for infection with all six major HCV genotypes in patients without cirrhosis and with compensated cirrhosis.[13,14] GLE and PIB each have potent in vitro antiviral activity against genotypes 1 through 6,[11] and a high genetic barrier to resistance with no or little loss of potency against common resistant-associated substitutions.

Section 3.0 Introduction
Subsection GLE/PIB
Heading "Overall Efficacy on the GLE/PIB Registrational Program and Among TN GT 1-, 2-, 4-, 5- or 6-Infected Subjects with Compensated Cirrhosis"
Heading previously read:

Overall Efficacy on the GLE/PIB Registrational Program and Among TN GT 1-, 2-, 4-, 5- or 6-Infected Subjects with Compensated Cirrhosis

Has been changed to read:

Overall Efficacy on the GLE/PIB Registrational Program and Among TN GT 1 - 6-Infected Subjects with Compensated Cirrhosis

Section 3.0 Introduction
Subsection GLE/PIB
Heading "Overall Efficacy on the GLE/PIB Registrational Program and Among TN GT 1-, 2-, 4-, 5- or 6-Infected Subjects with Compensated Cirrhosis"
Add: new last paragraph

In the registrational program, the SVR_{12} rate (ITT) was 98.5% (64/65) in HCV GT3-infected, treatment-naïve subjects with compensated cirrhosis treated for 12 weeks. No virologic failure was observed. Therefore, the PP SVR_{12} rate in this population was 100%.

Section 3.0 Introduction
Subsection GLE/PIB
Heading "Impact of Baseline Polymorphisms on Treatment Outcome"
Second and third paragraph previously read:

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

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

Has been changed to read:

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

The presence of baseline polymorphisms in NS3 and/or NS5A did not have an impact on SVR_{12} rates for GT1-, 2-, 4-, 5-, or 6-infected subjects. Baseline polymorphisms in NS3 did not have an impact on SVR_{12} in GT3-infected subjects. Among baseline polymorphisms in NS5A in GT3-infected subjects, Y93H did not have an impact on SVR_{12} rates except in treatment-experienced non-cirrhotic subjects receiving 12 weeks of treatment. A30K in NS5A at baseline was associated with lower SVR_{12} rates among non-cirrhotic treatment-naïve subjects receiving 8 weeks of treatment and treatment-experienced subjects receiving 12 weeks of treatment, but had no impact on SVR_{12} rates in treatment-naïve non-cirrhotic subjects receiving 12 weeks of treatment. The SVR_{12} rates in subjects with A30K at baseline were 77.8% (14/18), 25.0% (1/4), and 92.9% (13/14) among treatment-naïve subjects receiving 8 weeks, treatment-experienced subjects receiving 12 weeks, and treatment-naïve subjects receiving 12 weeks of treatment, respectively. Given the A30K prevalence of 6.3% among GT3-infected subjects, the difference in SVR_{12} attributable to the impact of A30K between the 8 and 12 weeks treatment duration is < 1%. Among treatment-experienced non-cirrhotic or cirrhotic subjects receiving 16 weeks of treatment, the impact of A30K is unclear due to the low prevalence of the polymorphism in this arm of the study.

Section 3.0 Introduction
Subsection <u>Glecaprevir/Pibrentasvir (GLE/PIB) PK Modeling for Study M16-135</u>
Subsection title previously read:

Glecaprevir/Pibrentasvir (GLE/PIB) PK Modeling for Study M16-135

Has been changed to read:

Glecaprevir/Pibrentasvir (GLE/PIB) Viral Dynamic Modeling for Study M16-135

Section 3.0 Introduction
Subsection Glecaprevir/Pibrentasvir (GLE/PIB) PK Modeling for Study M16-135
Second paragraph, last sentence previously read:

The clinical trial simulation scenarios for an 8-week treatment duration in non-cirrhotic, treatment-naïve subjects resulted in an SVR_{12} rate of approximately 98% in GT 1-, 2-, 4-, 5-, or 6-infected subjects and approximately 92% for GT3-infected subjects.

Has been changed to read:

The clinical trial simulation scenarios for an 8-week treatment duration in treatment-naïve subjects with compensated cirrhosis resulted in an SVR_{12} rate of approximately 98% in GT 1-, 2-, 4-, 5-, or 6-infected subjects and approximately 92% for GT3-infected subjects.

Section 3.0 Introduction
Subsection Glecaprevir/Pibrentasvir (GLE/PIB) PK Modeling for Study M16-135
Last paragraph previously read:

The objectives of this study are to evaluate the efficacy and safety of 8 weeks of GLE/PIB for the treatment of treatment-naïve subjects with chronic HCV GT 1, 2, 4, 5 or 6 infection and compensated cirrhosis.

Has been changed to read:

The objectives of this study are to evaluate the efficacy and safety of 8 weeks of GLE/PIB for the treatment of treatment-naïve subjects with chronic HCV GT 1 - 6 infection and compensated cirrhosis.

Section 3.1 Differences Statement
First sentence previously read:

The current Phase 3b Study M16-135 is the first study to evaluate the efficacy and safety of GLE/PIB in treatment-naïve adult subjects with chronic HCV GT 1, 2, 4, 5, or 6 infection with compensated cirrhosis for 8 weeks.

Has been changed to read:

The current Phase 3b Study M16-135 is the first study to evaluate the efficacy and safety of GLE/PIB in treatment-naïve adult subjects with chronic HCV GT 1 - 6 infection with compensated cirrhosis for 8 weeks.

Section 3.1 Differences Statement
Delete: third, fourth, fifth and sixth sentence

In the registrational program, 117 treatment naïve GT 1, 2, 4, 5 or 6 compensated cirrhotic subjects were treated with GLE/PIB for 12 weeks duration and 115 subjects achieved SVR_{12}. No virologic failure was observed. Two subjects did not achieve SVR_{12}: one discontinued treatment early and another had missing SVR_{12} data. Hence, the combined SVR_{12} rate for treatment naïve GT 1, 2, 4, 5, 6 compensated cirrhotic subjects was 100% (115/115), based on the PP population.

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

This Phase 3b study is a single arm study in which eligible HCV GT 1, 2, 4, 5, or 6 infected subjects with compensated cirrhosis will receive GLE/PIB for 8 weeks.

Has been changed to read:

This Phase 3b study is a single arm study in which eligible HCV GT 1 - 6 infected subjects with compensated cirrhosis will receive GLE/PIB for 8 weeks.

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

The results of these studies, together with PK modeling based on the registrational data, suggest that the likelihood of demonstrating a high SVR12 rate with an 8 week regimen in subjects with HCV GT 1, 2, 4, 5 or 6 infection with compensated cirrhosis is high.

Has been changed to read:

The results of these studies, together with PK modeling based on the registrational data, suggest that the likelihood of demonstrating a high SVR_{12} rate with an 8 week regimen in subjects with HCV GT 1 - 6 infection with compensated cirrhosis is high.

Section 3.2 Benefits and Risks
Second paragraph, last sentence previously read:

The GLE/PIB regimen is potent; according to a Phase 2 and 3 analysis SVR_{12} rates in treatment naïve cirrhotics treated for 12 weeks were 97.2% (69/71) for GT 1 and 100% (46/46) for GT 2, 4 – 6. Overall, the SVR_{12} rate is 98.3% (115/117) for GT 1, 2, 4, 5, or 6.

Has been changed to read:

The GLE/PIB regimen is potent; according to a Phase 2 and 3 analysis, SVR_{12} rates in treatment naïve cirrhotics treated for 12 weeks were 97.2% (69/71) for GT 1 and 100% (46/46) for GT 2, 4 – 6. Overall, the SVR_{12} rate was 98.3% (115/117) for GT 1, 2, 4, 5, or 6. The SVR_{12} rate in treatment naïve cirrhotics with GT3 infection treated for 12 weeks was 98.5% (64/65).

Section 3.2 Benefits and Risks
Seventh paragraph previously read:

An assessment of the post-treatment relapse rate will be performed when the first 30 subjects reach Post-treatment Week 4 and will be done periodically thereafter, in order to minimize exposure to a potentially suboptimal duration.

Has been changed to read:

An assessment of the post-treatment relapse rate occurring in this study in the non-GT3 and in the GT3 population will be performed on a periodic basis in order to minimize exposure to a potentially suboptimal duration (see Section 5.4.1.2).

Section 3.2 Benefits and Risks
Last paragraph previously read:

Overall, given the potential for achieving SVR_{12} with 8 weeks of treatment in this population of HCV GT 1, 2, 4, 5 or 6 infected subjects with compensated cirrhosis, the risk-benefit assessment is considered favorable.

Has been changed to read:

Overall, given the potential for achieving SVR_{12} with 8 weeks of treatment in this population of HCV GT 1 - 6 infected subjects with compensated cirrhosis, the risk-benefit assessment is considered favorable.

Section 4.1 Primary Objective
Bullet list previously read:

- To demonstrate the efficacy of the SVR_{12} rate of 8 weeks of treatment with glecaprevir/pibrentasvir compared to the historical SVR_{12} rate of 12 weeks of treatment with glecaprevir/pibrentasvir in treatment naïve adults with chronic HCV GT 1, 2, 4, 5 or 6 infection and compensated cirrhosis.
- To assess the safety of 8 weeks of treatment with glecaprevir/pibrentasvir in treatment naïve adults with chronic HCV GT 1, 2, 4, 5 or 6 infection and compensated cirrhosis.

Has been changed to read:

- To demonstrate the efficacy of the SVR_{12} rates of 8 weeks of treatment with glecaprevir/pibrentasvir compared to the historical SVR_{12} rates of 12 weeks of treatment with glecaprevir/pibrentasvir in treatment naïve adults with chronic HCV infection and compensated cirrhosis.
- To assess the safety of 8 weeks of treatment with glecaprevir/pibrentasvir in treatment naïve adults with chronic HCV infection and compensated cirrhosis.

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

This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of 8 weeks of GLE/PIB in HCV treatment-naïve adult subjects with chronic HCV GT 1, 2, 4, 5 or 6 infection and compensated cirrhosis.

Has been changed to read:

This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of 8 weeks of GLE/PIB in HCV treatment-naïve adult subjects with chronic HCV GT 1 - 6 infection and compensated cirrhosis. The study will initially enroll subjects with HCV GT 1, 2, 4, 5 and 6 infection followed by subjects with HCV GT3 infection. Once enrollment of subjects with HCV GT3 infection begins, enrollment of subjects with HCV GT 1, 2, 4, 5 or 6 infection will be closed.

Section 5.1 Overall Study Design and Plan: Description
Sixth paragraph previously read:

An efficacy assessment will evaluate the post-treatment relapse rate after the first 30 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to 12 weeks is needed for all subjects or for a particular subgroup of subjects who are on treatment or have completed treatment within the previous 7 days.

Has been changed to read:

An assessment of the post-treatment relapse rate occurring in this study in the non-GT3 and in the GT3 population will be performed on a periodic basis in order to minimize exposure to a potentially suboptimal duration (see Section 5.4.1.2).

Section 5.1 Overall Study Design and Plan: Description
Tenth paragraph, first sentence previously read:

The study is designed to enroll approximately 270 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Has been changed to read:

The study is designed to enroll approximately 330 subjects (approximately 270 with GT1, 2, 4, 5, or 6 infection and approximately 60 with GT3 infection) to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Section 5.1 Overall Study Design and Plan: Description
Last paragraph previously read:

The primary analysis will occur after all subjects have completed the Post-Treatment Week 12 Visit or prematurely discontinued from the study.

Has been changed to read:

Analyses will occur after subjects have completed the Post-Treatment Week 12 Visit or prematurely discontinued from the study, starting with HCV GT1, 2, 4, 5, and 6-infected subjects.

Section 5.2 Selection of Study Population
First sentence previously read:

The study population consists of treatment-naïve male and female adults aged 18 years or older with chronic HCV GT 1, 2, 4, 5, or 6 infection, with compensated cirrhosis.

Has been changed to read:

The study population consists of treatment-naïve male and female adults aged 18 years or older with chronic HCV GT 1 - 6 infection, with compensated cirrhosis.

Section 5.2.1 Inclusion Criteria
Criterion 4 previously read:

Screening central laboratory result indicating HCV GT1, 2, 4, 5, or 6-infection.

Has been changed to read:

Screening central laboratory result indicating HCV GT1 - 6-infection.

Section 5.2.2 Exclusion Criteria
Criterion 2 previously read:

HCV genotype performed by the central laboratory during screening indicating genotype 3 infection or co-infection with more than one HCV genotype.

Has been changed to read:

HCV genotype performed by the central laboratory during screening indicating co-infection with more than one HCV genotype.

Section 5.2.3.3 Prohibited Therapy
First paragraph previously read:

Subjects must be able to safely discontinue any prohibited medications or supplements listed in Table 4 at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of GLE/PIB and not use these during the entire Treatment Period and for 14 days following discontinuation of study drug.

Has been changed to read:

Medications or supplements prohibited to be administered with GLE/PIB are listed in Table 4. For subjects in the study in countries where GLE/PIB has received marketing authorization, any medications in the local label that are contraindicated to be administered with GLE/PIB are also considered to be prohibited medications. Subjects must be able to safely discontinue any prohibited medications or supplements at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of GLE/PIB and not

use these during the entire Treatment Period and for 14 days following discontinuation of study drug. The Informed Consent Form must be signed and dated prior to discontinuing any prohibited medications or supplements.

Table 4. Prohibited Medications and Supplements
Add:

Tipranavir/r, atazanavir, efavirenz

Table 4. Prohibited Medications and Supplements
Table note "*" previously read:

Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drug. Subjects receiving these statins should either (a) switch to pravastatin or rosuvastatin at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug or (b) interrupt statin therapy throughout the treatment period beginning at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug and until 14 days after the last dose of study drug, based on investigator's judgment. If switching to or continuing pravastatin or rosuvastatin, it is recommended to either 1) reduce the pravastatin or rosuvastatin dose in accordance with the ABT-493/ABT-530 approved local product label; or 2) reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drug if ABT-493/ABT-530 is not yet approved in the respective location.

Has been changed to read:

Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drug. After signing the consent form, subjects receiving these statins should either (a) switch to pravastatin or rosuvastatin at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug or (b) may interrupt statin therapy throughout the treatment period beginning at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug and until 14 days after the last dose of study drug, based on investigator's judgment. If switching to or continuing pravastatin or rosuvastatin, it is recommended to either 1) reduce the

pravastatin or rosuvastatin dose in accordance with the GLE/PIB approved local product label (if approved in the country); or 2) reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drug if GLE/PIB is not yet approved in the respective location.

Section 5.3.1.1 Study Procedures
Subsection HCV Genotype and Subgenotype
Subsection title previously read:

HCV Genotype and Subgenotype

Has been changed to read:

HCV Genotype and Subtype

Section 5.3.2.4 Measurement Methods
First sentence previously read:

Plasma concentrations of GLE and PIB will be determined using a validated method by the Drug Analysis Department at AbbVie.

Has been changed to read:

Plasma concentrations of GLE and PIB will be determined using a validated method by the Bioanalysis Department at AbbVie.

Section 5.4.1.2 Treatment Extension Criteria
Previously read:

An efficacy assessment will evaluate the post-treatment relapse rate when the first 30 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to 12 weeks is needed for all subjects or for a particular subgroup of subjects who are on treatment or have completed treatment within the previous 7 days.

The enrollment of additional subjects in this study will be terminated if extension of treatment is needed for all subjects. If the extension is needed for a particular subgroup of subjects, then the enrollment will be terminated for this particular subgroup but other subgroups will continue to be allowed to enroll in the study with 8 weeks treatment duration.

Retreatment of subjects who experience virologic failure with the GLE/PIB regimen for 8 weeks will be offered retreatment in the AbbVie Study M15-942.

Has been changed to read:

Because subjects with GT 1, 2, 4, 5 or 6 infection will be enrolled first, separate treatment extension criteria will apply to subjects with GT 1, 2, 4, 5 or 6 infection versus subjects with GT3 infection, as described below. However, if treatment is extended for all or a particular subgroup of subjects with GT 1, 2, 4, 5 or 6 infection, then enrollment of subjects with GT3 infection will be terminated and all GT3-infected subjects who are on treatment or have completed treatment within the previous 7 days will have their treatment extended to 12 weeks.

In subjects with GT 1, 2, 4, 5, or 6 infection, an efficacy assessment will evaluate the post-treatment relapse rate when the first 30 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to 12 weeks is needed for all GT 1, 2, 4, 5, and 6-infected subjects or for a particular subgroup of GT 1, 2, 4, 5, and 6-infected subjects who are on treatment or have completed treatment within the previous 7 days.

The enrollment of additional GT 1, 2, 4, 5, or 6-infected subjects in this study will be terminated if extension of treatment is needed for all GT 1, 2, 4, 5, or 6-infected subjects. If the extension is needed for a particular subgroup of GT 1, 2, 4, 5, or 6-infected subjects, then the enrollment will be terminated for this particular subgroup but other subgroups will continue to be allowed to enroll in the study with 8 weeks treatment duration.

In subjects with GT3 infection, an efficacy assessment will evaluate the post-treatment relapse rate after the first 20 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to 12 weeks is needed for all GT3-infected subjects or for a particular subgroup of GT3-infected subjects who are on treatment or have completed treatment within the previous 7 days.

The enrollment of additional GT3-infected subjects in this study will be terminated if extension of treatment is needed for all GT3-infected subjects. If the extension is needed for a particular subgroup of GT3-infected subjects, then the enrollment will be terminated for this particular subgroup but other subgroups will continue to be allowed to enroll in the study with 8 weeks treatment duration. Retreatment of subjects who experience virologic failure with the GLE/PIB regimen for 8 weeks will be offered retreatment in the AbbVie Study M15-942.

Section 5.6.1 Discussion of Study Design and Choice of Control Groups
Previously read:

The current study (Study M16-135) is a multicenter, single-arm, open-label, Phase 3b study evaluating the efficacy and safety of the co-formulated combination regimen of GLE 300 mg and PIB 120 mg QD administered for 8 weeks in treatment-naïve subjects with chronic HCV GT 1, 2, 4, 5 or 6 infection and compensated cirrhosis.

The 12-week regimen of GLE/PIB was studied in adults with chronic HCV GT 1, 2, 4, 5, or 6 infection and compensated cirrhosis in Study M14-172. Other Phase 3 studies also enrolled a few cirrhotic subjects. The integrated analysis of the registrational studies will serve as the historical control and reference point for the design of the current trial.

In the registrational program, 117 treatment naïve subjects with compensated cirrhosis infected with GTs 1, 2, 4, 5, or 6 were treated with GLE/PIB for a 12 weeks. Of those, 2 subjects did not achieve SVR_{12} (one discontinued treatment early and the other had missing SVR_{12} data). No virologic failure was observed. Hence, the historical SVR_{12} rate based on PP population (defined as subjects who receive at least one dose of study drug,

with the exception of subjects who experience breakthrough, or prematurely discontinue treatment prior to Week 8, or have no HCV RNA value in the SVR_{12} visit window or later) is 100%. The observed rate of non-virologic failure in the GLE/PIB registrational program was 1.2% (29/2369). For this reason, this study assumes that the historical SVR_{12} rate for the ITT population will be 99% (assuming 1% of non-virologic failures).

The observed SVR rates for the GLE/PIB 12 weeks duration in the Phase 2/3 development program is very high (> 97%) for the treatment naïve GT 1, 2, 4, 5, or 6 cirrhotic subjects. Given such a high SVR rate, an active control arm does not provide value in establishing the efficacy of the new regimen. That is, the efficacy of the new regimen can be established via an absolute criterion (comparison to a threshold) rather than a relative criterion (non-inferiority to an active control). Hence, the observed SVR rate from Phase 2/3 program will be used as historical control to provide a comparator for assessment of efficacy for the 8-week arm in this study for the treatment naïve cirrhotic patients.

A threshold for the primary efficacy endpoint of the 8 weeks GLE/PIB regimen to the historical control is determined by subtracting a margin of 6% from the historical SVR_{12} rate of 100% or 99% (for PP or ITT population, respectively) for GLE/PIB for 12 weeks.

A margin of 6% is selected to be used in this study to ensure a minimal loss of efficacy of the 8-week arm relative to the historical SVR_{12} rate for 12-week arm, and is in alignment with the GLE/PIB registrational program.

Thus, to establish efficacy of 8 weeks GLE/PIB to the 12 weeks GLE/PIB in treatment naïve cirrhotic subjects, the lower bound of the 95% CI for the SVR_{12} rate in the active arm must exceed 94% or 93% for PP and ITT population, respectively.

Has been changed to read:

The current study (Study M16-135) is a multicenter, single-arm, open-label, Phase 3b study evaluating the efficacy and safety of the co-formulated combination regimen of

GLE 300 mg and PIB 120 mg QD administered for 8 weeks in treatment-naïve subjects with chronic HCV GT 1 - 6 infection and compensated cirrhosis.

The 12-week regimen of GLE/PIB was studied in adults with chronic HCV GT 1, 2, 4, 5, or 6 infection and compensated cirrhosis in Study M14-172 and studied in adults with chronic HCV GT3 infection and compensated cirrhosis in Study M14-868. Other Phase 3 studies also enrolled a few cirrhotic subjects. The integrated analysis of the registrational studies will serve as the historical control and reference point for the design of the current trial.

In the registrational program, 117 treatment naïve subjects with compensated cirrhosis infected with GTs 1, 2, 4, 5, or 6 were treated with GLE/PIB for a 12 weeks. Of those, 2 subjects did not achieve SVR_{12} (one discontinued treatment early and the other had missing SVR_{12} data). No virologic failure was observed. Hence, the historical SVR_{12} rate based on PP population is 100% for GT1, 2, 4, 5, and 6-infected subjects. Similarly, the historical SVR_{12} rate based on a PP population is 100% for GT1-6-infected subjects, as 65 treatment naïve subjects with compensated cirrhosis infected with GT3 were treated with GLE/PIB for 12 weeks. Of those, 1 subject did not achieve SVR_{12} due to missing SVR_{12} data. No virologic failure was observed.

The observed rate of non-virologic failure in the overall GLE/PIB registrational program was 1.2% (29/2369). For this reason, this study assumes that the historical SVR_{12} rate for the ITT population for GT1, 2, 4, 5, and 6-infected and for GT1-6-infected subjects will be 99% (assuming 1% of non-virologic failures). The observed SVR rates for the GLE/PIB 12 weeks duration in the Phase 2/3 development program is very high (> 97%) for the treatment naïve GT 1, 2, 3, 4, 5, or 6-infected cirrhotic subjects. Given such a high SVR rate, an active control arm does not provide value in establishing the efficacy of the new regimen. That is, the efficacy of the new regimen can be established via an absolute criterion (comparison to a threshold) rather than a relative criterion (non-inferiority to an active control). Hence, the observed SVR rate from Phase 2/3 program will be used as historical control to provide a comparator for assessment of efficacy for the 8-week arm in this study for the treatment naïve cirrhotic patients.

A threshold for the primary and key secondary efficacy analyses of the 8 weeks GLE/PIB regimen to the historical control is determined by subtracting a margin of 6% from the historical SVR_{12} rate of 100% or 99% (for PP or ITT population, respectively) for GLE/PIB for 12 weeks.

A margin of 6% is selected to be used in this study to ensure a minimal loss of efficacy of the 8-week arm relative to the historical SVR_{12} rate for 12-week arm, and is in alignment with the GLE/PIB registrational program.

Thus, to establish efficacy of 8 weeks GLE/PIB to the 12 weeks GLE/PIB in treatment naïve cirrhotic subjects, the lower bound of the 95% CI for the SVR_{12} rate in the 8-week arm must exceed 94% or 93% for the PP and ITT populations, respectively.

Section 5.6.3 Suitability of Subject Population
First, second, and third paragraph previously read:

Results from the Registrational Program with GLE/PIB show that lower SVR_{12} rates were achieved in GT3-infected subjects (93.5%) than for other Genotypes (97.4 to 100%) (Table 2). Exposure-viral load modeling and simulations were conducted and predicted lower SVR_{12} rate for treatment naïve GT3 subjects with cirrhosis (92%) compared to the rate in treatment naïve non-GT3 subjects (98%), without accounting for failures due to non-virologic reasons. Therefore, subjects infected with GT3 were excluded from the population to be enrolled in this trial.

This subject population will include treatment-naïve subjects only. While predictive models suggest high SVR_{12} rates with 8 weeks of GLE/PIB, the ultrashort nature of this study risks an increase of post-treatment relapse or EOT failure in treatment-experienced patients.

This study will exclude subjects with HIV/HCV coinfection, as this sub-population is currently being evaluated in Study M14-730.

Has been changed to read:

HCV GT3-infected patients are known to be a more difficult to treat population for DAA-based regimens. Therefore, subjects infected with HCV GT1, 2, 4, 5 and 6 were enrolled first in this trial, while subjects infected with HCV GT3 were initially excluded. The protocol was later amended to include GT3-infected subjects based on the following registrational clinical data:

- SVR_{12} rate (ITT) of 98.5% (64/65) in treatment-naïve GT3-infected subjects with compensated cirrhosis treated for 12 weeks of GLE/PIB, with no virologic failures observed; the PP SVR_{12} rate was 100% (64/64).
- SVR_{12} rate (ITT) of 95.2% (177/186) and 95.6% (258/270) in treatment-naïve GT3-infected subjects without cirrhosis treated for 8 and 12 weeks of GLE/PIB, respectively; PP SVR_{12} rates were 97.3% (177/182) and 98.9% (258/261) for 8 and 12 weeks of GLE/PIB, respectively.[15]
- GLE/PIB for 8 weeks in treatment-naïve GT3-infected subjects without cirrhosis was determined to be non-inferior to GLE/PIB for 12 weeks in Study M13-594 (ENDURANCE-3).[16]

This subject population will include treatment-naïve subjects only. While high SVR_{12} rates with 8 weeks of GLE/PIB are expected, the ultrashort nature of this study risks an increase of post-treatment relapse or EOT failure in treatment-experienced patients.

This study will exclude subjects with HIV/HCV coinfection, as this sub-population is currently being evaluated in Study M14-730 (EXPEDITION-2).[17]

Section 5.6.4.2 GLE and PIB Dose and Treatment Duration
Previously read:

GLE/PIB 300 mg/120 mg QD regimens with 8-week and 12-week durations were evaluated in non-cirrhotic subjects in registrational trials. Efficacy of 8-week treatment duration is established for GT1- or GT2-infected non-cirrhotic subjects [R&D/16/0144, R&D/15/1230]. Fifty-two non-cirrhotic GTs 4, 5, or 6 subjects received 8-weeks of GLE/PIB and no virologic failure was observed. Overall, these results conclude that

8-weeks of GLE/PIB 300 mg/120 mg dose is efficacious for non-cirrhotic GT 1, 2, 4, 5, or 6 subjects.

Based on modeling simulations, assuming no subjects experiencing non-virologic failures, the predicted SVR_{12} rate in treatment-naïve HCV GT1-, GT2-, GT4-, GT5- and GT6-infected subjects with 8 weeks of GLE/PIB is approximately 98%.

Has been changed to read:

GLE/PIB 300 mg/120 mg QD regimens with 8-week and 12-week durations were evaluated in non-cirrhotic subjects in registrational trials. Efficacy of 8-week treatment duration is established for GT1-, GT2- and GT3- infected non-cirrhotic subjects [R&D/16/0144, R&D/15/1230]. Fifty-two non-cirrhotic GTs 4, 5, or 6-infected subjects received 8-weeks of GLE/PIB and no virologic failure was observed. Overall, these results conclude that 8-weeks of GLE/PIB 300 mg/120 mg dose is efficacious for non-cirrhotic GT 1 - 6-infected subjects.

Based on modeling and simulations, assuming no subjects experience non-virologic failures, following 8 weeks of GLE/PIB in treatment-naïve HCV-infected subjects with compensated cirrhosis, the predicted SVR_{12} rate is approximately 98% for GT1, 2, 4, 5, and 6-infected subjects, and approximately 92% for GT3-infected subjects.

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

[redacted]
Associate Medical Director
1 North Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Office:
Mobile:
eFAX:
Email:

Has been changed to read:

[redacted], MD
Medical Director
1500 Seaport Blvd.
Redwood City, CA 94063

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

Section 8.1 Statistical and Analytical Plans
First paragraph previously read:

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.

Has been changed to read:

Analyses will occur after subjects have completed the PT Week 12 Visit or prematurely discontinued study. The first analysis will occur after all HCV GT1, 2, 4, 5, and 6-infected subjects have completed the PT Week 12 Visit or prematurely discontinued study; the second analysis will occur after all HCV GT3-infected subjects have completed the PT Week 12 Visit or prematurely discontinued study; the third and final analysis will occur after all subjects have completed or prematurely discontinued from the study.

Section 8.1 Statistical and Analytical Plans
Sixth and seventh paragraph previously read:

The primary efficacy analyses will be performed on the PP and ITT populations. The secondary efficacy analyses will be performed on the ITT population.

Sensitivity analyses of SVR_{12}, when applicable, will be performed on the intention-to-treat population modified to exclude subjects who were enrolled with ineligible genotypes (e.g., GT3 according to phylogenetic analyses) (mITT-GT), and on the mITT-GT population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-GT-VF).

Has been changed to read:

The primary and key secondary efficacy analyses will be performed on the PP and ITT populations, as specified. The other secondary efficacy analyses will be performed on the ITT population, unless otherwise specified.

Sensitivity analyses of SVR_{12}, when applicable, will be performed on the intention-to-treat population modified to exclude subjects who were enrolled with ineligible genotypes (e.g., GT3 according to phylogenetic analyses for the group of non-GT3-infected subjects) (mITT-GT), and on the mITT-GT population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-GT-VF).

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

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, in addition to HCV genotype and subtype, baseline Child-Pugh score, tobacco and alcohol use status, history of bleeding disorders, history of depression or bipolar disorder, and history of cardiovascular disease.

Has been changed to read:

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, in addition to HCV genotype and subtype, baseline Child-Pugh score, tobacco and alcohol use status.

Section 8.1.2 Efficacy
First paragraph previously read:

The primary efficacy analyses will be performed on both the PP and ITT populations and all the secondary efficacy endpoints will be analyzed based on ITT population.

Has been changed to read:

The primary and key secondary efficacy analyses will be performed on both the PP and ITT populations, as specified. The other secondary efficacy analyses will be analyzed based on ITT population, unless otherwise specified.

Section 8.1.2.1 Primary Efficacy Endpoints
Previously read:

The two primary efficacy endpoints are comparisons of the SVR_{12} rate of the 8-week treatment duration to a historical SVR_{12} rate for 12 weeks in the Per-Protocol (PP) population and in the Intention-to-Treat (ITT) population. The primary efficacy analyses will be performed across genotypes following a fixed-sequence testing procedure:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of subjects in the 8-week treatment duration achieving SVR_{12} is greater than 94% in the PP population.
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of subjects in the 8-week treatment duration achieving SVR_{12} is greater than 93% in the ITT population.

The primary efficacy endpoints will be tested using the hierarchical order outlined above to control the Type I error rate. Only if success has been demonstrated for the first primary efficacy endpoint of SVR_{12} based on the PP population will the testing proceed to the second primary efficacy endpoint of SVR_{12} based on the ITT population.

For the first primary efficacy endpoint, the PP population will be used. The PP analysis is used to reduce the risk of bias toward no treatment difference that can occur due to dropouts or other measurement problems, since the subjects excluded in the PP population experience SVR failure for reasons that do not help in discriminating between treatment durations.

For both primary efficacy endpoints, the percentage of subjects achieving SVR_{12} and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial distribution, unless the number of subjects who failed to achieve SVR_{12} is less than 5, then the Wilson's score method will be used for the confidence interval instead.

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

Has been changed to read:

The two primary efficacy analyses are:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 94% in the PP population.
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 93% in the ITT population.

The two primary and two key secondary (defined in Section 8.1.2.2.1) efficacy analyses will be performed following a fixed-sequence testing procedure which is described in Section 8.1.2.6.

Only if success has been demonstrated for the first primary efficacy analysis of SVR_{12} based on the PP population in HCV GT1, 2, 4, 5, and 6-infected subjects will the testing proceed to the second primary efficacy analysis of SVR_{12} based on the ITT population in HCV GT1, 2, 4, 5, and 6-infected subjects. And only if success has been demonstrated for the second primary efficacy analysis will the testing proceed to the key secondary efficacy analyses described in Section 8.1.2.2.1.

For the first primary efficacy analysis, the PP population will be used. The PP analysis is used to reduce the risk of bias toward no treatment difference that can occur due to dropouts or other measurement problems, since the subjects excluded in the PP population experience SVR failure for reasons that do not help in discriminating between treatment durations.

For both primary efficacy analyses, the percentage of subjects achieving SVR_{12} and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial distribution, unless the number of subjects who failed to achieve SVR_{12} is less than 5, then the Wilson's score method will be used for the confidence interval instead.

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

Section 8.1.2.2 Secondary Efficacy Endpoints
Previously read:

The secondary efficacy endpoints are:

- The percentage of subjects with OTVF (defined as confirmed increase of > 1 log10 IU/mL above nadir during treatment, confirmed HCV RNA

≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and

- The percentage of subjects with post-treatment relapse ($Relapse_{12}$: defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug [up to and including the SVR_{12} assessment time point] among subjects who completed treatment as planned [defined as study drug duration ≥ 52 days for subjects assigned to 8 weeks of treatment] with HCV RNA < LLOQ at the end of treatment; excluding subjects who have been shown to be reinfected).

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

Has been changed to read:

8.1.2.2.1 Key Secondary Efficacy Endpoints

The two key secondary efficacy analyses included in the fixed-sequence are listed below:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 3, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 94% in the PP population;
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT1, 2, 3, 4, 5, and 6-infected subjects in the 8-week treatment duration achieving SVR_{12} is greater than 93% in the ITT population.

Only if success was demonstrated for both primary efficacy analyses will testing proceed to the two key secondary efficacy analyses in the order listed above. If success has been

demonstrated for the first key secondary efficacy analysis of SVR_{12} based on the PP population in HCV GT1-6-infected subjects, then testing will proceed to the second key secondary efficacy analysis of SVR_{12} based on the ITT population in HCV GT1-6-infected subjects.

8.1.2.2.2 Other Secondary Efficacy Endpoints

The other secondary efficacy analyses, which are not included in the fixed sequence, are listed below:

- The percentage of HCV GT3-infected subjects in the PP population who achieve SVR_{12};
- The percentage of HCV GT3-infected subjects in the ITT population who achieve SVR_{12};
- The percentage of subjects with OTVF (defined as confirmed increase of > 1 log10 IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and
- The percentage of subjects with post-treatment relapse ($Relapse_{12}$: defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug [up to and including the SVR_{12} assessment time point] among subjects who completed treatment as planned [defined as study drug duration ≥ 52 days for subjects assigned to 8 weeks of treatment] with HCV RNA < LLOQ at the end of treatment; excluding subjects who have been shown to be reinfected).

For the analyses of SVR_{12} among HCV GT3-infected subjects, the number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using Wilson's score method.

For the analysis of OTVF and post-treatment relapse, the number and percentage of subjects in the ITT population will be summarized along with a two-sided 95% confidence interval using Wilson's score method. Separate summaries will be provided

for all subjects across genotypes, within HCV GT1, 2, 4, 5, and 6-infected subjects combined, and within HCV GT3-infected subjects.

Section 8.1.2.3 Sensitivity Analysis
Last paragraph previously read:

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

Has been changed to read:

The two-sided 95% confidence interval using Wilson's score method will also be calculated if applicable, as a sensitivity analysis for the primary and key secondary efficacy analyses of SVR_{12} based on the PP and ITT populations.

Section 8.1.2.4 Subgroup Analysis
First bullet previously read:

HCV genotype and genotype 1 subtype;

Has been changed to read:

HCV genotype and subtype;

Section 8.1.2.4 Subgroup Analysis
Delete: fourth bullet

IL28B genotype;

Section 8.1.2.6 Multiplicity
Previously read:

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

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

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

Has been changed to read:

In order to control family-wise Type I error rate, a fixed-sequence testing procedure will be used for the two primary and two key secondary efficacy analyses of SVR_{12} as listed below. The fixed-sequence testing procedure will utilize the endpoint sequence of the first primary analysis followed by the second primary analysis, then the first key secondary analysis, and lastly the second key secondary analysis. For example, only if success has been demonstrated for the first primary efficacy analysis of SVR_{12} based on the PP population, will the testing proceed to the second primary efficacy analysis of SVR_{12} based on the ITT population, and so on.

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

1. Primary 1: Efficacy of the SVR_{12} rate of 8-week treatment duration compared to the historical 12 week treatment duration based on the PP population in HCV GT1, 2, 4, 5, and 6-infected subjects: If this endpoint is statistically significant, then proceed to the following efficacy endpoint. If this endpoint is not statistically

significant, then stop the testing procedure and declare that no endpoints in the study met statistical significance.

2. Primary 2: Efficacy of the SVR_{12} rate of 8-week treatment duration compared to the historical 12 week treatment duration based on the ITT population in HCV GT1, 2, 4, 5, and 6-infected subjects: If this endpoint is statistically significant, then declare the SVR_{12} endpoint is statistically significant on both the PP and ITT populations in HCV GT1, 2, 4, 5, and 6-infected subjects. If not, then announce that SVR_{12} endpoint is statistically significant based on only the PP population in HCV GT1, 2, 4, 5, and 6-infected subjects and stop testing.
3. Key Secondary 1: Efficacy of the SVR_{12} rate of 8-week treatment duration compared to the historical 12 week treatment duration based on the PP population in HCV GT1, 2, 3, 4, 5, and 6-infected subjects: If this endpoint is statistically significant, then declare the SVR_{12} endpoint is statistically significant on both the PP and ITT populations in HCV GT1, 2, 4, 5, and 6-infected subjects and on the PP population in HCV GT1-6-infected subjects. If not, then announce that SVR_{12} endpoint is statistically significant based on only the preceding populations and stop testing.
4. Key Secondary 2: Efficacy of the SVR_{12} rate of 8-week treatment duration compared to the historical 12 week treatment duration based on the ITT population in HCV GT1, 2, 3, 4, 5, and 6-infected subjects: If this endpoint is statistically significant, then declare the SVR_{12} endpoint is statistically significant on both the PP and ITT populations in HCV GT1, 2, 4, 5, and 6-infected subjects and on both the PP and ITT populations in HCV GT1-6-infected subjects. If not, then announce that SVR_{12} endpoint is statistically significant based on only the preceding populations and stop testing.

Table 8. 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 (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, 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, and 93	

Section 8.2 Determination of Sample Size
Previously read:

It is planned to enroll approximately 270 adult subjects with chronic HCV GT 1, 2, 4, 5 or 6 infection with compensated cirrhosis who are HCV treatment-naïve in the study.

With approximately 270 subjects, this study has approximately 91% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 94%) based on Per-Protocol (PP) population, assuming that 98% of the subjects receiving 8 weeks of treatment in PP population achieve SVR_{12}.

With approximately 270 subjects, this study has approximately 82% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 93%) based on Intention-to-Treat (ITT) population, assuming that 97% of the subjects receiving 8 weeks of treatment in ITT population achieve SVR_{12}.

Has been changed to read:

It is planned to enroll approximately 330 adult subjects with chronic HCV GT 1 - 6 infection with compensated cirrhosis who are HCV treatment-naïve in the study.

The study was initially designed to enroll about 270 non-GT3-infected subjects and amended to include GT3-infected subjects for a total of 330 GT1 - 6-infected (270 non-GT3 and 60 GT3) subjects.

With approximately 270 subjects with HCV GT1, 2, 4, 5, or 6 infection, this study has approximately 91% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 94%) based on Per-Protocol (PP) population, assuming that 98% of the GT1, 2, 4, 5, and 6-infected subjects receiving 8 weeks of treatment in PP population achieve SVR_{12}.

With approximately 270 subjects with HCV GT1, 2, 4, 5, or 6 infection, this study has approximately 82% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 93%) based on Intention-to-Treat (ITT) population, assuming that 97% of the GT1, 2, 4, 5, and 6-infected subjects receiving 8 weeks of treatment in ITT population achieve SVR_{12}.

With approximately 330 subjects with HCV GT1 - 6 infection, this study has approximately 90% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 94%) based on the PP population, assuming that 98% of the GT1 - 6-infected subjects receiving 8 weeks of treatment in the PP population achieve SVR_{12}.

With approximately 330 subjects with HCV GT1-6 infection, this study has approximately 81% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 93%) based on the ITT population, assuming that 97% of the GT1 - 6-infected subjects receiving 8 weeks of treatment in the ITT population achieve SVR_{12}.

Section 8.2.1 Justification of Success Criteria for SVR_{12}
Second paragraph previously read:

In the registrational program, 117 treatment naïve, compensated cirrhotic subjects, GT 1, 2, 4, 5, or 6 subjects were treated with GLE/PIB for 12 weeks duration. Two subjects did not achieve SVR_{12}, one discontinued treatment early and the other had missing SVR_{12} data. No virologic failure was observed among these subjects which means SVR_{12} rate based on PP population is 100%. Hence, for this study it assumed that the historical SVR_{12} rate for cirrhotic patients is 100%. To establish efficacy to the historical control, a margin of 6% is applied to the historical control rate of 100%, resulting in a threshold of 94%.

Has been changed to read:

In the registrational program, 117 treatment naïve, compensated cirrhotic subjects, GT 1, 2, 4, 5, or 6 subjects and 65 treatment naïve, GT3-infected subjects with compensated cirrhosis were treated with GLE/PIB for 12 weeks duration. Three subjects did not achieve SVR_{12}, one discontinued treatment early and two had missing SVR_{12} data. No virologic failure was observed among these subjects which means SVR_{12} rate based on PP population is 100%. Hence, for this study it assumed that the historical SVR_{12} rate for GT1-6-infected cirrhotic patients is 100%. To establish efficacy to the historical control, a margin of 6% is applied to the historical control rate of 100%, resulting in a threshold of 94%.

Section 14.0 Investigator's Agreement
"Protocol Title:" previously read:

A Single Arm, Open-label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis

Has been changed to read:

A Single Arm, Open-label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 - 6 Infection and Compensated Cirrhosis

Section 15.0 Reference List
Reference 12 previously read:

AbbVie. ABT-530 (Glecaprevir/Pibrentasvir) Investigator's Brochure Edition 2. 06 September 2016.

Has been changed to read:

12. AbbVie. ABT-530 (Glecaprevir/Pibrentasvir) Investigator's Brochure Edition 3. 29 August 2017.

13. Mavyret (glecaprevir and pibrentasvir tablets) [US package insert]. North Chicago, IL; AbbVie, 2017.

14. Marivet (glecaprevir and pibrentasvir tablets) [SmPC]. Maidenhead, UK; AbbVie, 2017.

15. Puoti M, et al. High SVR rates with eight and twelve weeks of pangenotypic glecaprevir/pibrentasvir: integrated efficacy analysis of genotype 1-6 patients without cirrhosis. Poster presentation at EASL 2017.

16. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-Pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. N Engl J Med. 2018;378(4):354-69.

18. Rockstroh JK, Lacombe K, Viani RM, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients co-infected with hepatitis C virus and human immunodeficiency virus-1: the EXPEDITION-2 study. Clin Infect Dis. 2018 Mar 16. doi: 10.1093/cid/ciy220. [Epub ahead of print]

Appendix B. List of Protocol Signatories
Previously read:

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

Has been changed to read:

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