1.0 Title Page

Clinical Study Protocol M16-123

An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Subjects with Genotypes 1 – 6 Chronic Hepatitis C Virus (HCV) Infection (DORA)

Incorporating Administrative Change 1 and Amendments 1, 2 and 3

AbbVie Investigational Product:	Glecaprevir/Pibrentasvir
Date:	22 March 2019
Development Phase:	2/3
Study Design:	This is a non-randomized, open-label, multicenter study.
EudraCT Number:	2016-004102-34
Investigator(s):	Multicenter. Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc.
Sponsor/Emergency Contact:	[redacted] Associate Medical Director Infectious Diseases Development [redacted] 1 North Waukegan Road North Chicago, IL 60064 Phone: Mobile: Fax: [redacted]

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

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	15 December 2016
Amendment 1	10 July 2017
Amendment 1.01	25 July 2017
Amendment 2	09 March 2018
Amendment 2.01	16 March 2018
Administrative Change 1	29 June 2018

The purpose of this amendment is to:

- Update the proposed dosing for subjects who will enroll in Cohorts 2, 3, and 4 throughout protocol.

  Rationale: *Proposed dosing for subjects in Cohorts 2, 3, and 4 have been updated, including in the Dose Selection Strategy in the Introduction, Section 3.0, sub-section titled "GLE/PIB Dose Selection Strategy for the Pediatric Population." These are the doses based on the current knowledge of the PK and safety of the pediatric doses of glecaprevir and pibrentasvir.*
- Update Section 3.3.

  Rationale: *Additional details regarding the pediatric requirement were added for completeness.*
- Update Section 5.5.2, Identity of Investigational Products, with the dose and storage requirements for the GLE/PIB granules, including the addition of a footnote.

  Rationale: *Add the final GLE and PIB doses in mg as packaged into sachets, and provide details on the use of the nomenclature "pellets" and "granules" for GLE and PIB. The nomenclature is interchangeable, as both terms refer to the same pediatric formulation, however, "granules" has been added as this is the preferred regulatory term in certain regions.*
- Update Section 6.1.5 Adverse Event Reporting

Rationale: *The SUSAR reporting process has been added as per updated company guidance.*

- Update Section 6.1.7.2 Management of ALT Elevations as per prior Administrative Change 1 dated 29 June 2018.

  Rationale: *To clarify the title of the eCRF questionnaire that would need to be completed in the event of an active Hepatitis B infection.*

- Update the primary contact in Section 7.0.
- Update Section 8.1.2 Primary, Secondary, and Efficacy Analyses

  Rationale: *To add clarification language on the pharmacokinetic analysis, and to clarify the section headers.*

- Update Section 8.1.7 Pharmacokinetic and Exposure-Response Analyses
- ***Rationale:*** *To add clarification language on the pharmacokinetic analysis.*
- Update Appendix C Treatment Period footnote j as per prior Administrative Change 1 dated 29 June 2018.

  Rationale: *To clarify in the table note j that FibroScan completion is required 6 months prior to screening, consistent with other protocol sections.*

- Update Appendix C Treatment Period footnote h and Post Treatment Period footnote b.

  Rationale: *To clarify the lab draw procedures for the coagulation panel.*

- Update Appendix C Post Treatment Period footnote f.

  Rationale: *To clarify as to when the resistance sample should be drawn during the post treatment period.*

- Increase the overall number of subjects that the study will enroll.

  Rationale: *To enroll an adequate number of subjects at the final proposed dose.*

- Update Appendix D Estimated Blood Loss for Pediatric Subjects.

  Rationale: *To reflect the maximum possible blood loss for visits as per updated blood loss calculations.*

- Update typographical errors throughout protocol.

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-123
Name of Study Drug: Glecaprevir (GLE)/Pibrentasvir (PIB)	**Phase of Development:** 2/3
Name of Active Ingredient: Glecaprevir (GLE)/Pibrentasvir (PIB)	**Date of Protocol Synopsis:** 22 March 2019
Protocol Title: An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Subjects with Genotypes 1 – 6 Chronic Hepatitis C Virus (HCV) Infection (DORA)	
Objective: Assess the pharmacokinetics, safety, and efficacy of GLE/PIB in pediatric subjects.	
Investigator: Multicenter	
Study Site: Approximately 40 sites globally	
Study Population: HCV genotype 1 – 6-infected pediatric subjects ≥ 3 to < 18 years of age, who are either treatment-naïve, treatment-experienced to interferon (IFN – alpha, beta or pegylated interferon [pegIFN]) with or without ribavirin (RBV) or treatment-experienced to sofosbuvir with IFN and/or RBV. Subjects may be non-cirrhotic or have compensated (Child-Pugh A) cirrhosis. Subjects with HCV/HIV-1 co-infection are eligible for study inclusion.	
Number of Subjects to be Enrolled: Approximately 125 subjects	
Methodology: The study will enroll approximately 125 HCV-infected pediatric subjects, divided into four (4) age groups, 3 to < 6, 6 to < 9, 9 to < 12, and 12 to < 18 years of age. Enrollment will begin in Part 1 of the study, into the age group 12 to < 18 years old who are willing to swallow the adult formulation of GLE/PIB. Part 2 of the study will enroll the remaining age groups; those will receive the pediatric formulation of GLE/PIB. Within each age group, approximately 12 HCV-infected pediatric subjects will be enrolled for intensive pharmacokinetics (IPK) in order to adequately characterize the pharmacokinetics (PK) of a particular age group for dose confirmation, and the remainder of subjects will be enrolled for the evaluation of safety and efficacy of each age group until the total pediatric study population reaches approximately 125 subjects. Additional PK assessments will be obtained for subjects enrolled in Japan for the purpose of further characterization within Japanese subjects; this is not included within the aforementioned 12 subjects. Intensive PK sampling is designed to allow for dose adjustment, based on available pharmacokinetic and clinical data to achieve therapeutic exposures that have been safe and efficacious in adult subjects. Area under the concentration curve (AUC) will be the primary measure for dose adjustment. The duration(s) of treatment will be 8, 12, or 16 weeks of therapy dependent on patient genotype, cirrhosis status, and prior HCV treatment history. All subjects who receive at least one dose of study drug will be followed for 144 weeks after completing or prematurely discontinuing the study treatment to assess long-term safety and durability of SVR_{12}.	

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female ≥ 3 to < 18 years of age at time of enrollment.
2. HCV infection demonstrated by positive anti-HCV Ab and HCV RNA ≥ 1000 IU/ mL.
3. Subject must have a weight consistent with the recommended weight band (Table 12) for their age at the time of screening. Subjects that fall out of the weight band for their age at the time of screening may be screened only into the safety and efficacy parts of the study upon TA MD approval.
4. Parent or legal guardian with the willingness and ability to provide written informed consent and subject willing and able to give assent, as appropriate for age and country.

Main Exclusion:

1. Females who are pregnant or breastfeeding.
2. Positive test result for Hepatitis B surface antigen (HbsAg) or positive test result for HBV DNA.
3. Subjects with other known liver diseases.
4. Decompensated cirrhosis defined as: presence of ascites, history of variceal bleeding, lab values consistent with Child's class B or C cirrhosis.

Investigational Products: Adult formulation: Glecaprevir/Pibrentasvir 100 mg/40 mg film-coated tablet

Pediatric formulation: Glecaprevir/Pibrentasvir 15.67%+8.25% film-coated pellets/granules

Proposed Doses:

Cohort	Age (yrs); Weight Band	GLE/PIB Dose
1	12 – < 18; ≥ 45 kg	300 mg/120 mg
2	9 – < 12 30 – < 45 kg	250 mg + 100 mg
3	6 – < 9; 20 – < 30 kg	200 mg + 80 mg
4	3 – < 6; 12 – < 20 kg	150 mg + 60 mg

Mode of Administration: Oral, taken with food

Duration of Treatment: All subjects will receive GLE/PIB for 8, 12, or 16 weeks depending on their genotype, cirrhosis, and prior treatment experience status.

Criteria for Evaluation:

Pharmacokinetic:

Plasma concentrations of GLE and PIB will be determined at each study visit for each subject during the treatment period. A single blood sample will be collected without regard to the time of dosing. For those participating in the intensive pharmacokinetic sampling, samples will be collected at the Week 2 visit immediately prior to dose (0 hour) and at 2, 4, 6, and 12 hours post dose. The pre-dose blood sample (0 hour) will be used for steady state assessment of GLE and PIB. For subjects enrolled in Japan, additional pharmacokinetic sampling will be collected at the Week 2 visit; samples will either be collected immediately prior to dose (0 hour) and at 2, 4, 6, and 12 hours post dose, or immediately prior to dose (0 hour) and at 2 and 4 hours post dose.

Efficacy:

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

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests, and vital signs. Palatability/acceptability, for the pediatric formulation only, will also be assessed.

Resistance:

The polymorphisms at signature resistance-associated amino acid positions at baseline will be tabulated and summarized for all subjects receiving study drugs in Part 1. For subjects in Part 2 of the study, baseline polymorphisms will be determined based on availability of samples. For all subjects who experience virologic failure and have an HCV RNA $\geq$ 1000 IU/mL, post-baseline substitutions relative to the baseline sequence and to the appropriate prototypic reference sequence will be tabulated and summarized.

Statistical Methods:

Pharmacokinetic:

The primary endpoint will be steady state AUC of GLE and PIB estimated by non-compartmental pharmacokinetic analysis or population pharmacokinetic analysis, including AUC at Week 2 in subjects with intensive pharmacokinetics samples and AUC in all subjects with or without intensive PK samples. The main secondary endpoint is C_{max} and clearance of GLE and PIB. Non-compartmental pharmacokinetic analysis or population pharmacokinetic analysis will be performed using intensive or overall pharmacokinetic data to facilitate potential GLE and PIB dose modification in each age group. The distribution of AUC values for GLE and PIB in each age group corresponding to the final proposed doses will be estimated. The 95% confidence interval for the geometric mean of AUC values will be calculated. Other parameters including C_{max}, C_{trough} and clearance will be estimated and summarized for each age group, and summarized separately for subjects recruited in Japan.

Statistical Methods (Continued):

Efficacy:

The secondary endpoint is the percentage of subjects who achieve SVR_{12} overall and by age group. The percentage will be calculated along with a 2-sided 95% confidence interval calculated using the normal approximation to the binomial distribution, unless the number of subjects who fail to achieve SVR_{12} is less than 5, where the Wilson's score method will be used for the confidence interval instead.

Additional secondary endpoints include the percentage of subjects who experience post-treatment relapse, the percentage of subjects who experience on-treatment virologic failure (i.e., breakthrough or failure to suppress at the end of treatment), and the percentage of subjects with new HCV infection (i.e., re-infection) at any time up to the last study visit.

Safety:

The number and percentage of subjects reporting treatment-emergent adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term overall and by age group. Laboratory samples will be collected at Baseline, at Weeks 2, 4, 8, 12 and 16 (if applicable depending on treatment duration) and at Post-Treatment Weeks 4 through 144. Laboratory values that are potentially clinically significant, according to predefined criteria, will be identified, and the percentage of subjects with potentially clinically significant values during the Treatment Period will be summarized overall and by age group. Palatability/acceptability will be assessed for the pediatric formulation only. Additional summary statistics for safety data will be performed if deemed appropriate.

Resistance:

For all subjects receiving study drugs in Part 1, and subjects with available samples in Part 2 of the study, the polymorphisms at signature resistance-associated amino acid positions at baseline identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed.

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

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AUC	Area under the concentration curve
aPTT	Activated partial thromboplastin time
APRI	Aspartate Aminotransferase to Platelet Ratio Index
ART	Antiretroviral Treatment
AST	Aspartate aminotransferase
BID	Twice Daily
BMI	Body mass index
BSA	Body surface area
BA	Bioavailability
BUN	Blood urea nitrogen
CDC	Center for Disease Control
CI	Confidence interval
CKD	Chronic kidney disease
CRF	Case report form
DAA	Direct-acting antiviral agent
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DORA	**D**AA f**O**r Cu**R**e of Hep**A**titis
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLE	Glecaprevir

GT	Genotype
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropic
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HIV Ab	Human immunodeficiency virus antibody
HIV-1	Human immunodeficiency virus type 1
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon
INR	International normalized ratio
IPK	Intensive pharmacokinetic
iPSP	Initial Pediatric Study Plan
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to treat
IU	International units
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NS3	Nonstructural viral protein 3
NS4A	Nonstructural viral protein 4A
NS5A	Nonstructural viral protein 5A
NS5B	Nonstructural viral protein 5B
PCR	Polymerase chain reaction
pegIFN	Pegylated-interferon alfa-2a or 2b
PI	Protease inhibitor
PIP	Pediatric Investigational Plan
PIB	Pibrentasvir
PK	Pharmacokinetic

POR	Proof of Receipt
PRO	Patient Reported Outcomes
PT	Post-Treatment
QD	Once daily
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Statistical Analysis System
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
SOF	Sofosbuvir
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
SVR_4	Sustained virologic response 4 weeks Post-Treatment
SVR_{12}	Sustained virologic response 12 weeks Post-Treatment
SVR_{24}	Sustained virologic response 24 weeks Post-Treatment
TA MD	Therapeutic Area Medical Director
TE	Treatment-experience
TE-PRS	Treatment-experience to interferon, pegylated interferon, ribavirin and/or sofosbuvir
TN	Treatment-naïve
ULN	Upper limit of normal
WBC	White blood cells
WOCBP	Women of Childbearing Potential

Definition of Terms

Study Drugs	Glecaprevir/Pibrentasvir
Screening Period	Up to 42 days prior to Study Day 1
Study Day 1	First day a subject takes study drugs
Treatment Period (TP)	Baseline/Study Day 1 through last dose of study drugs
Post-Treatment Period (PTP)	Day after the last dose of study drugs through Post-Treatment Week 144

Pharmacokinetic and Statistical Abbreviations

AUC	Area under the concentration curve
C_{max}	Maximum observed plasma concentration
C_{trough}	Pre-dose trough plasma concentration

2.0 Table of Contents

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3.0 Introduction

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

Prevalence data, specific to the pediatric population, is also found in NHANES (Table 1). Prevalence estimates based on diagnosed pediatric cases of HCV infection are a small fraction compared to the overall anti-HCV antibody prevalence in this population, suggesting many children are not diagnosed during childhood. The most robust estimates from NHANES come from NHANES III, which covered the years 1988 to 1994 where 2,762 and 2,905 children ages 6 to 11 and 12 to 19 years, respectively, were screened. The prevalence of anti-HCV antibody was 0.2% for children 6 to 11 years and 0.4% for children 12 to 19 years during this timeframe (genotype [GT] was not specified).[6] Estimates from the 1999 through 2002 NHANES survey also indicate a prevalence of HCV antibody in 6- to 11-year-olds of 0.2% (95% confidence interval [CI] 0.04%, 0.6%) and 0.4% (95% CI 0.2%, 0.9%) in 7- to 19-year-olds (GT not specified).[7] Similar low anti-HCV antibody prevalence rates of 0.1% were found in a cross-sectional, serologic survey of 1,034 urban children aged 1 to 11 years conducted in the years 2000 through 2002 (GT not specified).[8] In addition, a retrospective evaluation of dried heel stick blood spots from 2,806 live births in southern California in 2003 found an anti HCV antibody prevalence of 0.25% (GT not specified).[9]

Table 1. Pediatric Prevalence of HCV in the US (All Genotypes)

Population (N)	Results	Years	Source
NHANES 6 – 11 y (N = 2762) 12 – 19 y (N = 2905)	Anti-HCV 6 – 11 y 0.2% (95% CI 0.04, 0.6%) Anti-HCV 12 – 19 y 0.4% (95% CI 0.2, 0.9%)	1988 – 1994	Alter 1999[6]
Urban children 1 – 11 y (N = 1034)	Anti-HCV 0.1%	2000 – 2002	El-Kamary 2003[8]
Dried heel stick blood spots from newborn infants in CA (N = 2806)	Anti-HCV 0.25%	2003	Bradley 2011[9]
Children < 19 y in Florida (N = 4,103,700 in 2009)	Anti-HCV 0.035% (i.e., 1444/4, 201, 700). Mandatory reporting for anti-HCV: 1444 unique reports representing 11.7% of the expected population based on NHANES III estimated pediatric prevalence	2009	Delgado-Borrego 2012[7]
Optum Insight Beneficiaries < 18 y (N = 2,229,472)	2 HCV diagnostic codes: 0.004%	2000 – 2009, annual prevalence for 2009	Data on file, AbbVie
Florida Medicaid Beneficiaries < 18 y (N = 2,493,472 includes adults and children; 579 diagnosed with HCV and < 18 y)	2 HCV diagnostic codes: 0.033%	FY 1999 – 2009, annual prevalence for FY 2008 – 2009	Data on file, AbbVie

CI = confidence interval; FY = fiscal year; HCV = hepatitis C virus; NHANES = National Health and Nutrition Examination Survey; y = years

According to the Centers for Disease Control (CDC), the incidence of acute HCV infection (confirmed and reported) in the general population in the US was highest (2.4 cases per 100,000 population) in 1992;[10] generally declined until 2003, remained relatively stable until 2010, and increased 75% from 2010 to 2012, with the largest increases occurring in the population aged 0 to 19 years.[10,11] In the population aged 0 to 19 years in the US, the incidence of acute HCV infection (confirmed and reported) decreased from 0.11 to 0.05 cases per 100,000 population from 2000 to 2010[10] but increased from 0.05 to 0.11 cases per 100,000 population from 2010 to 2012.[11]

The primary differences in HCV infection between adults and pediatrics are differences in the mode of infection (e.g., perinatal transmission in children and increased intravenous drug abuse in adults) and natural history of disease. Studies comparing the natural history of HCV infection in both adults and children have been limited by small sample sizes, with an average sample size of 22 patients.[12] Despite this, progression to advanced liver disease appears to be less common in children than in adults, occurring in about 2% of pediatric patients.[13] Duration of infection appears to be an important factor accounting for this difference.[14] However, when histology was compared between 21 children and 52 adults, the children had significantly milder histologic disease and alanine aminotransferase (ALT) elevations even after controlling for duration of disease and other potentially confounding variables.[15] Differences in rates of severe disease and cirrhosis between adults and children may also be related to differences in exposure to alcohol, drugs, and superinfections more commonly found in adults.[16] Extra hepatic manifestations of HCV are rare in children, which may also reflect slower disease progression in children.[17]

During the last 10 years, vertical transmission has become the primary mode of transmission in children, and transmission via transfusion or health care is exceedingly rare in developed countries.[18] Therefore, appropriate serologic and virologic screening of infants born to HCV-infected mothers is a cornerstone of early diagnosis. In infants, the presence of anti-HCV antibody may be due to passive transplacental passage from the mother. Thus antibody testing for perinatal infection is unreliable until approximately 12 to 18 months of age. In patients with detectable antibody, diagnosis of chronic HCV infection is generally made by the persistence of HCV ribonucleic acid (RNA) for at least 6 months. In perinatal transmission, loss of HCV RNA could reflect transient viremia or a resolved infection. The chronicity rate in perinatal transmission is high; spontaneous clearance generally occurs by the third year of life, and clearance beyond age 4 is unlikely.

According to the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), all children aged 3 to 17 years who are chronically infected

with HCV may be considered candidates for treatment, and should be considered for treatment if they develop consistently elevated serum aminotransferase levels or liver fibrosis.[19] The American Association for the Study of Liver Diseases (AASLD) recommends that DAA regimens should be recommended independent of disease severity, if a regimen is available dependent upon the child's age group.[30] The combinations of ledipasvir/sofosbuvir, and sofosbuvir + ribavirin have been approved for use in adolescents, though neither combination covers all major genotypes alone.[28,29] To date, there are no treatment regimens approved for use in HCV-infected patients aged < 3 years. There are several studies of interferon-free regimens in children including sofosbuvir/ledipasvir for GT1 (NCT02249182), sofosbuvir (SOF) plus RBV for GT2 and 3 (NCT02175758), and ombitasvir/paritaprevir/ritonavir with or without dasabuvir for GT1 and GT4 (NCT02486406). Results with direct-acting antiviral (DAA) therapy are promising, showing high SVR_{12} rates in adolescents, similar to adults. In one clinical trial, 100 adolescents with GT1 infection treated with sofosbuvir/ledipasvir achieved an SVR_{12} rate of 97%.[21] A high SVR_{12} rate of 98% has also been in seen adolescents with GT2 and GT3 infection after treatment with SOF + RBV.[22]

AbbVie has developed two "next generation" DAAs Glecaprevir (GLE, formerly known as ABT-493), an HCV NS3/4A PI, and pibrentasvir (PIB, formerly known as ABT-530), an NS5A inhibitor, for use in combination for the treatment of HCV. GLE and PIB each have potent *in vitro* antiviral activity against genotypes 1 through 6,[23] 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 adult patients with a convenient once-daily (QD), fixed-dose combination treatment regimen (three tablets QD) to maximize treatment compliance. A pediatric formulation comprised of film-coated pellets/granules of GLE and PIB, respectively, in a single container for a convenient QD oral administration with a dosing vehicle has been developed.

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.[24]

Glecaprevir and Pibrentasvir (GLE and PIB)

Overview of GLE/PIB Registrational Phase 3 Program and Supportive Phase 2 Studies

The GLE/PIB registrational program included a broad subject population including subjects with compensated liver disease and subjects with severe renal insufficiency across 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-experience (TE) subjects to any combination of pegylated IFN (pegIFN), RBV, SOF, NS5A inhibitors, or PIs were allowed in the program. In addition, the program included subjects with human immunodeficiency virus (HIV) co-infection (Study M13-590), subjects with chronic kidney disease [CKD] Stages 4 – 5, including those on hemodialysis (Study M15-462), subjects with compensated cirrhosis (Studies M14-172, M15-462, and M14-868 Part 3), and subjects with or without cirrhosis who failed a previous regimen containing an NS5A inhibitor and/or an NS3/4A PI (Study M15-410).

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

Table 2. Overview of Clinical Studies by Subject Population

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

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

Efficacy

In treatment-naïve (TN) or 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 human immunodeficiency virus type 1 (HIV-1) co-infection (Table 3).

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

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

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

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}.

Impact of Baseline Polymorphisms on Treatment Outcome

The association between baseline polymorphisms and treatment outcome in subjects who receive 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.

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

Amino Acid Substitutions in Subjects Experiencing Virologic Failure

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

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

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

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

Integrated Safety Results

A summary of treatment-emergent adverse events (AEs) from pooled analyses of the registrational studies and supportive Phase 2 studies along with the AEs occurring with a frequency > 5% are headache, fatigue, nausea and diarrhea (Table 4). The majority of subjects experienced an AE, which were mostly considered to be mild in severity by the investigator (Grade 1). Rates of AEs that were serious, led to premature study drug discontinuation or had a severity Grade ≥ 3 were low. Including data from

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

Table 4. 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. One additional death occurred in Study M15-462.

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

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

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 (increase from nadir grade) and total bilirubin ≥ 2 × ULN in the context of multiple gallstones and was not consistent with 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 co-infection, and CKD Stage 4 or 5.

Common study drug-related AEs occurring in ≥ 5% of subjects were headache, fatigue and nausea. Adverse drug reactions (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.

The objectives of this study are to evaluate the efficacy and safety of GLE/PIB used together for the treatment of those with chronic HCV GT1 to 6-infection in the pediatric population.

Overview of GLE/PIB Phase 3 Clinical Studies in Japan

Two Phase 3 Studies (Studies M15-594 and M15-828) conducted in Japan enrolled 332 adults with chronic HCV GT1 – GT3 infection who were treated with GLE/PIB 300/120 mg QD for 8 or 12 weeks. These studies included treatment-naïve, both IFN based-experienced and DAA-experienced subjects, subjects without cirrhosis and with compensated cirrhosis, and with or without severe renal impairment. A high overall SVR_{12} rate of 98.3% was observed across DAA-naïve subjects treated with GLE/PIB at the recommended durations regardless of HCV genotype or comorbidities (cirrhosis or renal impairment). In addition, a high SVR_{12} rate of 93.9% was observed in subjects with previous DAA-experience who were treated with GLE/PIB for 12 weeks.

The most common AEs (≥ 5% of subjects) across the two Japan Phase 3 studies were nasopharyngitis, pruritis, and headache. The majority of TEAEs were Grade 1 or 2 in severity. Serious TEAEs, and TEAEs leading to discontinuation of study drug were rare. No TEAE deemed related to GLE/PIB occurred in ≥ 5% of subjects across the two Japan Phase 3 studies. There were no hematological or blood chemistry findings of concern. No cases of DILI or hepatic decompensation were identified. Overall, the type, frequency and severity of AEs in subjects with compensated cirrhosis were similar to subjects without cirrhosis. In addition, no unique safety signal or toxicity was identified from the use of GLE/PIB in subjects with severe renal insufficiency including those on dialysis.

GLE/PIB Dose Selection Strategy for the Pediatric Population

AbbVie's pediatric formulation development strategy is to develop a dosage form that provides suitable and flexible dosing across the pediatric age range of 3 to < 18 years. Development of a suitable pediatric formulation was guided by considerations of solubility, dose flexibility, stability, compatibility, and ease and reliability of the manufacturing process. It is likely the adult tablets will be suitable for adolescent subjects 12 years of age and older with weights ≥ 45 kg. This population is able to swallow tablets and utilizing the adult tablet would enable earlier enrollment of this population. In Part 1 of Study M16-123, a total of 47 adolescent subjects received daily administration of GLE/PIB 300 mg/120 mg. PK results showed that the exposures of GLE and PIB in HCV-infected adolescent subjects (12 to < 18 years of age) were similar to the exposures observed in HCV-infected adult subjects following administration of GLE/PIB 300 mg/120 mg.

GLE and PIB exhibit low aqueous solubility. Due to probable requirement of solvent(s) that are undesirable for pediatric patients for any oral solution, and [redacted] AbbVie developed a pediatric formulation based on the solid oral formulations used to manufacture the adult tablets.

[redacted]

To provide exposures in pediatric subjects comparable to adult exposures using the pediatric formulation, the GLE and PIB dose in pediatric patients of 3 to < 12 years of age were revised from originally proposed doses. Preliminary PK results from the initial

proposed pediatric doses demonstrated that though GLE and PIB exposures were within the range of exposure for efficacy and safety in adults for each of the pediatric cohorts, the average exposures in each of the cohorts were lower than the targeted AUC and led to a dose adjustment. Additional subjects were enrolled and the intensive PK results obtained, and additional population PK modeling performed, confirming that the adjusted doses demonstrate exposures that would allow for bridging of adult data, using a 50/20 mg dose ratio. These doses (Table 11) are proposed to be used in the subjects enrolling in the non-IPK portion of Part 2, in order to confirm that the doses would provide similar exposures observed in HCV-infected adult subjects, close to the targeted AUC.

3.1 Differences Statement

This is the first study to evaluate the pharmacokinetics, efficacy and safety of GLE/PIB in HCV-infected pediatric subjects (under 18 years old). The pharmacokinetics, safety, and efficacy of the adult formulation of GLE/PIB will be evaluated in Part 1 in 12 to < 18 years of age who can swallow the adult formulation. Part 2 will evaluate the pharmacokinetics, safety, and efficacy of the pediatric formulation in 3 to < 12 years of age. The study populations for Part 1 and Part 2 will include GT1 – 6 infected subjects with or without compensated cirrhosis. Those subjects undergoing intensive pharmacokinetic (IPK) analysis must be HCV treatment naïve and HIV negative. Subjects who are treatment experienced (prior IFN, peg-IFN, RBV, SOF) and/or co-infected with HIV-1 may enroll in the safety and efficacy portion of the study. Long-term safety and efficacy will be evaluated in a 144-week Post-Treatment Period for all subjects enrolled.

3.2 Benefits and Risks

Efficacy of GLE/PIB has been demonstrated in adult subjects with chronic HCV infection within the GLE/PIB Registrational program. Since there is no difference in disease symptomatology and only minor differences in the natural progression of disease between adults and children, which are largely age related, the effectiveness of GLE/PIB against chronic HCV infection is expected to be similar between the two populations. Part 1 of

this study encompasses those who are between the ages of 12 to < 18 years of age, and who are able to swallow the adult co-formulated fixed-dose tablets. Eligible subjects will receive GLE/PIB for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience in accordance with each developmental program (Global and Japan) for the use of GLE/PIB in adults. Part 2 of this study encompasses those who are between the ages of 3 to < 12 years of age who will take the pediatric formulation. Study drug duration will be for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience in accordance with each developmental program (Global and Japan) for the use of GLE/PIB in adults.

In the pediatric population, the risks associated with GLE/PIB, which have been limited and manageable to date, are anticipated to be similar to the adult population. The efficacy of this regimen has not yet been defined in pediatric populations, and it is possible that the treatment failure rate may be higher than what was observed in the Phase 3 trials in adults. Adverse events that are known, and those not previously described, may occur with the combination of the two DAAs, as detailed in the informed consent 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 in combination are detailed above and in the Investigator's Brochure.

Given the potential high SVR rate in populations of HCV-infected subjects, the benefit-risk profile for co-administered GLE/PIB as treatment for chronic HCV infection is favorable.

3.3 Pediatric Study Plan and Pediatric Investigational Plan

This study design was developed in accordance with the agreed initial Pediatric Study Plan (iPSP) and Pediatric Investigational Plan (PIP) for GLE/PIB for the treatment of Hepatitis C virus infection (IND Number 127,416, Reference ID: 3959249; EMA reference EMEA-001832-PIP01-15).

The Pediatric Committee (PDCO) of the European Medicines Agency (EMA) issued a positive opinion on the PIP for GLE/PIB on April 29, 2016. Upon AbbVie request, a waiver was granted for the pediatric population younger than 3 years of age "on the grounds that the specific medicinal product does not represent a significant benefit over existing treatment for pediatric patients" in this age group.

Similarly, on July 15, 2016, the FDA confirmed its agreement with the iPSP for GLE/PIB, dated June 16, 2016. In the agreed iPSP, AbbVie indicated its plans to request a waiver for the pediatric population younger than 3 years of age. On December 14, 2016, AbbVie submitted its waiver request as part of the original New Drug Application (NDA) 209394 (eCTD Sequence 0000). On August 03, 2017, FDA waived the pediatric requirement for children younger than 3 years of age because the necessary studies are impossible or highly impracticable (Reference ID: 4134372).

4.0 Study Objective

4.1 Primary Objective

The primary objectives are to:

- assess the steady state AUC, and to assess the pharmacokinetics (PK) of GLE/PIB in pediatric subjects following multiple dosing by age group;
- evaluate the safety and tolerability of GLE/PIB by age group, cirrhosis status and across all subjects

4.2 Secondary Objective

The secondary objectives are to assess:

- C_{max} and clearance of GLE and PIB,
- The percentage of subjects with sustained virologic response for 12 weeks post treatment (SVR_{12}) in HCV GT1 – 6 infected pediatric subjects summarized for each age group and overall;

- The percentage of subjects with on-treatment HCV virologic failure (i.e., breakthrough or failure to suppress at the end of treatment) summarized for each age group and overall;
- The percentage of subjects with post-treatment HCV relapse summarized for each age group and overall;
- The percentage of subjects with new HCV infection (or re-infection) summarized for each age group and overall;
- Pharmacokinetics and emergence/persistence of viral variants in subjects with available samples;
- Palatability/acceptability of pediatric formulation.

The pharmacokinetic primary and secondary objectives for subjects enrolled in Japan will be summarized separately.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

The study is designed to enroll approximately 125 subjects to meet scientific, regulatory and clinical 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. All subjects must undergo a mandatory Fibrosis Assessment prior to enrollment into Part 1 or Part 2 of the study (refer to Section 5.3.1.1 for more details).

Part 1 of the study allows for enrollment of approximately 44 HCV infected, GT1 – 6 pediatric subjects into the 12 to < 18 years old age group who weigh ≥ 45 kg and are able to swallow (whole tablets – without crushing or breaking) the adult formulation of GLE/PIB. Part 2 of the study allows for enrollment of approximately 81 HCV infected, GT1 – 6 pediatric subjects divided into the 3 to < 6, 6 to < 9 and 9 to < 12 years old age groups. Subjects will receive the pediatric formulation of GLE/PIB in Part 2.

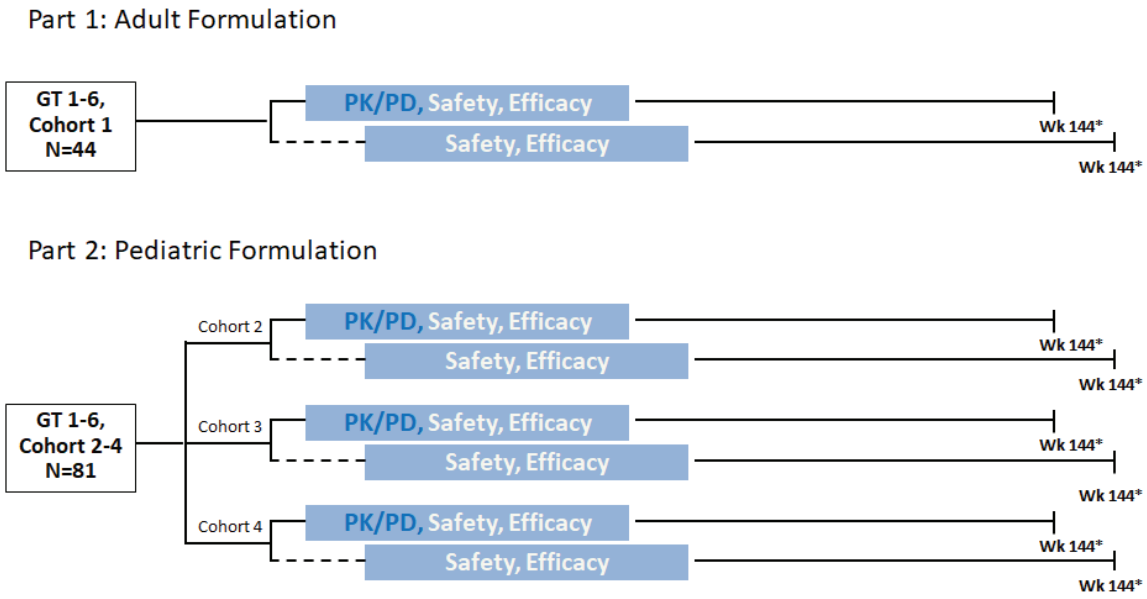
Each age group in Part 1 and Part 2 will enroll approximately 12 HCV infected subjects to adequately characterize the pharmacokinetics of a particular age group. Those individuals will undergo an intensive PK sample draw at the Week 2 visit with blood samples taken immediately prior to dose (0 hour) and at 2, 4, 6, and 12 hours post dose. After the approximately first six (6) subjects per age cohort complete the intensive PK at the Week 2 visit, the PK samples of those subjects will be analyzed to determine dose adjustments of GLE/PIB in an age cohort, if needed. After the intensive PK analysis results are available, enrollment will resume with approximately six (6) additional subjects per age cohort and intensive PK of all approximately twelve (12) subjects will be evaluated to determine if the study drug doses have achieved therapeutic exposures which have been demonstrated to be safe and efficacious in adult subjects. Additional subjects may be required for further intensive PK analysis per age cohort if therapeutic exposure targets have not been achieved. Once doses have been confirmed based on intensive PK data for a respective age group, enrollment into the safety/efficacy portion of that age group may begin.

For each subject enrolled into the intensive PK portion, the initial dose of GLE/PIB will be based on the subject's body weight and age at screening (Table 11). Enrollment will first start into the intensive PK portion of Part 1 for the 12 to < 18 years old age group. Once the pediatric study drug formulation is available, Part 2 enrollment will be opened. Pediatric subjects will be enrolled first into the intensive PK portion of each of the Part 2 age groups (3 to < 6, 6 to < 9, and 9 to < 12 years) in parallel.

Enrollment for subjects in Japan in Part 1 and Part 2 will start upon dose confirmation of the intensive PK portions of the study. Eligible Japanese subjects will be given the option to participate in Japan specific intensive PK sampling (J-IPK) to maximize data collection and to better characterize GLE and PIB exposures in children in Japan. Consent to collect blood samples up to 12 hours post dose (0, 2, 4, 6, and 12 hours) will be requested of all participants from Japan. However, if patients are not willing to participate in the J-IPK portion of the study then a reduced number of PK samples will be collected at the Week 2

visit immediately prior to dose (0 hour) and at 2 and 4 hours post dose. At least 2 to 3 subjects will be enrolled in each of the age cohorts in Part 1 and Part 2 at sites in Japan.

Figure 1. Study Schematic



The intensive PK portions of Part 1 and Part 2 will allow enrollment of pediatric subjects with or without compensated cirrhosis who are treatment naïve and who meet the weight bands for their age (Table 11). The HCV genotype must be identified (i.e., Screening laboratory result indicating HCV genotype 1, 2, 3, 4, 5, or 6-infection) for those participating in the intensive PK portions of the study. The safety/efficacy portion of both Part 1 and Part 2 will include pediatric patients with or without compensated cirrhosis that are treatment naïve or treatment experienced (prior IFN [alpha, beta or pegIFN], RBV or SOF exposure), with or without HIV-1 co-infection, or subjects with mixed or indeterminate HCV genotype.

Pediatric subjects that fall outside of the weight bands for their age (Table 11) may be included in the safety and efficacy parts of Part 1 and Part 2 only with approval of the AbbVie Therapeutic Area Medical Director after consideration of risks and benefits. All

subjects will receive GLE/PIB for 8, 12 or 16 weeks, depending on their HCV genotype, cirrhosis and prior HCV treatment status. No dose adjustments of GLE/PIB will be made as a consequence of weight change during the Treatment Period. For patients with an indeterminate or mixed genotype including GT3, treatment duration will default to the respective GT3 duration based upon treatment-experience and cirrhosis status. Patients with a mixed GT other than GT3, treatment duration will default to the longer treatment duration based on GT, treatment-experience and cirrhosis status.

Both Parts 1 and 2 will consist of a Screening Period (Section 5.1.1), a Treatment Period (Section 5.1.2), and a Post Treatment Period (Section 5.1.3). Subjects who prematurely discontinue during the Treatment Period in Part 1 or Part 2 will be followed-up in the Post-Treatment Period through Week 144. After completing the Treatment Period in Part 1 or Part 2, the subjects will be followed-up for 144 weeks in the Post-Treatment Period. Subjects who prematurely discontinue from the Post-Treatment Period will be discontinued from the study.

The pharmacokinetic and clinical data from age groups of 3 to < 6, 6 to < 9, and 9 to < 12 years old may be combined for final analyses if exposures from these three (3) age groups are comparable to each other.

In both Parts 1 and 2, for each of the analytes (GLE and PIB), the geometric mean and individual AUC values from these pediatric subjects from the Week 2 intensive PK sampling will be compared with the distribution of individual AUCs across Phase 2/3 studies in adults on an ongoing basis. Dose adjustments may be made for each component of the DAA regimen if the respective geometric mean AUC in pediatric subjects is significantly deviated from the geometric mean AUC values in adults.

AUC will be the primary measure for dose adjustment. Other pharmacokinetic exposure parameters including C_{max} and C_{trough} will be considered to provide similar therapeutic exposures that have been safe and efficacious in adult subjects.

Additional safety and efficacy criteria may be considered for making dose adjustment decisions for Parts 1 and 2 to ensure safe and efficacious exposures.

5.1.1 Screening

Prior to any study specific procedures being performed on the subject at the Screening Visit for Part 1 or Part 2, parent(s)/guardian(s) must provide written (signed and dated) informed consent and the subject must provide assent (as appropriate for age and country) respectively.

Subjects will receive a unique subject number via the Interactive Response Technology (IRT) system and will undergo the study procedures identified in Section 5.3.1 associated with the Screening Visit. The investigator or his/her designated and qualified representatives will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 for the Part in which they are enrolling during the period from the Screening Visit through Study Day 1 prior to dosing and record the results of this assessment and the details of the informed consent and assent process in the subject's medical records.

Eligible subjects have up to 42 days following the Screening Visit to enroll into Part 1 or Part 2 of the study.

5.1.1.1 Rescreening

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

- A positive Hepatitis B surface antigen (HBsAg);
- Hepatitis B DNA > lower limit of quantitation (LLOQ);
- A positive serum pregnancy test (if female).

Otherwise, subjects may be retested or rescreened only once before requiring approval from the Primary Therapeutic Area Medical Director to rescreen again.

Retesting:

Subjects who have exclusionary laboratory parameter(s) per Exclusion Criterion 8 (Section 5.2.2) are allowed to retest on the related panel(s) (e.g., exclusionary albumin requires a repeat chemistry panel) within the same screening period and must meet all other eligibility laboratory criteria on the panel that is repeated. If the retest result(s) are also exclusionary, the subject may only be rescreened or retested again with approval from the Primary Therapeutic Area Medical Director.

Rescreening:

Subjects that exceed the initial 42-day screening period should be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary at the first screening attempt (with the exception of HBsAg, Hepatitis B virus (HBV) DNA, and positive serum pregnancy test) (Section 5.2.2).

The Primary Therapeutic Area Medical Director should be contacted for approval prior to rescreening. Subjects that are beyond the initial 42-day screening period may still be allowed to enroll within a reasonable time period if they continue to meet all eligibility criteria and have received approval by the Primary Therapeutic Area Medical Director. If rescreened, the 42 day screening period restarts, and subjects retain their initial subject number.

For subjects who rescreen and still do not meet the study eligibility criteria upon retest/rescreen, the site personnel must register the subject as a screen failure in both IRT and electronic data capture (EDC) systems.

5.1.2 Treatment Period (TP)

After meeting all the eligibility criteria, subjects will be enrolled to a study regimen according to their genotype, cirrhosis and prior HCV treatment status as shown in Table 5. for global subjects and Table 6 for subjects in Japan. The treatment duration for subjects in Japan is consistent with the currently proposed label in Japan. There are some minor differences from the Global regimen, mostly in subpopulations not common in Japan

(e.g., GT5 and 6) after review of the Japan specific Registrational program, consisting of majority GT1 and 2.

Table 5. Treatment Regimen and Duration (Excluding Subjects in Japan)

Patient Population	Duration
GT1 – 6 NC, TN GT1, 2, 4 – 6 NC, TE	8 weeks
GT1 – 6 C, TN GT1, 2, 4 – 6 C, TE	12 weeks
GT3 TE	16 weeks

Legend: C = Cirrhotic; NC = Non-Cirrhotic; TE = Treatment experienced to IFN (alpha, beta or pegIFN) ± RBV or SOF/RBV ± pegIFN; TN = Treatment Naïve

Table 6. Treatment Regimen and Duration (Subjects in Japan)

Patient Population	Duration
GT1 – 2 NC, TN, TE – IFN	8 weeks
GT1 – 2 C, TN, TE – IFN GT3 – 6 NC, C, TN, TE – IFN GT1 – 6 TE – SOF	12 weeks

Legend: C = Cirrhotic; NC = Non-Cirrhotic; TE – IFN = Japan Treatment experienced to IFN (alpha, beta or pegIFN) ± RBV; TE – SOF = Japan Treatment experienced to SOF/RBV; TN = Treatment Naïve

GLE/PIB will be administered as described in Section 5.5.1 (Treatments Administered). Subjects and their parent(s)/guardian(s) will receive instructions about the study drugs at the Day 1 Visit. The study drugs will be dispensed at the visits as indicated in Appendix C.

After the Day 1 visit, all subjects will continue to return to the site on an outpatient basis for the study visits and procedures as identified in Appendix C. Subjects could also return to the site for an unscheduled study visit for additional safety assessments if the investigator or sponsor feels it is necessary. Sites should ensure that subjects adhere to the study visits listed in Appendix C. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drug prior to their next study

visit. Study drug compliance is critical to ensure adequate drug exposure and optimal treatment outcome.

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 5.5.1. Ideally, this should occur on the day of study drug discontinuation, but is recommended to be no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy if applicable. Following completion or premature discontinuation of study drug treatment, all subjects in either Part 1 or Part 2 will be followed in the associated Post-Treatment Period of Part 1 or Part 2.

5.1.3 Post-Treatment Period

All subjects who receive at least one dose of the study drug will enter into the Post-Treatment Period. The Post-Treatment will begin the day following the last dose of study drug treatment and continue through Week 144 as outlined in Appendix C. Subjects who prematurely discontinue during the Post-Treatment Period should return to the site for a discontinuation visit and undergo the study procedures as outlined in Appendix C.

Subjects may also return to the site for an unscheduled study visit for additional safety assessments if the investigator or sponsor feels it is necessary.

The Post Treatment Period will assess safety, antiviral response, and growth and development.

Growth and development will be assessed using BMI, weight z score, height z score, and growth rate at Post-Treatment Weeks 12, 48, 96, 144. Growth rate is defined as the change in height over change in age from the previous visit.

5.2 Selection of Study Population

The study population in Parts 1 and 2 consists of HCV genotype 1 – 6-infected pediatric subjects (ages 3 < 18 years of age) with or without compensated cirrhosis who are naïve to HCV treatment or who are IFN (IFN or pegIFN with or without RBV) or SOF/RBV treatment experienced. Subjects who are co-infected with HIV-1 may be enrolled in the study.

Subjects who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

1. Male or female ≥ 3 to < 18 years of age at time of enrollment.
2. Willingness to participate in the study for up to 40 months.
3. If female, subject must be either pre-menarche and not sexually active, permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) OR for Women of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Screening through at least 30 days after the last dose of study drug.

For male subjects, no contraception is required.

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

   Females of non-childbearing potential (as defined above) at Screening do not require pregnancy testing.

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

6. Chronic HCV infection defined as being positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening.

7. Subjects participating in the intensive pharmacokinetic part, must be HCV treatment-naïve, with or without compensated cirrhosis (Child-Pugh A), HIV-1 negative and must have a Screening laboratory result indicating HCV genotype 1, 2, 3, 4, 5, or 6-infection.

8. Subject screened into the safety and efficacy part must be HCV treatment-naïve (i.e., subject has not received a single dose of any approved or investigational anti-HCV medication) or HCV treatment experienced (subject has failed prior treatment with IFN [alpha, beta or pegIFN] with or without RBV or sofosbuvir with RBV with or without pegIFN), with or without compensated cirrhosis. Previous HCV treatment must have been completed ≥ 2 months prior to screening.

9. Subject co-infected with HIV-1 must be on a stable antiretroviral therapy (ART) for at least 8 weeks prior to screening, consisting of the qualifying ART regimens as outlined in Section 5.2.3.1 (Concomitant HIV-1 Antiretroviral Therapy). HIV-co-infected subjects are eligible for enrollment into the safety and efficacy parts of the study.

10. Subjects on a stable ART regimen must have the following:

    - CD4+ count ≥ 200 cells/mm^3 (or CD4+ % ≥ 14%) at Screening, and
    - Plasma HIV-1 RNA less than 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once during the

12 months prior to Screening (by an approved plasma HIV-1 RNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTi*m*e HIV-1 assay).

11. Subject must have a weight consistent with the recommended weight band (Table 11) for their age at the time of screening. Subjects that fall out of the weight band (Table 11) for their age at the time of screening, may be screened into the safety and efficacy parts of the study upon therapeutic area medical director (TA MD) approval.

12. For subjects in Part 1: Willingness to swallow tablets.

13. Parent or legal guardian with the willingness and ability to provide written informed consent and subject willing and able to give assent, as appropriate for age and country.

Rationale for Inclusion Criteria

1, 2, 5 – 12	In order to select the appropriate subject population with appropriate disease characteristics for evaluation
3, 4	The impact of GLE/PIB on pregnancies has not been established. However, assessment of the complete nonclinical reproductive toxicology studies indicates that there is no drug-related effect on teratogenicity/fetotoxicity. In addition, the compounds are non-genotoxic
13	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

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

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.

2. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol in the opinion of the investigator.
3. Clinically significant abnormalities or co-morbidities, other than HCV infection that make the subject an unsuitable candidate for this study in the opinion of the investigator.
4. Any cause of liver disease other than chronic HCV infection including but not limited to the following:
    - Hemochromatosis
    - Alpha-1 antitrypsin deficiency
    - Wilson's disease
    - Autoimmune hepatitis
    - Alcoholic liver disease
    - Steatohepatitis on liver biopsy considered to be the primary cause of the liver disease rather than concomitant/incidental with HCV infection.
5. Current HBV infection on screening tests, defined as:
    - A positive test result for HBsAg, or
    - HBV DNA > LLOQ in subjects with isolated positive Anti-HBc (i.e., negative HBsAg and Anti-Hbs).
6. Current enrollment in another interventional clinical study, previous enrollment in this study, prior or current use of any investigational DAA or commercially available anti-HCV agents (other than IFN [alpha, beta or pegIFN], RBV or SOF), including telaprevir, boceprevir, ombitasvir, dasabuvir, paritaprevir, ledipasvir, velpatasvir, daclatasvir, simeprevir, elbasvir or grazoprevir.
7. History of solid organ transplant.
8. Screening laboratory analyses showing any of the following abnormal laboratory results:
    - Albumin < 2.8 g/dL

- Platelets < 40,000 cells per mm^3
- Direct bilirubin > 2.0 mg/dL

9. Any current or past clinical evidence of Child-Pugh B or C Classification (Child-Pugh Score ≥ 7) or clinical history of liver decompensation such as ascites (noted on physical exam), variceal bleeding or hepatic encephalopathy.
10. Confirmed presence of hepatocellular carcinoma indicated on imaging techniques such as computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or on an ultrasound performed at Screening for subjects with cirrhosis (a positive ultrasound result will be confirmed with CT scan or MRI).
11. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive Glecaprevir/Pibrentasvir.
12. History of severe, life-threatening or other significant sensitivity to any excipients of the study drugs.
13. Subjects who cannot participate in the study per local law.

Rationale for Exclusion Criteria

1, 3, 5, 7 – 13	To ensure safety of the subjects throughout the study
2, 6	To avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications
4	To exclude subjects with liver diseases other than chronic HCV GT1 to 6 infection

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving from the time of signing the consent through the Treatment Period and 30 days after study drugs are stopped, must be recorded in the electronic case report form (eCRF) along with the reason for use,

date(s) of administration including start and end dates, and dosage information including dose, route and frequency. The investigator should review all concomitant medications for any potential interactions.

For subjects on an HIV-1 ART: information regarding each subjects qualifying, stable HIV-1 ART medications including start date, dose and frequency will be recorded into the eCRF at Screening. In addition, subjects will be requested to record in a HIV-1 Medication Card, the information for the last two doses of their HIV-1 ART medications taken (dosing dates, times, and number of pills) prior to the study visits detailed in Appendix C, and site personnel will record this information in the eCRF.

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

5.2.3.1 Concomitant HIV-1 Antiretroviral Therapy

Qualifying HIV-1 Antiretrovirals allowed within this study are as follows:

- Raltegravir (RAL) PO BID
- Dolutegravir (DTG) PO QD or PO BID
- Rilpivirine (RPV) PO QD
- Tenofovir disoproxil fumarate (TDF) PO QD
- Tenofovir alafenamide (TAF) PO QD
- Abacavir (ABC) PO QD or BID
- Emtricitabine (FTC) PO QD
- Lamivudine (3TC) PO QD or BID

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

5.2.3.2 Prior HCV Therapy

For Parts 1 and 2, prior or current use of any investigational or commercially available anti-HCV agents other than IFN, pegIFN, RBV, or SOF, excludes a subject from this study. Subjects who previously participated in trials of investigational anti-HCV agents may be enrolled if they can produce documentation that they received only placebo or only SOF/RBV.

Subjects could be HCV treatment-naïve or prior treatment experienced. Prior treatment, such as interferons, with or without RBV, or SOF plus RBV with or without pegIFN, is acceptable. Subjects will be categorized as:

- Treatment-naïve: subject has never received any treatment for HCV infection.
- Subjects **with an allowed prior treatment** will be categorized as:
  - **Non-responder:** HCV RNA detected at the end of a prior treatment course (except for breakthrough, which is captured separately). These subjects are further categorized as:
    - Null responder: failed to achieve a 1 $\log_{10}$ IU/mL reduction in HCV RNA by Week 4 or a 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior treatment course;
    - Partial responder: achieved at least a 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior treatment course but failed to achieve HCV RNA undetectable at the end of treatment;
    - Unknown or unable to specify: insufficient data to categorize as null or partial responder.
  - **Breakthrough:** confirmed $\geq$ 1 $\log_{10}$ IU/mL increase from nadir or achieved HCV RNA undetectable (or unquantifiable) during a prior treatment course but HCV RNA was quantifiable during or at the end of treatment.

- **Relapse:** achieved HCV RNA undetectable at the end of a prior treatment course but HCV RNA was detectable following cessation of therapy.
- **Other:** subject received a prior treatment course and reason for not achieving SVR is other than above.
- **Unknown:** subject received a prior treatment course and reason for not achieving SVR is unknown.

Subjects must have discontinued prior therapy at least 2 months prior to the Screening Visit in order to be eligible for the study.

5.2.3.3 Concomitant Therapy

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

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.

5.2.3.4 Prohibited Therapy

Subjects must be able to safely discontinue any prohibited medications or supplements listed in Table 8 at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of GLE/PIB and not use these during the entire Treatment Period and for 14 days following discontinuation of study drugs.

Table 7. Prohibited Medications and Supplements

Medication or Supplement Name
Any herbal medicines or supplements [including milk thistle, red yeast rice (monacolin K), St. John's Wort]
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin*
Astemizole, cisapride, terfenadine
Atazanavir, efavirenz, etravirine, nevirapine
Pitavastatin, bosentan, oxcarbazepine, silodosin
Ethinyl estradiol-containing contraceptives

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drugs. Subjects receiving these statins should either (a) switch to pravastatin or rosuvastatin 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drugs 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 or limit the pravastatin or rosuvastatin dose in accordance with the GLE/PIB product label (if approved in the country); or 2) reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drug if GLE/PIB is not yet approved in the country.

Use of ethinyl estradiol containing oral contraceptives with GLE and PIB combination was associated with ALT increases in some healthy female subjects. Hormonal contraceptives (including oral, topical [including vaginal rings], injectable, or implantable varieties) containing ethinyl estradiol may not be used from 2 weeks prior to the first dose of GLE/PIB until 14 days after the end of GLE/PIB dosing. Progestin-only contraceptives, such as those containing norethindrone, desogestrel, or levonorgestrel, without ethinyl estradiol, may be used with GLE/PIB. Hormone replacement therapy i.e., estradiol, esterified or conjugated estrogens, as long as they do not contain ethinyl estradiol, may be used with GLE/PIB at the discretion of the Investigator.

GLE/PIB is not recommended for use in patients requiring stable cyclosporine doses > 100 mg per day. GLE/PIB may be initiated in subjects receiving cyclosporine ≤ 100 mg per day and cyclosporine doses may be adjusted up to 400 mg per day following standard therapeutic monitoring practices.

5.2.4 Contraception Recommendations and Pregnancy Testing

The contraception recommendations in this paragraph are summarized in relation to the potential risk of the investigational products used in this study. All female subjects who are experiencing menses or are nearing sexual maturation in the opinion of the Investigator, or who are of child-bearing potential should undergo pregnancy testing according to Section 5.3.1.1.

If female, subject must be:

- Pre-menarche and not sexually active, or
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), or
- Practicing at least one of the following methods of birth control, starting at Screening (or earlier) through at least 30 days after stopping study drug.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion/ligation.
- Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success, and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Male or female condom with or without spermicide. Condom without spermicide is acceptable only in countries where spermicide is not available.
- Cap, diaphragm or sponge with spermicide.
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier method).

- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

For Japan specific sites: Note that both contraceptive sponge and vaginal ring with spermicidal jellies or creams are unapproved in Japan.

For male study subjects no contraception is required.

5.3 Efficacy, Pharmacokinetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Study Procedures

The study procedures outlined in Appendix C are discussed in detail in this section with the exception of the assessment of concomitant medications (Section 5.2.3), and the collection of adverse event information (Section 6.0). All study data will be recorded in the subject's source documentation and then on the appropriate eCRFs, with the exception of laboratory data which will be provided to the Sponsor electronically from the laboratory(ies).

Informed Consent/Assent

Signed study-specific informed consent and assent (as appropriate for age and country) will be obtained from the parent(s)/guardian(s) and subject before any study procedures are performed. If a subject becomes of legal age during the course of the study, the subject will need to be consented using the approved informed consent form. Details

about how informed consent and assent will be obtained and documented are provided in Section 9.3.

Medical History

A complete medical history, including history of tobacco, nicotine containing products and alcohol use, will be taken from each subject during the Screening Visit. An updated medical history will be obtained prior to study drug administration and will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will be performed at visits specified in Appendix C. 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.

Vital Signs, Weight, Height and Body Mass Index (BMI)

Body temperature, blood pressure, pulse, body weight, height, and BMI will be measured at the visits specified in Appendix C, or upon subject discontinuation. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes. The vital signs performed on Study Day 1 will serve as the baseline for clinical assessment. Height will be measured standing without shoes using a stadiometer.

12-Lead Electrocardiogram

The ECG obtained at Screening will serve as the baseline assessment. The ECG should be performed prior to blood collection. An ECG can be performed at subsequent visits if deemed clinically necessary.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign, and date 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 8 at the visits indicated in Appendix C.

An overview about the volume of blood drawn for each of the study visits is listed in Appendix D of this protocol. The Investigator/designee should refer to the local recommendations on blood drawn in pediatric patients (e.g., the guide on *"Ethical Considerations for Clinical Trials on Medical Products With the Pediatric Population" or "Blood Drawing For Human Subject Research" by Duke University*). The Investigator/designee should document exceptions to the local blood loss recommendations in the subject's source along with a justification as appropriate.

At the Study Day 1 visit, a blood sample is to be collected prior to the first dose of study drug which is to be administered at site during the visit. Subjects should be reminded to eat prior to their first dose of study drug after the sample is collected (e.g., suggest they bring a light snack). 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 certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study. The certified laboratory chosen for this study is Covance. Samples will be sent to the following address:

North and South American sites:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214-2985 USA
Tel: (317) 271-1200
Fax: (317) 273-4030

European sites:

Covance Central Laboratory Services
Rue Moïse-Marcinhes 7
1217 Meyrin/Genève-CH
Tel: +41 58-822-7000
Fax: +41 58-822-6999

Japanese sites:

Covance Central Laboratory Services
c/o BML General Laboratory
1361-1, Matoba, Kawagoe City
Saitama, Japan 350-1101
Tel: +81-3-6837-9536
Fax: +81-3-6220-3667

Table 8. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Additional Tests
Hematocrit	Blood Urea Nitrogen (BUN)	Anti-HCV Ab[c]
Hemoglobin	Creatinine	Anti-HIV Ab[c]
Red Blood Cell (RBC) count	Total bilirubin[a,b]	FSH[f]
White Blood Cell (WBC) count	Direct and indirect bilirubin	Urine and Serum Human Chorionic Gonadotropin (hCG)[g]
Neutrophils	Serum glutamic-pyruvic transaminase (SGPT/ALT)	HCV RNA
Bands, if detected	Serum glutamic-oxaloacetic transaminase (SGOT/AST)	HCV genotype and subtype[c]
Lymphocytes	Albumin[a]	HBsAg[c,h]
Monocytes	Alkaline phosphatase	Anti-HBcIgM[h]
Basophils	Sodium	Anti-HBc Total[c,h]
Eosinophils	Potassium	Anti-HBs[c,h]
Platelet count (estimate not acceptable)	Calcium	HBV DNA[k]
Prothrombin Time/INR[a]	Inorganic phosphate	Anti-HAVIgM[h]
Activated partial thromboplastin time (aPTT)	Total protein	Anti-HAVIgG[h]
Urinalysis	Glucose	Anti-HEVIgG[h]
Specific gravity	Bicarbonate/CO_2	Anti-HEVIgM[h]
Ketones	Chloride	HEV RNA[h]
pH	Magnesium	HIV-1 RNA[i]
Protein	Creatinine clearance (Cockcroft-Gault calculation for subjects ≥ 12 years old and Schwartz formula for those < 12 years old)	Flow Cytometry[i]
Glucose	Alpha2-macroglobulin[b]	HIV Resistance[j]
Blood	Gamma-glutamyl transferase (GGT)[b]	
Urobilinogen	Haptoglobin[b]	
Bilirubin	Apolipoprotein A1[b]	
Leukocyte esterase	Alpha fetoprotein	
Microscopic (reflex)	Gamma-globulin[d]	
	Hyaluronate[d]	
	eGFRJ (MDRD modified)[e]	

a. Also a component of the Child-Pugh Assessment.

b. Also a component of FibroTest.

c. Performed at Screening.

d. For Japan subjects only: Component of Discriminant Score and collected only if needed during the Screening Period.

e. eGFR calculated by the MDRD formula, modified for the Japanese population.

f. Performed only at Screening. FSH will be taken for female subjects aged ≥ 9 to <18 years old.

Table 8. Clinical Laboratory Tests (Continued)

g. Serum and urine pregnancy testing only required for female subjects who are experiencing menses or are nearing sexual maturation in the opinion of the PI, or who are of child-bearing potential.
h. Performed for management of transaminase elevation (Section 6.1.7.2).
i. Only for HCV/HIV co-infected subjects.
j. Only in HCV/HIV co-infected subjects who develop plasma HIV-1 RNA level ≥ 500 copies/mL after starting the study.
k. Performed at Screening for subjects who have occult HBV infection (positive Anti-HBc Total with negative HBsAg and Anti-HBs) and also performed for management of transaminase elevation (Section 6.1.7.2).

Palatability Questionnaire (Acceptability Questionnaire)

The parent(s)/guardian(s) of the subject will complete a Palatability Questionnaire to provide feedback on the perception of the dosage form of the pediatric formulation in Part 2. The parent(s)/guardian(s) of the subject will be asked of their overall impression towards the dosage form and the administration via dosing vehicle to the subject; such as duration of administration, volume of dosing vehicle, swallowability, and the convenience of administration.

The questionnaire will be completed at the visits as indicated in Appendix C. The parent(s)/guardian(s) will indicate their answers on the questionnaire, which will be kept as part of the study record and transcribed into EDC by site personnel. Site personnel will encourage completion of the questionnaire at all applicable visits and will ensure that a response is entered for all items.

Pregnancy Testing

Females of non-childbearing potential (either pre-menarche and not sexually active or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing. All female subjects who are experiencing menses or are nearing sexual maturation in the opinion of the Investigator, or who are of child-bearing potential:

- A serum pregnancy test will be performed for all female subjects of childbearing potential at Screening. Additional urine pregnancy tests will be

performed at all visits indicated in Appendix C. Pregnancy testing is not required for females of non-childbearing potential.

- Urine pregnancy testing will be performed on-site during the study visit if there is a scheduled visit. The pregnancy result will be captured in the source document and recorded in the eCRF by site personnel. If there is not a scheduled study visit, subjects may either have pregnancy testing performed at the site as an unscheduled study visit or a urine pregnancy test may be conducted by the subject at home with a pregnancy test kit provided by the site. If a urine pregnancy test is performed at home, site personnel should contact these female study subjects to capture the results of any study-related pregnancy tests in the source records only.
- If a urine pregnancy result is positive, a confirmatory hCG serum test should be collected and sent to the central lab.

Concomitant Medication Assessment

Please refer to Section 5.2.3.

Hepatitis B and HIV Screen

HBsAg (hepatitis B surface antigen), anti-HCV Ab and anti-HIV Ab will be performed at Screening. A positive anti-HIV Ab test must be confirmed for subjects without a previous history of HIV infection. The investigator or his/her representatives must discuss any local reporting requirements to local health agencies with the subject's parent(s)/legal guardian(s). The site will report these results per local regulations, if necessary.

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/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. 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.

Historical Liver Biopsy or FibroScan or Screening FibroTest

An assessment of liver fibrosis is mandatory prior to enrollment. Subjects with no history of cirrhosis that have not had a liver biopsy within 24 months or FibroScan within 6 months prior to screening will undergo a non-invasive FibroTest to determine presence or absence of cirrhosis.

Subject must be documented as non-cirrhotic or cirrhotic defined as meeting one of the following criteria:

Non-Cirrhotic

- A liver biopsy within 24 months prior to or during Screening demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, New Inuyama, or Laennec fibrosis score of ≤ 3, Ishak fibrosis score of ≤ 4; or
- A FibroScan® score of < 12.5 kPa within ≤ 6 months of Screening or during Screening period; or
- A Screening FibroTest score of ≤ 0.72

Cirrhotic

- Previous histologic diagnosis of cirrhosis on liver biopsy, e.g., METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, New Inuyama, or Laennec fibrosis score of > 3, Ishak score of > 4 or on a liver biopsy conducted during Screening; or
- A FibroScan® score of ≥ 12.5 kPa within ≤ 6 months of Screening or during Screening period; or
- A Screening FibroTest result that is > 0.72.

The resulting cirrhosis status and HCV genotype/subtype will be documented via recording in the Interactive Response Technology (IRT) system for each subject to determine the duration and regimen of the study drug for each subject.

For subjects participating in sites specific to Japan, cirrhosis determination may be performed (in addition to the methods listed above) using the following Discriminant Score criteria at the time of screening:

- Non-Cirrhotic: screening Discriminant Score (z) less than zero, according to the following formula: $z = 0.124 \times [\text{gamma-globulin (\%)}] + 0.001 \times [\text{hyaluronate } (\mu g \times l^{-1})] - 0.075 \times [\text{platelet } (\times 10^4 \text{ cells/mm}^3)] - 0.413 \times \text{gender (male, 1; female, 2)} - 2.005$.
  - Subjects with indeterminate Discriminant Score (score = 0), must have a qualifying FibroScan® or liver biopsy.
- Cirrhotic: screening Discriminant Score (z) greater than zero, according to the following formula: $z = 0.124 \times [\text{gamma-globulin (\%)}] + 0.001 \times [\text{hyaluronate } (\mu g \times l^{-1})] - 0.075 \times [\text{platelet } (\times 10^4 \text{ cells/mm}^3)] - 0.413 \times \text{gender (male, 1; female, 2)} - 2.005$.
  - Subjects with indeterminate Discriminant Score (score = 0), must have a qualifying FibroScan® or liver biopsy.

Longitudinal Fibrotest and APRI

All subjects will undergo assessment of FibroTest and APRI at Screening or Day 1 and FibroTest and APRI at PT Weeks 12, 48, 96 and 144 or premature discontinuation. Any subject that does not have a FibroTest and APRI performed during Screening will have them performed at Day 1.

Child-Pugh Score and Category

The Child-Pugh score will be calculated and documented prior to Day 1 visit for cirrhotic subjects only. Subjects who were considered to be non-cirrhotic at the screening visit but identified as cirrhotic (according to definitions listed here) during the screening process will return to the site prior to the Day 1 visit for Child-Pugh assessment. Any subject with a Child-Pugh > 6 prior to the Day 1 visit will no longer be eligible for study participation.

The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments). Child-Pugh score will be determined at the screening visit as indicated in Appendix C. The Child-Pugh score will be automatically calculated prior to Day 1 by EDC (RAVE) once the investigator or designated site personnel enters the subject's parameters (as listed in Table 9). A total score of 5 – 6 is considered Class A (compensated disease); 7 – 9 is Class B (significant functional compromise); and 10 – 15 is Class C (decompensated disease).

Table 9. Child-Pugh Classification of Severity of Cirrhosis

	Points Assigned for Observed Findings		
	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)

* 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.

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

Hepatocellular Carcinoma Screening: Liver Ultrasound and Alpha Fetoprotein

In order to monitor for the presence of hepatocellular carcinoma (HCC), an ultrasound of the liver and alpha fetoprotein testing will be performed as indicated in Appendix C for subjects with compensated cirrhosis only.

Subjects with a historical negative liver ultrasound, CT or MRI (within 3 months prior to screening) are not required to undergo a screening ultrasound.

A positive ultrasound result suspicious for HCC during the treatment or Post-Treatment Period will be confirmed with CT scan or MRI.

HCV Resistance Testing Plasma Sample

A plasma sample for baseline HCV resistance testing will be collected on Day 1 from all subjects in Part 1, and from subjects in Part 2 in which the sample for baseline HCV resistance testing will be within the allowable blood volume limits. HCV resistance testing is required for all subjects who meet virologic failure criteria at the visits indicated in Appendix C. Specific instructions for preparation and storage of the samples will be provided by the central laboratory, the Sponsor, or its designee.

Flow Cytometry, HIV-1 RNA and HIV Resistance Testing Samples

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

If a subject's HIV-1 RNA level is ≥ 200 copies/mL, the subject's HIV-1 RNA is to be repeated as noted in Section 5.4.1.2. At the time the repeat plasma HIV-1 RNA is drawn, a sample should be obtained for HIV-1 genotypic resistance testing. If the subject's repeat HIV-1 RNA is ≥ 500 copies/mL, the sample obtained for HIV-1 genotypic resistance testing may be analyzed.

HIV-1 protease (PR), reverse transcriptase (RT) and integrase (IN) sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assay.

If the subject's repeat HIV-1 RNA is < 200 copies/mL, then the subject will resume routine plasma HIV-1 RNA assessments as shown in Appendix C and described in Section 5.4.1.2.

Specific instructions for preparation and storage of flow cytometry, plasma HIV-1 RNA, and HIV resistance samples, if applicable, will be provided by the central laboratory, AbbVie, or its designee.

Patient Reported Outcomes (PRO) Instrument (PedsQL)

Subjects will complete the PRO instrument, PedsQL, with the assistance of a parent/guardian (where allowed per local regulatory guidelines) on the study days specified in Appendix C. The PRO should be administered as the first procedure at each visit. Subjects will be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Site personnel will encourage completion of each instrument at all applicable visits and will ensure that a response is entered for all items.

The PedsQL Generic Core Scales is a 23 item questionnaire designed to measure the core dimension of health as defined by the World Health Organization (WHO), in addition role (school) functioning. The PedsQL consists of 4 Multidimensional Scales (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and 3 Summary Scores (Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score). Completion of the PedsQL should take around 4 minutes to complete. Subjects who are older than 5-years of age and are able to read and understand the questions should complete the questionnaire by themselves. For subjects who are 5-years of age or younger or who are not comfortable with reading the questions, their parent(s)/guardian(s) should complete the parent/guardian proxy-report.

Assignment of Subject Numbers

A subject number is assigned at screening via IRT system. Subject numbers will be unique 6-digit numbers and will begin with [redacted]

[redacted] Enrolled subjects will keep their subject number throughout the study.

Study Drug Dispensation

Study drugs will be dispensed at the visits as indicated in Appendix C.

Study Drug Dosing Card

Study drug dosing cards will be dispensed to subjects in Part 1 and Part 2 at the study visits indicated in Appendix C. Parent(s)/legal guardian(s) and the subject will be instructed by the site to record the date and time (to the nearest minute) of the 2 study drug doses prior to each scheduled visit in the treatment periods of Part 1 and Part 2. The subject must bring the completed study drug dosing card with them to each visit. Site personnel will record the information from the completed dosing card into the eCRF and file the completed dosing card in the subject's source documents. In the event that the dosing card is not available, the site may obtain dosing information via parent(s)/legal guardian(s) and/or subject interview and record this information into the eCRF and into the subject's source documents.

HIV-1 Medication Card

HIV medication cards will be dispensed to HIV co-infected subjects in Part 1 and Part 2 at the study visits indicated in Appendix C. Parent(s)/legal guardian(s) and the subject will be instructed by the site to record the date and time (to the nearest minute) of the 2 study drug doses prior to each scheduled visit in the treatment periods of Part 1 and Part 2. The subject must bring the completed HIV medication card with them to each visit. Site personnel will record the information from the completed HIV medication card into the eCRF and file the HIV medication card in the subject's source documents. In the event that the HIV medication card is not available, the site may obtain HIV medication information via parent(s)/legal guardian(s) and/or subject interview and record this information into the eCRF and into the subject's source documents.

Study Drug Compliance

At the Study Drug accountability visits noted in Appendix C, the returned study drug will be accounted for by the study site and recorded electronically in the IRT system. Additional information regarding treatment compliance can be found in Section 5.5.6.

5.3.1.2 Meals and Dietary Requirements

Subjects should be reminded that, in order to maximize absorption, each dose of the study drugs should be taken with food. Subjects who participate in the Week 2 intensive PK analysis should be instructed to not have a full meal before the visit, so that study drugs can be taken with food during the visit.

All study drugs should be dosed together and administered with food, i.e., the morning dose of GLE/PIB should be taken together with food.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

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

Study treatment visits will occur at Day 1, Week 2, Week 4, Week 8, Week 12 and Week 16 if applicable.

Subjects Who Participate in the Intensive PK Sample Collection of Part 1 and Part 2, and Subjects in Japan Who Consent to J-IPK:

The PK samples will be collected at the following time points:

- Day 1: 4 hours post-dose (the morning doses will be administered with food in the clinic)
- Week 2: immediately prior to dose (0 hour), 2, 4, 6, and 12 hours post dose (the morning doses will be administered with food in the clinic)

- Other visits (Week 4, 8, 12, and 16 if applicable): a PK sample regardless of the dosing time

Subjects in Japan Unwilling to Participate in J-IPK Sample Collection of Part 1 and Part 2:

- Day 1: 4 hours post-dose (the morning doses will be administered with food in the clinic)
- Week 2: immediately prior to dose (0 hour), 2 and 4 hours post dose (the morning doses will be administered with food in the clinic)
- Other visits (Week 4, 8, and 12 if applicable): a PK sample regardless of the dosing time

Subjects Who do not require Intensive PK Sample Collection (Not Applicable for Subjects in Japan):

The PK samples will be collected at the following time points:

- Day 1: 4 hours post-dose (the morning doses will be administered with food in the clinic)
- Other visits (Week 2, 4, 8, 12, and 16 if applicable): a PK sample regardless of the dosing time

The date and time of each blood sample collection and the two doses of study drugs prior to each blood sample collection will be recorded to the nearest minute in the source documents if applicable. Additionally, the date and time of the two doses of study drugs prior to each blood sample collection will be recorded to the nearest minute on the eCRF if applicable. The time that each blood sample is collected will be recorded to the nearest minute on the lab requisitions.

For subjects who participate in the intensive PK sample collection, the maximum amount of blood drawn for pharmacokinetic samples will be approximately 10 mL during a 24-hour period (at Week 2) and approximately 14 mL during the 30-day period from Day 1 to Week 4 and additional 2 ml PK blood drawn at each following study visit during

treatment period as indicated in Appendix D. For subjects who participate in the sparse PK sample collection, the maximum amount of blood drawn for pharmacokinetic samples will be approximately 2 mL at each study visit during treatment period and approximately 6 mL during the 30-day period from Day 1 to Week 4 as indicated in Appendix D.

For subjects in Japan who do not consent to intensive PK sample collection, the maximum amount of blood drawn for pharmacokinetic samples will be approximately 6 mL during a 4-hour period (at Week 2) and approximately 10 mL during the 30 day period from Day 1 to Week 4 and additional 2 mL PK blood drawn at each following study visit during treatment period as indicated in Appendix D.

5.3.2.2 Handling/Processing of Samples

Specific instructions for collection of blood samples and subsequent preparation and storage of the plasma samples for the pharmacokinetic assays of GLE, possible GLE metabolites, PIB, and possible PIB metabolites 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, possible GLE metabolites, PIB, and possible PIB metabolites will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory.

Specific instructions for shipping to the analytical lab from the central laboratory will be provided by the central laboratory, the Sponsor, or its designee.

The central laboratory will then ship the plasma samples to:

Sample Receiving
[redacted]
c/o: Delivery Services
1150 S. Northpoint Blvd.
Waukegan, IL 60085

Phone: [redacted]
Fax:
Email:

An inventory of the samples included will accompany the package and an electronic copy of the Manifests (including subject number, study day, the time of sample collection and barcode) will be sent to the contact person at [redacted]

5.3.2.4 Measurement Methods

Plasma concentrations of GLE and PIB will be determined using validated analytical methods under the supervision of the [redacted] Plasma concentrations of possible metabolites of GLE and PIB may also be determined using validated or non-validated methods.

5.3.3 Primary and Secondary Variables

5.3.3.1 Primary Variables

The primary PK endpoints from Part 1 and Part 2 are:

Steady state AUC values for GLE and PIB estimated by non-compartmental analysis or population pharmacokinetic analysis, including AUC at Week 2 in subjects with intensive PK samples and AUC in all subjects with or without intensive PK samples.

5.3.3.2 Secondary Variables

The secondary endpoints in Part 1 and Part 2 are:

- C_{max} and clearance of GLE and PIB at Week 2
- Percentage of subjects with SVR_{12} by age group and overall

- The percentage of subjects with on-treatment virologic failure (i.e., breakthrough or failure to suppress at end of treatment) by age group and overall
- The percentage of subjects with post-treatment relapse by age group and overall
- The percentage of subjects with new HCV infection (i.e., re-infection) at any time up to the last study visit by age group and overall
- Assessment of palatability/acceptability of the pediatric formulation

The pharmacokinetic primary and secondary objectives for subjects enrolled in Japan will be summarized separately.

5.3.4 HCV Resistance Variables

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

The following resistance information will be analyzed for subjects receiving GLE/PIB who do not achieve 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 sequences, 2) the amino acid substitutions in available post-baseline samples at signature resistance-associated positions identified by NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral substitutions by NGS.

5.3.5 Safety Variables

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

5.3.6 Growth and Development Variables

The following evaluations for growth and development outcomes will be analyzed during the study: growth rate, weight and height z score, and BMI standardized score.

5.3.7 Pharmacokinetic Variables

Individual plasma concentrations of GLE and PIB will be measured for Part 1 and Part 2.

Values for the pharmacokinetic parameters of GLE and PIB including the C_{max}, T_{max}, C_{trough}, and area under the concentration curve (AUC) will be determined by non-compartmental methods using data from subjects who participate in the initial intensive PK sample collection and evaluation.

Individual model-predicted steady-state AUC values for GLE and PIB corresponding to the final proposed doses will be estimated by population pharmacokinetic analysis.

Additional parameters may be determined if useful in the interpretation of the data.

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 a subject prematurely discontinues during the Treatment Period, Post-Treatment Period or the Long-term Follow-up Period, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Appendix C. Ideally for study drug discontinuation, 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 and monitored for HCV RNA and the emergence and persistence of resistant viral substitutions in the post-treatment period. The last dose of any study drug and reason for discontinuation from the Treatment Period will be recorded in the EDC system.

If a subject has an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range at the time of study drug discontinuation, 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 DAAs may be continued at the investigator's discretion after discussion with the subject and parent(s)/guardian(s), if the benefit of continuing DAAs is felt to outweigh the potential risk. Specific instructions regarding subject pregnancy can be found in Section 6.1.6. Subjects will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

5.4.1.1 HCV Virologic Failure Criteria

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

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

When confirmatory testing is required it should be completed as soon as possible and the subject should remain on study treatment until the HCV virologic failure criterion has been confirmed. Subjects meeting a virologic failure criterion will be discontinued from

study drug and will continue to be followed in the Post-Treatment Period for the emergence and persistence of resistant viral variants until 144 weeks post-treatment.

5.4.1.2 Failure to Maintain HIV Virologic Suppression

HIV-1 RNA will be assessed at scheduled study visits during the Treatment and Post-Treatment Period, as detailed in Appendix C.

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

- HIV-1 RNA ≥ 200 copies/mL confirmed on 2 consecutive tests at least 2 weeks apart, in a subject compliant with their HIV ART therapy.

At the time a confirmatory HIV-1 RNA is drawn, a sample for HIV-1 genotypic resistance testing should also be obtained; this sample may be analyzed if the subject's repeat plasma HIV-1 RNA is ≥ 500 copies/mL. A subject should remain on HCV study drug treatment and his/her current ART regimen while the failure to maintain HIV virologic suppression is being confirmed. A confirmatory HIV-1 RNA and HIV-1 genotypic resistance blood draw can be done as an unscheduled visit. However, if this blood draw falls on the date of

a scheduled study visit (Appendix C), only a single HIV-1 RNA and HIV-1 genotypic resistance blood draw needs to be performed at this visit.

During the Treatment Period, subjects with confirmed failure to maintain HIV-1 RNA suppression should continue study drug treatment unless there is a requirement for prohibited concomitant medications (see Section 5.2.3.1) to construct a new HIV ART regimen.

Clinical management of failure to maintain HIV-1 virologic suppression during the study (Treatment Period and Post-Treatment Period) will be handled by the site investigator according to current HIV treatment guidelines and local standard of care.

If the investigator wishes to change the HIV-1 ART regimen for a subject, it must be discussed with the AbbVie Study Designated Physician prior to the change being made, unless the change is being made to address an immediate safety concern.

5.4.2 Discontinuation of Entire Study

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

5.5 Treatments

5.5.1 Treatments Administered

Each dose of open-label DAA study drugs (GLE and PIB) will be dispensed in the form of adult co-formulated tablets or a pediatric formulation. Study drugs will be dispensed at the visits listed in Appendix C.

Part 1 Adult Formulations:

The study drug (GLE/PIB) will be dispensed in the form of co-formulated tablets at the visits listed in Appendix C. Subjects will be instructed to take study drugs at the same time every day with food. Subjects will be instructed to swallow study drugs whole. Prior to all visits with pharmacokinetic sampling, the date and time of the two previous doses will be recorded to the nearest minute in the source documents and the eCRF.

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.

Part 2 Pediatric Formulation:

Glecaprevir and Pibrentasvir (GLE/PIB) will be provided by the Sponsor as separate 15.67% and 8.25% film-coated pellets/granules. GLE/PIB will be taken orally and will be dosed QD based on body weight/age.

The film-coated pellets/granules are packed in unit doses and are to be administered at once QD into a dosing vehicle. The legal guardian(s) should be counselled by site to check that the study drug units have been emptied completely into the dosing vehicle to assure the complete dose is taken by the subject. A reference to the dosing vehicles is included in the dosing card to be used for Part 2.

For both Parts 1 and 2, on the morning of Study Day 1, at the site, subjects will be administered study drugs by the study site personnel and receive instructions for self-administration of all study drugs from the Day 1 through study Week 8, 12, or 16, depending on subject's genotype, treatment-experience and cirrhosis status, of the Treatment Period. The date and time of administration of the first dose of each drug will be recorded in the subject's source and eCRF.

Following enrollment, the site will use the IRT system for drug dispensation. Study drugs must not be dispensed without contacting the IRT system, and only for subjects enrolled in the study through the IRT system.

All subjects who receive at least one dose of study drugs who fail to achieve virologic suppression, or who experience virologic breakthrough on DAA therapy will be discontinued from treatment and enter the Post-Treatment Period, unless alternative management is agreed to with Primary Therapeutic Area Medical Director. The investigator can prescribe another regimen, as deemed appropriate, which will not be provided or reimbursed by AbbVie.

5.5.2 Identity of Investigational Products

Information regarding the study drugs to be used in this study is presented in Table 10.

Table 10. Identity of Investigational Product

Study Part	Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
1	GLE/PIB	AbbVie	Oral	film-coated Tablets	100 mg/40 mg
2	GLE	AbbVie	Oral	film-coated pellets	15.67%
2	PIB	AbbVie	Oral	film-coated pellets	8.25%
2	GLE/PIB	AbbVie	Oral	Film-coated granules[a]	50 mg/20 mg unit dose

a. Film-coated pellets and granules are the same formulation, and the terminology is considered interchangeable. They are listed separately, however, to reflect the changes in the packaging and labeling from pellets in bottles to granules in sachets.

5.5.2.1 Packaging and Labeling

Adult Formulation:

The adult formulation study drug will be supplied in bottles.

Each bottle will be labeled 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.

Pediatric Formulation:

The pediatric formulation study drug will be supplied in bottles to be used in the intensive PK portion of the study. The study drug to be used in the sparse PK portion will be supplied in sachets.

Each study drug unit will be labeled per country requirements.

The labels must remain affixed to the study drug units. 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
GLE/PIB film-coated Tablets	15° to 25°C (59° to 77°F)
GLE/PIB film-coated pellets	15° to 25°C (59° to 77°F), Protect from moisture
GLE/PIB film-coated granules	2° to 25°C (36° to 77°F)[a]

a. Film-coated pellets and granules are the same formulation and terminology is considered interchangeable. They are listed separately, however, to reflect the changes in the packaging and labeling from pellets in bottles to granules in sachets.

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 the AbbVie. The GLE/PIB Pediatric formulation will be supplied in bottles or in sachets in the intensive PK or in the sparse PK portions of the study, respectively. The Pediatric formulation can be administered in a dosing vehicle as outlined on the dosing card applicable for Part 2. Upon receipt of study drugs, the site will acknowledge receipt within the IRT system.

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 (or who are unable to enroll before enrollment has closed), the site personnel must contact the IRT system and identify the subject as a screen failure.

First, the subjects in the ≥ 12 to 18 year age group of the intensive PK portion of Part 1 who are ≥ 45 kg and willing to swallow the adult formulations will be enrolled. Enrollment into the safety/efficacy portion of Part 1 will begin when the dosing recommendations of GLE/PIB adult formulation are available based on the pharmacokinetic and clinical data from the intensive PK part of Part 1 (Section 5.1). Enrollment into the intensive PK portion of Part 2 will begin with the current proposed doses in Table 11. Enrollment into the safety/efficacy portion of each of the age groups in Part 2 will begin when the dosing recommendations per age group of GLE/PIB pediatric formulation are available based on the pharmacokinetic and clinical data from the intensive PK part of Part 2 (Section 5.1). Subjects who are enrolled will retain their subject number assigned at the Screening Visit throughout the study.

In Part 1 of the study, the cap on the number of subjects in IRT will be employed to ensure that approximately 44 subjects are enrolled.

In Part 2 of the study, caps on the number of subjects in each age group (3 to < 6, 6 to < 9, 9 to < 12 years of age) will be employed in IRT to ensure that approximately 22 subjects on the final recommended dose regardless of prior treatment experience and cirrhotic status are enrolled per age group.

Contact information and user guidelines for IRT use will be available for each study site.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.6.5. The daily dose for each subject in Part 1 will be assigned by IRT as the standard 300/120 mg dosing. The daily

doses for Part 2 of the study will be assigned by IRT as Glecaprevir 15.67% and Pibentasvir 8.25%.

Study drug dosing will be initiated at the Study Day 1 Visit. GLE/PIB will be dosed QD. All study drugs should be dosed together and administered with food at approximately the same time every day.

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.

All study drugs will be dispensed to subjects by study-site personnel under the direction of the investigator. At the start of the study, each subject along with their parent(s)/guardian(s) should receive counseling regarding the importance of dosing adherence with the treatment regimen with regard to virologic response and potential development of resistance. The start and stop dates of all study drugs will be recorded in the source documents and eCRFs.

During the Treatment Period, subjects will be instructed to bring all study drug units (full, partial or empty) to the study site at each study visit. The study site personnel will inspect the contents of the study drug units and account for the returned study drug electronically at each Study Drug Accountability visit indicated in Appendix C. If poor adherence is noted, the subject and parent(s)/guardian(s) should be counseled and this should be documented in the subject's source document.

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 per subject by the investigator. An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the Treatment Period. The monitor will review study drug accountability on an ongoing basis. Final accountability will be verified by the monitor at the end of study drug treatment at the site.

During the study, should an enrolled subject misplace or damage a study drug unit, the IRT system must be contacted and informed of the misplaced or damaged study drug. If the study drug unit 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 subject's source. Date of the first dose and the last dose of the regimen will be documented in the subject's source documents and recorded on the appropriate eCRF.

The return status of each study drug unit and the date of reconciliation will be documented at Study Drug Accountability Visits in Appendix C.

Detailed instructions regarding study drug accountability are provided below.

Adult Formulation

The number of tablets of each type of study drug returned in each bottle will be noted in the IRT system and on a drug accountability log (if appropriate). Labels must remain affixed to the bottles.

Pediatric Formulation

The status of each returned bottle or sachet will be noted in the IRT system and on a drug accountability log (if appropriate). The Investigator/designee must document the status of the returned bottles or sachets as "full sealed" or "empty" or "unsealed but not empty" in the IRT system. Labels must remain affixed to the bottles.

Upon completion of or discontinuation from the Treatment Period, all original study drug units (containing unused study drugs) will be returned to the Sponsor (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. All empty original study drug units shall be disposed of onsite following completion of study drug accountability and reconciliation procedures. Labels must remain attached to the study drug units.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design

The combination regimen of GLE/PIB completed registrational Phase 3 trials in adults in several countries including the US, the EU, and Japan. The dose, durations, and regimens have been optimized in adults. These same durations and regimens are anticipated to be similarly successful in children as long as the drug exposures are comparable, so further regimen/duration exploration is not warranted. In addition, no interferon-free regimens or ribavirin free regimens are approved for use in children less than 12 years old; the historical standard of care (pegIFN/RBV) has notably lower efficacy rates and a worse safety profile than the interferon-free DAA regimens and requires longer treatment duration, making a comparative study unethical and difficult to enroll. A non-randomized study design with regimens/duration and drug exposure comparable to the recommended adult regimens is the best method for evaluation.

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. The PedsQL instrument is standard in the literature and thoroughly validated in studies of the pediatric population and in pediatric subjects who have chronic health conditions.

5.6.3 Suitability of Subject Population

This is a multicenter, Phase 2/3, open label study in treatment naïve and treatment experienced HCV GT1 – 6 infected pediatric subjects, with and without compensated cirrhosis, with or without HIV-1 co-infection, designed to evaluate the pharmacokinetics, safety, and efficacy of GLE/PIB administered QD for 8, 12 or 16 weeks. Evaluation for the treatment duration is supported by the data from the Registrational program with high SVR and favorable safety profile in adults. Evaluation of the dosages to be used in this population is supported by current pharmacokinetic data in adults, based on multiple Phase 1 and 2 studies, with modeling to support the intended pediatric dosing.

This study plans to enroll subjects from ≥ 3 to < 18 years old with genotype 1 – 6 HCV infection as agreed upon in the Pediatric Investigation Plans (PIP) and Pediatric Study Plan (PSP). The older subjects who are willing to swallow the adult formulations and are ≥ 45 kg will be studied using the adult co-formulated tablets. A pediatric formulation of the DAAs has been developed for children in the ≥ 3 to < 12 year old age groups.

5.6.4 Selection of Doses in the Study

In the PIP and the PSP for Glecaprevir/Pibrentasvir, the proposed pediatric doses were targeting providing comparable exposures to adult subjects.

AbbVie has developed a separate pediatric formulation for GLE + PIB for use in Part 2 of the present study.

The mg doses for a given weight range for each of the age groups as proposed in the PIP and PSP were adjusted to express each age group dose as a multiple of a proposed unit

dose of a sachet, which provides a simplified dosing approach for patients and physicians and is expected to help reduce potential dispensing and dosing errors while meeting the objectives of the weight based dosing. Given the wide therapeutic window of GLE and PIB, the updated doses will not anticipate to change the efficacy/safety profiles.

For the present study, the final proposed doses by weight band range are shown in Table 11.

Table 11. Proposed Glecaprevir and Pibrentasvir Doses for the Pediatric Population

Formulation	Age Group (yrs) & Weight Band (kg)	Final Proposed Doses (mg)	
		Glecaprevir	Pibrentasvir
Pediatric formulation	3 to < 6 yr 12 to < 20 kg	150	60
	6 to < 9 yr ≥ 20 to < 30 kg	200	80
	9 to < 12 yr ≥ 30 to < 45 kg	250	100
Adult formulation	12 to < 18 yr ≥ 45 kg	300	120

The doses of the pediatric formulation were adjusted based upon the intensive pharmacokinetic analysis of the first approx. 17 subjects enrolled across the age cohorts. The final proposed dosing for each age cohort has been confirmed by additional IPK analysis. These drug dose changes are included in this protocol amendment. Dose adjustments were made as necessary to ensure safe and efficacious exposures, but did not exceed the adult dose of 300/120 mg of GLE/PIB.

For Part 1, enrollment commenced with pediatric subjects ≥ 12 to < 18 years old who are ≥ 45 kg and willing to swallow the adult formulation. Part 2 enrollment initiated in pediatric subjects ≥ 3 to < 12 years old with the pediatric formulation. Based on current modeling and available PK data at the completion of the IPK portion of Part 2, the above proposed doses of the pediatric formulation are the target doses for use in children

< 12 years of age. The pharmacokinetic and clinical data will be used to confirm appropriate exposure in each of the ≥ 3 to < 12 years old age groups.

Details on the dose adjustment considerations for Part 1, the enrollment sequence in Part 1, and the considerations for enrollment in Part 2 are provided in Section 5.1.

5.6.5 Maximum Dose

For Parts 1 and 2, the maximum dose of GLE and PIB will not exceed 300 mg and 120 mg per day for 16 weeks.

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

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

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

ADL = Activities of Daily Living

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

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

6.1.3 Relationship to Study Drug

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

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

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

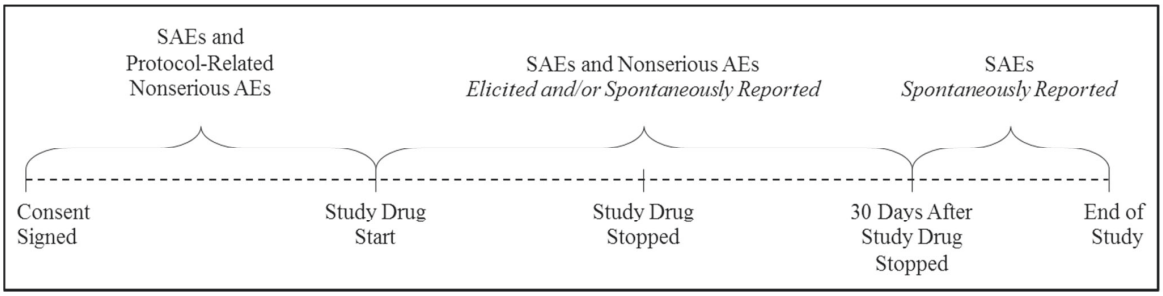
For serious adverse events, if an investigator's opinion of "no reasonable possibility of being related to study drug" is given, an "Other" cause of event must be provided by the investigator.

6.1.4 Adverse Event Collection Period

All serious adverse events as well as protocol-related non-serious 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 (non-serious AEs will not be collected).

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

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

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

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Antiviral Safety Team at:

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

Office: [redacted]
Email:

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

Primary Therapeutic Area Medical Director:

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

Telephone Contact Information:
Office:
Fax:
Mobile:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup Primary Therapeutic Area Medical Director:

Phone: [redacted]

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

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 5.4.1.

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

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

6.1.7 Toxicity Management

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

Specific toxicity management guidelines apply to the instances of increases in ALT (Section 6.1.7.2).

Where an interruption is required the study drugs should not be interrupted for more than 7 days. If study drugs need to be interrupted for more than 7 days, the Primary Therapeutic Area Medical Director should be contacted and consideration should be given to discontinue the subject.

6.1.7.1 Severe Adverse Events

If a subject experiences a severe adverse event (Grade 3+) or a serious adverse event that the investigator considers to have a reasonable possibility of relationship to study drug, the investigator should assess whether the adverse event can be managed medically without interruption of study drug, or whether study drugs should be interrupted until the event improves. If study drugs are interrupted and restarted and the adverse event recurs, then study drugs should be permanently discontinued.

If a subject experiences a severe adverse event (Grade 3+) or serious adverse event that is considered unrelated (no reasonable possibility) to the study drugs, it is not necessary to interrupt study drugs unless an interruption is required because of the nature of the event (e.g., unable to take oral medications).

The investigator should ensure that all serious adverse events are reported to AbbVie within 24 hours of awareness. Serious adverse event follow-up information, including associated dose interruptions (or discontinuations), must be reported to AbbVie within 24 hours of awareness by entering updated SAE information into the appropriate eCRFs.

Severe adverse events and any associated dose interruptions (or discontinuations) should be entered into the appropriate eCRFs.

6.1.7.2 Management of ALT Elevations

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

- Evaluate for alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain additional testing as appropriate.
- Evaluate for a new viral hepatitis infection, including hepatitis A, B and E.
    - If the subject is found to have an active hepatitis B infection, additional evaluation by completion of the eCRF Transaminase Elevations Questionnaire should be performed by the investigator.

- Manage the subject as medically appropriate.
- Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and international normalized ratio (INR) within 1 week. Repeat liver chemistries as indicated until resolution.
- Discontinue study drugs 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 Primary Therapeutic Area Medical Director.

If the investigator wishes to pursue alternative management of study drugs in the setting of confirmed ALT increases described above, then approval of the Primary Therapeutic Area Medical Director must be obtained.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any complaint (see Section 6.0 for the definition) related to the drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

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

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

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

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

7.0 Protocol Deviations

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

Primary Contact:	Alternate Contact:
[redacted] Study Management Associate [redacted] One North Waukegan Road North Chicago, IL 60064	[redacted] Study Project Manager AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen, Germany
Office: [redacted]	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.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The analysis of pharmacokinetic endpoints will be performed when 12 subjects complete the 2 week intensive PK (IPK) measurements, and these analyses will be done within each age group. For subjects enrolled in Japan, the pharmacokinetic parameters will be summarized separately.

The efficacy, durability of response, resistance, growth and development, patient-reported outcomes, and safety analyses will be performed by age group and overall (across Parts 1 and 2 combined).

The first interim analysis will occur once all subjects participating in IPK in Part 1 complete PT Week 12 or prematurely discontinue from the study. A second interim analysis will occur once all subjects in Part 1 complete PT Week 12 or prematurely discontinue from the study. A third interim analysis will occur once all subjects participating in the IPK portion in Part 2 complete PT Week 12 or prematurely discontinue from the study. A fourth interim analysis will occur once all subjects in

Parts 1 and 2 complete PT Week 12 or prematurely discontinue the study. Final analysis will occur after the completion of the whole study.

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

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

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

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

No data will be imputed for any efficacy or safety analysis except for analyses of SVR endpoints (HCV RNA data). HCV RNA values will be selected for the analyses of all SVR endpoints (e.g., SVR_4, SVR_{12}, and SVR_{24}) based on defined statistical visit windows. A backward imputation method will be used to impute missing responses for SVR analyses. Detailed statistical methods for all endpoints will be provided in the Statistical Analysis Plan (SAP).

8.1.1 Demographics

Demographics and baseline characteristics will be summarized by age group and overall. As a sensitivity analysis, subjects who receive a dose lower than the final dose chosen for the subject's age group might be summarized separately. The baseline value refers to the last non-missing measurement collected before the first dose of study drug is received in Part 1 or Part 2. Demographics include age, birth year, weight, height, body mass index (BMI), BMI z score (BMI z score will be calculated using WHO published BMI-for-age

z-score tables), weight and height z scores (weight and height z scores will be calculated using WHO published weight-for-age z-score and height-for-age z-score tables), gender, race ethnicity, geographic region and country. Baseline characteristics will include HCV genotype, prior HCV treatment history if applicable, baseline platelets (< 90 or $\geq 90 \times 10^9$/L), baseline albumin (< 35 or ≥ 35 g/L), baseline alpha fetoprotein (< 20 or ≥ 20 ng/mL), baseline HCV RNA levels (continuous) and (< 1,000,000, ≥ 1,000,000 to < 2,000,000, ≥ 2,000,000 IU/mL), baseline fibrosis stage (F0-1, F2, F3, F4), baseline Fibrotest score, baseline APRI, and baseline Child-Pugh score (non-cirrhotic, 5 or 6).

Descriptive statistics will be provided, such as the number of observations (N), mean, and standard deviation (SD) for continuous variables (e.g., age, weight and height z-score) and counts and percentages for discrete variables (e.g., gender and race).

8.1.2 Primary, Secondary, and Efficacy Analyses

The primary and secondary analyses of PK parameters will be performed on subjects in the ITT population with available PK samples, unless otherwise specified.

All efficacy analyses will be performed on the ITT population unless otherwise specified. Subjects who receive a dose lower than the final dose chosen for the subject's age group might be summarized separately. Efficacy analyses will be performed within each age group and overall population.

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

8.1.2.1 Primary Endpoints

The primary endpoint will be steady state AUC of GLE and PIB estimated by non-compartmental pharmacokinetic analysis or population pharmacokinetic analysis,

including AUC at Week 2 in subjects with intensive pharmacokinetics samples and AUC in all subjects with or without intensive PK samples. The 95% confidence interval for the geometric mean of AUC values will be calculated. For subjects enrolled in Japan, the pharmacokinetic parameters will be summarized separately.

8.1.2.2 Secondary Endpoints

The secondary endpoints are:

1. C_{max} and clearance of GLE and PIB at Week 2;
2. The percentage of subjects with SVR_{12} by age group and overall;
3. The percentage of subjects with on-treatment virologic failure (i.e., breakthrough, defined as confirmed increase of > 1 log_{10} IU/mL above nadir during treatment or 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) by age group and overall;
4. The percentage of subjects with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment; excluding subjects who have been shown to be re-infected) by age group and overall;
5. The percentage of subjects with new HCV infection (i.e., re-infection) at any time up to the last visit by age group and overall;
6. Assessment of palatability/acceptability of the pediatric formulation by age group and overall.

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

In addition, a summary of reason for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse, reinfection, other) will be provided for each age group.

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

For the assessment of palatability/acceptability, the number and percentage of subjects with each categorical answer marked will be presented for each question in the palatability questionnaire at each applicable treatment visit by age group and overall. A listing of palatability questionnaire results and comments for each applicable subject over applicable treatment visits will be produced.

8.1.2.3 Additional Efficacy Endpoints

1. The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
2. The percentage of subjects with SVR_4 by age group and overall;
3. The percentage of subjects with SVR_{24} by age group and overall;
4. The percentage of subjects who relapsed after achieving SVR_{12} by age group and overall;
5. Change from baseline to all post-baseline visits in Fibrotest score and APRI by age group and overall.

All rates will be presented with 2-sided 95% confidence intervals using the Wilson's score method.

In addition, a summary of reason for SVR_{24} non-response (e.g., on-treatment virologic failure, relapse, reinfection, other) will be provided for each age group.

8.1.2.4 Subgroup Analysis

The number and percentage of subjects with SVR_{12} will be presented along with the 2-sided 95% confidence interval for the following subgroups if applicable. The subgroup analysis might be restricted to subjects who receive the final dose for the corresponding age group.

- HCV genotype;
- Prior HCV treatment history;
  - For treatment experienced subjects, type of non-response to previous treatment;
- Sex (male or female);
- Baseline fibrosis stage (F0-F1, F2, F3 or F4);
- Baseline HCV RNA level (< 1,000,000, ≥ 1,000,000 to < 2,000,000, ≥ 2,000,000 IU/mL);
- Race (Black versus non-black);
- Ethnicity (Hispanic/Latino versus none);
- Geographic region (North America, Europe, Japan);
- Country (as appropriate);
- Height z-score (< –1, –1 to 1 or > 1);
- BMI z-score (< 25, ≥ 25 to < 30, or ≥ 30 kg/m^2);
- Drug compliance (< 80% versus ≥ 80%);
- In adolescents, former injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no);
- Baseline platelets (< 90, ≥ 90 × 10^9/L);
- Baseline albumin (< 35, ≥ 35 g/L).

The two-sided 95% confidence intervals will be produced using the Wilson's score method if there are at least 10 subjects in the subgroups.

8.1.2.5 Sensitivity Analysis

As sensitivity analyses, the number and percentage of subjects in the mITT-VF population achieving SVR_{12}, as applicable, will be summarized along with a two-sided 95% confidence interval using the normal approximation and a two-sided 95% confidence interval using the Wilson's score method. The two-sided 95% confidence interval using Wilson's score method will also be calculated as a sensitivity analysis for SVR_{12} based on ITT population.

8.1.3 Growth and Development

The following growth and development endpoints will be calculated in the ITT population.

- Growth rate at Post-Treatment Weeks 12, 48, 96 and 144 (defined as change in height over change in age from the previous visit)
- Weight z score[25]
- Height z score[25]
- Body mass index (BMI) z score[25]

Growth rate will be summarized with N, mean and SD together, median and range together at each applicable post baseline visit by gender for all and for age group separately. Weight, height and BMI z scores will be summarized with N, mean and SD together, median and range together at each applicable post baseline visit for all and by age group. Change from baseline in weight and height will be summarized together with other vital signs such as temperature and blood pressure.

8.1.4 Patient Reported Outcomes

At Baseline, End of Treatment, and Post-Treatment, general quality of life will be assessed using the PedsQL. The PedsQL was designed to measure the core dimensions of

health, as well as role (school) functioning. The PedQL consists of 4 multidimensional scales (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and 3 summary scales (Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score).

Across subjects enrolled in Part 1 and 2 (based on ITT population), summary statistics of change from baseline (n, mean, SD, minimum and maximum) of 3 summary scale scores will be provided by age group and overall. In addition the same summaries will be created separately for subjects who complete all the questionnaires by themselves and for subjects whose parent(s)/guardian(s) always complete the parent/guardian proxy-report.

8.1.5 Safety

The secondary safety endpoints are rates of adverse events and clinically significant laboratory abnormalities. All subjects who receive at least one dose of study drug will be included in the safety analyses. The safety analysis will be carried out for all subjects by for each age group and overall. Subjects who receive a dose lower than the final dose chosen for the subject's age group might be summarized separately. A listing of any SAEs recorded in the Post-Treatment Period will be included.

8.1.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT). The tabulation of the number of subjects with treatment-emergent adverse events by grade (Grades 1 – 5) and relationship to study drug also will be provided.

Additional analyses will be performed if useful and appropriate.

8.1.5.2 Clinical Laboratory Data

Clinical laboratory tests will be summarized at each visit. The baseline value will be the last measurement prior to the initial dose of study drug. Mean changes from baseline to each post baseline visit will be summarized descriptively.

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

8.1.5.3 Vital Signs Data

Mean changes in temperature, systolic and diastolic blood pressure, pulse, weight, height, and BMI from Day 1 to each post baseline visit will be summarized descriptively.

8.1.6 Resistance Analysis

8.1.6.1 HCV Drug-Resistance Analyses

The secondary endpoint of resistance associated viral variants will be analyzed as follows. For all subjects in Part 1 and subjects with available samples in Part 2, full length NS3/4A or NS5A from baseline samples will be sequenced by NGS. For all subjects who experience virologic failure (on-treatment virologic failure or post-treatment relapse), full length NS3/4A and NS5A genes from the first sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS. An appropriate subtype-specific prototypic reference sequence will be used for comparison with sequences from samples. Subjects treated with study drug who do not achieve SVR_{12} due to reasons other than virologic failure but have a time point with HCV RNA ≥ 1000 IU/mL after treatment discontinuation, will have the sample at that time point sequenced.

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

points for analyses on samples from subjects who do not achieve SVR12 are 1) the sample closest in time after failure/discontinuation with an HCV RNA level of ≥ 1000 IU/mL, and 2) 24 weeks post-DAA treatment, provided that resistance-associated substitutions were detected by NGS at the time of HCV virologic failure/treatment discontinuation.

For each DAA target, signature amino acid positions and a key subset of amino acid positions are listed in Table 12 Appropriate subtype specific prototypic reference sequence will be used for comparison with sequences from samples.

Table 12. 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, 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, 4, 5, 6 NS5A	24, 28, 29, 30, 31, 32, 58, 92, 93	

The following definitions will be used in the resistance analyses:

- Baseline polymorphism: an amino acid 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 signature amino acid position: polymorphism (relative to reference) present in a baseline or substitution (relative to baseline) present in a post-baseline sample at a signature amino acid position.
- Post-baseline substitution: an amino acid substitution in a post-baseline time point sample that was not detected at baseline (< 2%) in the subject and is detectable in ≥ 2% of the sequences from the post-baseline sample.

- Enriched polymorphism: polymorphism present in both the baseline and a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post-baseline % – baseline %) ≥ 20].
- Treatment-emergent substitution by NGS: A post-baseline substitution or an enriched polymorphism.

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

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

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

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

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

Analysis 3: In subjects with or without polymorphisms in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A at the key subset of amino acid positions at 15% detection threshold, the 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 substitutions at signature amino acid positions relative to the baseline amino acid sequence will be provided for each DAA target (NS3/4A and NS5A).

The persistence of post-baseline substitutions at signature amino acid positions for each target will be assessed by NGS through Post-Treatment Week 144. A listing by subject

and time point of all post-baseline substitutions relative to the baseline amino acid sequence will be provided for each DAA target.

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

HCV Genotype/Subtype

Phylogenetic analysis will be conducted on HCV NS3/4A and/or NS5A sequence from baseline samples from subjects in Part 1, and from subjects with available samples in Part 2 in order to accurately determine genotype/subtype. If the phylogenetic analysis is not available, then the result from Sanger sequencing of a region of NS5B by AbbVie or by the Central laboratory will be used to determine the subject's HCV genotype/subtype, if available. Finally, if neither the phylogenetic analysis result nor the Sanger sequencing assay results is available, then the Inno-LIPA assay results from the Central laboratory will be used to categorize the subject. This information will be presented in summaries of efficacy subgroup analyses.

8.1.6.2 HIV Drug-Resistance Analyses

If a subject develops a confirmed, plasma HIV-1 RNA level ≥ 500 copies/mL after starting the study, the subject's HIV-1 PR, RT, and/or IN sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assays. The number of subjects who demonstrate HIV genotypic resistance and the genotypic resistant mutations detected in the samples obtained from these subjects will be tabulated and summarized. Resistance will be defined as described by the IAS-USA Panel.[26]

8.1.7 Pharmacokinetic and Exposure-Response Analyses

Plasma concentrations of GLE and PIB will be tabulated and summarized for subjects in Part 1 and Part 2 by age group, actual dose administered, and overall.

Non-compartmental pharmacokinetic analysis or population pharmacokinetic analysis will be performed to facilitate potential GLE and PIB dose modification in each age group.

Values for the pharmacokinetic parameters of GLE and PIB including the C_{max}, C_{trough}, and AUC will be tabulated and summarized for subjects by age group, actual dose administered, and overall. Additional parameters or summaries may be determined if useful in the interpretation of the data.

Plasma concentration data from Part 1 and Part 2 of this study may be combined with data from other studies and analyzed using the following general methodology.

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

Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM.

Relationship between exposure 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 using graphical and/or logistic regression analyses.

Additionally, relationship between exposure and efficacy/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 a total of approximately 125 subjects into this study. The primary endpoint will be steady state AUC of GLE and PIB. Practical considerations include the expected larger number of adolescents within this population, in comparison to the younger age cohorts.

The proposed sample size of 48 subjects (12 subjects for each age cohort) for intensive pharmacokinetic sampling (separate from sampling performed in subjects in Japan) is expected to adequately characterize the pharmacokinetics of GLE and PIB to enable dose selection in pediatric subjects.

Approximately 10 subjects will undergo additional PK sampling to support characterization of GLE and PIB exposures in children from Japan.

Additional subjects will be enrolled to reach the proposed total of 125 subjects to provide safety and efficacy information.

8.3 Randomization Methods

There is no randomization in this study. Enrolled subjects will receive treatment per the planned study schematic outlined in Section 5.1.2.

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 International Conference on Harmonization (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's parent(s)/legal guardian(s) and answer all questions regarding this study. Pediatric subjects will be included in all the discussions in order to obtain written assent. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by subject's parent(s)/legal guardian(s) and the person who administered the informed consent, and

any other signatories according to local requirements. Additionally, in keeping with each institution's IEC requirements, if applicable, an informed assent form will also be obtained by each subject, as appropriate for age and country, prior to any study-related procedures being performed. If a subject becomes of legal age during the course of the study, that subject will need to be consented using the approved informed consent form. A copy of the informed consent form and assent form will be given to the subject and subject's parent(s)/legal guardian(s) and the originals 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 and assent (if applicable) were obtained prior to any study-related procedures and that the subject and parent(s)/legal guardian(s) received signed copies of the informed consent and assent forms.

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.

9.3.1 Informed Consent Form and Explanatory Material (Japan Site Specific)

In Japan, the principal investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

Consent to collect samples up to 12-h post dose (0, 2, 4, 6, and 12 hours) will be requested of all participants in Japan. However, if consent and assent cannot be obtained for 12-h post dose PK sampling, then a reduced PK collection duration (0, 2 and 4 hours) will be performed.

9.3.2 Revision of the Consent Form and Explanatory Material (Japan Site Specific)

In Japan, when important new information related to the subject's consent becomes available, the principal investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

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

Not applicable for this study.

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/director of the site in Japan and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator/director and AbbVie. The investigator/director 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/director must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator/director 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/Pibrentasvir 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:	An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Subjects With Genotypes 1 – 6 Chronic Hepatitis C Virus (HCV) Infection (DORA)
Protocol Date:	22 March 2019

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

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

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

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

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

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Program Development
		Protocol Author Clinical Program Development
		Therapeutic Area Infectious Disease
		Data and Statistical Sciences
		Pharmacokinetics

Appendix C. Study Activities

Treatment Period

Activity	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8[b]	Wk 12[b]	EOT*/Premature D/C[b]
Informed Consent[c]	X						
Medical History[d]	X	X					
Physical Exam[e]	X	X		X	X	X	X
Vital Signs, Weight, Height, Body Mass Index	X	X	X	X	X	X	X
ECG[f]	X		X[f]				
Pregnancy Test (serum [s] urine [u])[g]	X (s)	X (u)		X (u)	X(u)	X (u)	X (u)
Hematology/Chemistry/Urinalysis/Coagulation Panel[h]	X	X	X	X	X	X	X
FSH[i]	X						
HbsAg, Anti-HCV Ab, Anti-HIV Ab	X						
HCV Genotype and Subtype	X						
Historical Liver Biopsy or FibroScan assessment or Screening FibroTest, Discriminant Score or liver biopsy for liver cirrhosis[j]	X						
Longitudinal Fibrotest & APRI[k]		X					
Child Pugh Score[l]	X						
HCC Assessment: Liver ultrasound[m] and Alpha fetoprotein[m]	X						X
Concomitant Medication Assessment	X	X	X	X	X	X	X
Adverse Event Assessment[n]			X	X	X	X	X
Study Drugs Dispensation		X		X	X[o]	X[o]	
Dispense/Collect/Review Study Drug Dosing Card and HIV-1 Medication Card (if applicable)	X[w]	X	X	X	X[p]	X[p]	X

Activity	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8[b]	Wk 12[b]	EOT*/Premature D/C[b]
Study Drug Accountability and/or Review of Study Drug Adherence			X	X	X	X	X
PK Sampling		X	X[q]	X	X	X	X
HIV RNA Samples[r]	X	X		X	X	X	X
Flow Cytometry[r]	X	X		X			X
HCV RNA Samples	X	X	X	X	X	X	X
Assignment of Subject Number via IRT[s]	X						
Enrollment		X					
HCV Resistance Sample[t]		X					
Patient Reported Outcome[u]		X					X
Palatability Questionnaire[v]			X				X

D/C = Discontinuation; EOT (End of Treatment) = Final Treatment Visit; Day 1 = Baseline Visit

* The EOT visit can be at Week 8, Week 12, or Week 16 in accordance with Section 5.1 and activities should be conducted that are located in the EOT column. Treatment duration will be assigned according to Subjects HCV genotype, cirrhosis and prior HCV treatment experience status.

a. All procedures to be performed prior to first dose, with the exception of the PK sample which will be obtained 4 hours post-dose.

b. The Week 8 study visits apply to all subjects whose treatment duration is 12 weeks and 16 weeks in accordance with Section 5.1. The Week 12 study visits apply to all subjects whose treatment duration is 16 weeks in accordance with Section 5.1. Subjects who prematurely discontinue the Treatment Period should return to the site to complete the Premature D/C Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy).

c. Parent(s)/guardian(s) need to sign an IRB/IEC approved informed consent for the study prior to performing any screening or study-specific procedures. Additionally an assent from the subject will be obtained to meet the institution's IEC requirements, as applicable.

d. A complete medical history will be taken at Screening and will be updated at the Study Day 1 Visit prior to study drug administration and will serve as the Baseline for clinical assessment.

e. A symptom-directed physical examination may be performed at any other visit, when necessary.

f. ECG will be measured only in the intensive PK portion of both parts, prior to any blood collection procedures, excluding subjects in Japan.

g. A positive urine pregnancy test requires a confirmatory serum test. (Refer to Section 5.3.1.1 [Pregnancy Test] for additional details.) Females who are experiencing menses or are nearing sexual maturation in the opinion of the PI or who are of childbearing potential should have urine pregnancy testing done through Post-Treatment Week 4. Females of non-childbearing potential (as defined per protocol Inclusion Criteria 3) at Screening do not require pregnancy testing.

h. For non-cirrhotic subjects: Coagulation panel performed only at Day 1, at EOT/premature D/C, and as clinically indicated.
For cirrhotic subjects: Coagulation panel is required at all treatment visits, including the EOT/premature D/C visit.

i. FSH for all female subjects aged 9 to < 18 years old.

j. Subjects with no history of cirrhosis who have not had a liver biopsy within 24 months prior to screening, or Fibroscan within 6 months prior to screening will have a screening FibroTest and APRI to determine the presence or absence of cirrhosis for the purpose of treatment assignment. Subjects who have a liver biopsy or FibroScan indicating cirrhosis at any time in the past will not need a Fibrotest and APRI to be performed at screening as evidence of cirrhosis.

k. Perform a Fibrotest and APRI at Day 1 for any subject who did not have a FibroTest and APRI done during Screening.

l. Applies only to subjects with cirrhosis. The Child-Pugh score will be calculated in the EDC RAVE system. Subjects who were considered to be non-cirrhotic at the Screening visit but identified as cirrhotic (according to definitions listed in Section 5.3.1.1) during the screening period will return to the site prior to the baseline visit for Child-Pugh assessment.

m. HCC assessment for subjects with compensated cirrhosis only: Liver ultrasound will be performed at the screening visit. Subjects with a historical negative liver ultrasound, CT or MRI (within 3 months prior to screening) are not required to undergo a screening ultrasound.

n. See specific information regarding the adverse event collection in Section 6.1.1.1.

o. Study drugs are dispensed at Week 8 for subjects on 12 weeks of treatment and at Weeks 8 and 12 for subjects on 16 weeks of treatment.

p. Dosing card is filled out with date and time (to the nearest minutes) of the 2 doses before PK draws in Part 1 and Part 2. Dosing cards should not be dispensed at Weeks 8 or 12 if those are EOT visits for the subject (Section 5.3.1.1).

q. Intensive PK sampling will be done at Week 2 for the first approximately 12 subjects in each of the age groups and subjects in Japan participating in J-IPK (Section 5.3.2.1). Intensive PK samples will be collected at Week 2 visit at time points zero (0) and after two (2), four (4), six (6) and twelve (12) hours of drug intake. For subjects in Japan who will not participate in the J-IPK schedule, samples will be collected at Week 2 visit at time points zero (0) and after two (2) and four (4) hours of drug intake.

r. Only applicable for HCV/HIV-1 co-infected subject.

s. The Subject will retain the subject number throughout the course of the study.

t. Resistance sample will be collected at Day 1. For a subject who meets virologic failure criteria, a resistance sample must be drawn at the confirmatory visit. If HCV RNA is < 1000 IU/mL in the sample collected at the confirmatory visit, another resistance sample will be collected in the following visit to ensure the HCV RNA is ≥ 1000 IU/mL.

u. The PRO should be administered as the first study procedure.

v. Only subjects in Part 2 will complete the palatability questionnaire, at Week 2 and EOT or premature discontinuation visit.

w. Dispense HIV-1 Medication Card at screening, if applicable.

Post Treatment Period

Activity	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wk 96	PT Wk 144	Premature D/C
Vital Signs, Weight, Height, Body Mass Index	X	X	X	X	X	X	X	X
Urine Pregnancy Test[a]	X							X[a]
Longitudinal Fibrotest and APRI		X			X	X	X	X
Hematology/Chemistry/Urinalysis[b]/Coagulation Panel[b]	X	X			X	X	X	X
HCC Assessment: Liver Ultrasound[c]			X			X	X	X
HCC Assessment: Alpha fetoprotein[c]			X		X	X	X	X
Concomitant Medication Assessment[d]	X	X	X	X	X	X	X	X
Adverse Event Assessment[e]	X	X	X	X	X	X	X	X
HCV RNA Samples	X	X	X	X	X	X	X	X
HCV Resistance Sample[f]	X	X	X	X	X	X	X	X
Patient Reported Outcome[g]		X						X[g]
HIV RNA Samples[h]	X	X						
Flow Cytometry[h]	X							

D/C = Discontinuation

a. A positive urine pregnancy test requires a confirmatory serum test. (Refer to Section 5.3.1.1 [Pregnancy Test] for additional details.) Females who are experiencing menses or are nearing sexual maturation in the opinion of the PI or who are of childbearing potential should have urine pregnancy testing done through Post-Treatment Week 4. Pregnancy testing will be performed at PT Premature D/C visit only if the subject discontinues prior to PT Wk 4.

b. Urinalysis will not be conducted after the Post-Treatment Week 4 visit. Urinalysis will be performed at PT Premature D/C visit only if the subject discontinues prior to PT Wk 4. The coagulation panel will be obtained at PTW4 for all patients. For non-cirrhotic subjects: Perform the coagulation panel at visits only if clinically indicated after post treatment Week 4.

c. HCC assessment for subjects with compensated cirrhosis only.

d. Concomitant medication will be collected for 30 days after study drug has been stopped, thereafter only antiviral medicines taken for the treatment of HCV and medications taken for SAEs will be recorded. See section 5.2.3.

e. Non-serious AEs and all SAEs will be collected until 30 days post dosing. Only spontaneously reported SAEs will be collected thereafter. See Section 6.1.

f. Resistance samples are only collected for patients that meet virologic failure criteria and should be drawn at the confirmatory visit, and if confirmed, at all subsequent visits.

g. The PRO should be administered as the first study procedure. PRO will be accessed at the Premature D/C visit only if the subject discontinues prior to PT Wk 12.

h. Only applicable for HCV/HIV-1 co-infected subject.

Appendix D. Estimated Blood Loss for Pediatric Subjects

Treatment Period – Part 1: Excluding Subjects in Japan

	Screening	Day 1	Wk 2*	Wk 4	Wk 8	Wk 12	Wk 16 or EOT	Premature D/C from Treatment
Estimated Whole Blood Drawn (mL) for standard tubes	45.3	38.8	23.3	26.3	21.3	21.3	28.8	28.8

* For those not participating in IPK, the estimated whole blood drawn at Wk 2 is 15.3 mL.

Post-Treatment Period – Part 1: Excluding Subjects in Japan

	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wk 96 and 144	Premature D/C
Estimated Whole Blood Drawn (mL) for standard tubes	24.3	20.8	8.5	6	17.3	17.3	18.3

An HCV resistance sample may be obtained per protocol in addition to the above blood drawn. The estimated whole blood drawn for the HCV Resistance sample is 6.0 mL.

Treatment Period – Part 1: Subjects in Japan

	Screening	Day 1	Wk 2*	Wk 4	Wk 8	Wk 12 or EOT	Premature D/C from Treatment
Estimated Whole Blood Drawn (mL) for standard tubes	52.8	38.8	23.3	26.3	21.3	28.8	28.8

* For those not participating in J-IPK, the estimated whole blood drawn at Wk 2 is 19.3 mL.

Post-Treatment Period – Part 1: Subjects in Japan

Estimated Whole Blood Drawn (mL) for standard tubes	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96 and 144	Premature D/C
	24.3	20.8	8.5	6	17.3	17.3	18.3

An HCV resistance sample may be obtained per protocol in addition to the above blood drawn. The estimated whole blood drawn for the HCV Resistance sample is 6.0 mL.

Treatment Period – Part 2: Excluding Subjects in Japan

Estimated Whole Blood Drawn (mL)	Screening	Day 1	Wk 2*	Wk 4	Wk 8	Wk 12	Wk 16 or EOT	Premature D/C from Treatment
for standard tubes	45.3	34.8	23.3	26.3	21.3	21.3	28.8	28.8
for pediatric tubes	32.3	29.2	17.7	22.1	17.1	17.1	23.2	23.2

* For those not participating in IPK, the estimated whole blood drawn at Wk 2 is 15.3 mL (for standard tubes)/ 9.7 mL (for pediatric tubes).

Post-Treatment Period – Part 2: Excluding Subjects in Japan

Estimated Whole Blood Drawn (mL)	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96 and 144	Premature D/C
for standard tubes	24.3	20.8	8.5	6	17.3	17.3	18.3
for pediatric tubes	20.1	14.8	5.1	4	9.9	9.9	11.3

An HCV resistance sample may be obtained per protocol in addition to the above blood drawn. The estimated whole blood drawn for the HCV Resistance sample is 6.0 mL.

Treatment Period – Part 2: Subjects in Japan

Estimated Whole Blood Drawn (mL)	Screening	Day 1	Wk 2*	Wk 4	Wk 8	Wk 12 or EOT	Premature D/C from Treatment
for standard tubes	52.8	34.8	23.3	26.3	21.3	28.8	28.8
for pediatric tubes	40.8	31.3	20.3	23.3	18.3	25.3	25.3

* For those not participating in J-IPK, the estimated whole blood drawn at Wk 2 is 19.3 mL (for standard tubes)/ 16.3 ml (for pediatric tubes).

Post-Treatment Period – Part 2: Subjects in Japan

Estimated Whole Blood Drawn (mL)	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96 and 144	Premature D/C
for standard tubes	24.3	20.8	8.5	6	17.3	17.3	18.3
for pediatric tubes	21.3	17.8	6	4	13.8	13.8	14.3

An HCV resistance sample may be obtained per protocol in addition to the above blood loss. The estimated whole blood drawn for the HCV Resistance sample is 6.0 mL.

Appendix E. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.2 Synopsis
Subsection Number of Subjects to be Enrolled:
Previously read:

Approximately 110 subjects

Has been changed to read:

Approximately 125 subjects

Section 1.2 Synopsis
Subsection Methodology:
First paragraph, first sentence previously read:

The study will enroll approximately 110 HCV-infected pediatric subjects, divided into four (4) age groups, 3 to < 6, 6 to < 9, 9 to < 12, and 12 to < 18 years of age.

Has been changed to read:

The study will enroll approximately 125 HCV-infected pediatric subjects, divided into four (4) age groups, 3 to < 6, 6 to < 9, 9 to < 12, and 12 to < 18 years of age.

Section 1.2 Synopsis
Subsection Methodology:
Second paragraph, first sentence previously read:

Within each age group, approximately 12 HCV-infected pediatric subjects will be enrolled for intensive pharmacokinetics (IPK) in order to adequately characterize the pharmacokinetics (PK) of a particular age group for dose confirmation, and the remainder of subjects will be enrolled for the evaluation of safety and efficacy of each age group until the total pediatric study population reaches approximately 110 subjects.

Has been changed to read:

Within each age group, approximately 12 HCV-infected pediatric subjects will be enrolled for intensive pharmacokinetics (IPK) in order to adequately characterize the pharmacokinetics (PK) of a particular age group for dose confirmation, and the remainder of subjects will be enrolled for the evaluation of safety and efficacy of each age group until the total pediatric study population reaches approximately 125 subjects.

Section 1.2 Synopsis
Subsection Investigational Products:
"Pediatric formulation:" previously read:

Pediatric formulation: Glecaprevir/Pibrentasvir 15.67%+8.25% film-coated pellets

Has been changed to read:

Pediatric formulation: Glecaprevir/Pibrentasvir 15.67%+8.25% film-coated pellets/granules

Section 1.2 Synopsis
Subsection Proposed Doses:
Previously read:

Cohort	Age (yrs); Weight Band	GLE/PIB Dose
1	12 – < 18; ≥ 45 kg	300 mg/120 mg
2	9 – < 12 30 – < 45 kg	200 mg + 75 mg*
3	6 – < 9; 20 – < 30 kg	160 mg + 60 mg*
4	3 – < 6; 12 – < 20 kg	120 mg + 45 mg*

* Exposures of Glecaprevir and Pibrentasvir will be evaluated in approximately 12 subjects with intensive PK samples in each Cohort and compared to the exposures observed in Adults. Following analysis, target doses may be adjusted.

Has been changed to read:

Cohort	Age (yrs); Weight Band	GLE/PIB Dose
1	12 – < 18; ≥ 45 kg	300 mg/120 mg
2	9 – < 12 30 – < 45 kg	250 mg + 100 mg
3	6 – < 9; 20 – < 30 kg	200 mg + 80 mg
4	3 – < 6; 12 – < 20 kg	150 mg + 60 mg

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

NDA New Drug Application

Section 3.0 Introduction
Sixth paragraph, second and third sentence previously read:

For first-line treatment for chronic HCV infection in children, the American Association for the Study of Liver Diseases (AASLD) recommends the combination of pegylated interferon 2b (pegIFN-2b) and ribavirin (RBV), which is approved by the United States Food and Drug Administration (FDA) for use in children aged 3 to 17 years.[20] In addition, the combinations of ledipasvir/sofosbuvir, and sofosbuvir + ribavirin have been approved for use in adolescents, though neither combination covers all major genotypes alone.[28,29]

Has been changed to read:

The American Association for the Study of Liver Diseases (AASLD) recommends that DAA regimens should be recommended independent of disease severity, if a regimen is available dependent upon the child's age group.[30] The combinations of ledipasvir/sofosbuvir, and sofosbuvir + ribavirin have been approved for use in adolescents, though neither combination covers all major genotypes alone.[28,29]

Section 3.0 Introduction
Sixth paragraph, fifth and sixth sentence previously read:

There are several ongoing studies of interferon-free regimens in children including sofosbuvir/ledipasvir for GT1 (NCT02249182), sofosbuvir (SOF) plus RBV for GT2 and 3 (NCT02175758), and ombitasvir/paritaprevir/ritonavir with or without dasabuvir for GT1 and GT4 (NCT02486406). Early results with direct-acting antiviral (DAA) therapy are promising, showing high SVR_{12} rates in adolescents, similar to adults.

Has been changed to read:

There are several studies of interferon-free regimens in children including sofosbuvir/ledipasvir for GT1 (NCT02249182), sofosbuvir (SOF) plus RBV for GT2 and 3 (NCT02175758), and ombitasvir/paritaprevir/ritonavir with or without dasabuvir for GT1 and GT4 (NCT02486406). Results with direct-acting antiviral (DAA) therapy are promising, showing high SVR_{12} rates in adolescents, similar to adults.

Section 3.0 Introduction
Seventh paragraph, last sentence previously read:

A pediatric formulation comprised of film-coated pellets of GLE and PIB, respectively, in a single container for a convenient QD oral administration with a dosing vehicle has been developed.

Has been changed to read:

A pediatric formulation comprised of film-coated pellets/granules of GLE and PIB, respectively, in a single container for a convenient QD oral administration with a dosing vehicle has been developed.

Section 3.0 Introduction
Subsection <u>GLE/PIB Dose Selection Strategy for the Pediatric Population</u>
Previously read:

AbbVie's pediatric formulation development strategy is to develop a dosage form that provides suitable and flexible dosing across the pediatric age range of 3 to < 18 years.

Development of a suitable pediatric formulation was guided by considerations of solubility, dose flexibility, stability, compatibility, and ease and reliability of the manufacturing process. It is likely the adult tablets will be suitable for adolescent subjects 12 years of age and older with weights ≥ 45 kg. This population is able to swallow tablets and utilizing the adult tablet would enable earlier enrollment of this population.

GLE and PIB exhibit low aqueous solubility. Due to probable requirement of solvent(s) that are undesirable for pediatric patients for any oral solution, and [redacted], AbbVie developed a pediatric formulation based on the solid oral formulations used to manufacture the adult tablets.

Current dose selection strategy for the purposes of this protocol is based on BSA normalization and age appropriate scaling. The objective was to select a dose for each age group in mg that provides exposures in the target range shown to be safe and efficacious in adults based on the formulation available currently. Clinical trial simulations have been performed to assist in dose selection in the pediatric population. From the clinical trial simulations performed at the proposed GLE and PIB doses in the pediatric population, summary statistics for each age group for GLE and PIB and the percent of subjects with exposures ≤ 0.5× and ≥ 2× the target AUC were estimated and are shown in Table 5.

Table 5. Summary Statistics of the Simulations for the Estimated AUC of Each Age Group for GLE and PIB

		Estimated AUC (ng•hr/mL)				% Subjects with Exposures ≤ 0.5× and ≥ 2× of the Target AUC	
Age Group (yr)	**Dose (mg)**	**5% Percentile**	**Median**	**Geometric Mean**	**95% Percentile**	**≤ 0.5×**	**≥ 2×**
GLE							
≥ 3 to < 6	100	990	5100	5100	26000	27	22
6 to < 9	140	1100	5400	5400	28000	25	24
9 to < 12	175	1000	5300	5300	27000	26	23
12 to < 18	250	1100	5700	5700	29000	23	25
Observed in Adults	*300*	*980*	*5300*	*5500 (Target AUC)*	*29000*	*22*	*22*
PIB							
≥ 3 to < 6	40	500	1300	1300	3300	14	9
6 to < 9	56	530	1400	1400	3500	12	11
9 to < 12	70	520	1300	1300	3400	13	10
12 to < 18	100	550	1400	1400	3700	10	12
Observed in Adults	*120*	*590*	*1400*	*1400 (Target AUC)*	*3400*	*14*	*12*

At the doses listed in Table 5, the geometric mean and median exposures are comparable within each age group for GLE and PIB. The variability in each age group is expected to be similar to the variability observed in adults.

The doses shown in Table 5 are based on currently available clearance data in adult subjects with HCV infection in Phase 2 studies.

[redacted]

[redacted] The final proposed doses are listed in Table 12.

For adolescents (12 to less than 18 years), in order to address the medical need in this population as well as provide valuable information on pediatric formulation development for younger age groups, AbbVie initiated the study using the adult formulation. As indicated in the report of the pediatric hepatitis C therapy expert meeting that occurred on 09 December 2014, "these patients would also generally use the adult formulation and dose."[27] Although the BSA-based dose selection suggested a GLE dose of 250 mg and a PIB dose of 100 mg in this age group would provide comparable exposure to adults, adolescent patients will be administered the adult doses of GLE 300 mg and PIB 120 mg. In adult patients, safety has been established in HCV cirrhotic patients with 3- to 5-fold higher exposure than the target efficacious non-cirrhotic level. Therefore, using the slightly higher (20%) GLE and PIB doses in adolescents are not expected to significantly increase the safety risk for this population.

Has been changed to read:

AbbVie's pediatric formulation development strategy is to develop a dosage form that provides suitable and flexible dosing across the pediatric age range of 3 to < 18 years. Development of a suitable pediatric formulation was guided by considerations of solubility, dose flexibility, stability, compatibility, and ease and reliability of the manufacturing process. It is likely the adult tablets will be suitable for adolescent subjects 12 years of age and older with weights ≥ 45 kg. This population is able to swallow tablets

and utilizing the adult tablet would enable earlier enrollment of this population. In Part 1 of Study M16-123, a total of 47 adolescent subjects received daily administration of GLE/PIB 300 mg/120 mg. PK results showed that the exposures of GLE and PIB in HCV-infected adolescent subjects (12 to < 18 years of age) were similar to the exposures observed in HCV-infected adult subjects following administration of GLE/PIB 300 mg/120 mg.

GLE and PIB exhibit low aqueous solubility. Due to probable requirement of solvent(s) that are undesirable for pediatric patients for any oral solution, and [redacted] AbbVie developed a pediatric formulation based on the solid oral formulations used to manufacture the adult tablets.

[redacted]

To provide exposures in pediatric subjects comparable to adult exposures using the pediatric formulation, the GLE and PIB dose in pediatric patients of 3 to < 12 years of age were revised from originally proposed doses. Preliminary PK results from the initial proposed pediatric doses demonstrated that though GLE and PIB exposures were within the range of exposure for efficacy and safety in adults for each of the pediatric cohorts, the average exposures in each of the cohorts were lower than the targeted AUC and led to a dose adjustment. Additional subjects were enrolled and the intensive PK results obtained, and additional population PK modeling performed, confirming that the adjusted doses demonstrate exposures that would allow for bridging of adult data, using a 50/20 mg dose ratio. These doses (Table 11) are proposed to be used in the subjects enrolling in the non-

IPK portion of Part 2, in order to confirm that the doses would provide similar exposures observed in HCV-infected adult subjects, close to the targeted AUC.

Section 3.3 Pediatric Study Plan and Pediatric Investigational Plan
Last paragraph
Add: new third and fourth sentence

On December 14, 2016, AbbVie submitted its waiver request as part of the original New Drug Application (NDA) 209394 (eCTD Sequence 0000). On August 03, 2017, FDA waived the pediatric requirement for children younger than 3 years of age because the necessary studies are impossible or highly impracticable (Reference ID: 4134372).

Section 4.2 Secondary Objective
First paragraph previously read:

The secondary objectives are to assess the efficacy of GLE/PIB by assessing:

Has been changed to read:

The secondary objectives are to assess:

Section 4.2 Secondary Objective
Sixth and seventh bullet previously read:

- Assess pharmacokinetics and emergence/persistence of viral variants in subjects with available samples;
- Assessment of palatability/acceptability of pediatric formulation.

Has been changed to read:

- Pharmacokinetics and emergence/persistence of viral variants in subjects with available samples;
- Palatability/acceptability of pediatric formulation.

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

The study is designed to enroll approximately 110 subjects to meet scientific, regulatory and clinical 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 125 subjects to meet scientific, regulatory and clinical objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Section 5.1 Overall Study Design and Plan: Description
Second paragraph, second sentence previously read:

Part 2 of the study allows for enrollment of approximately 66 HCV infected, GT1 – 6 pediatric subjects divided into the 3 to < 6, 6 to < 9 and 9 to < 12 years old age groups.

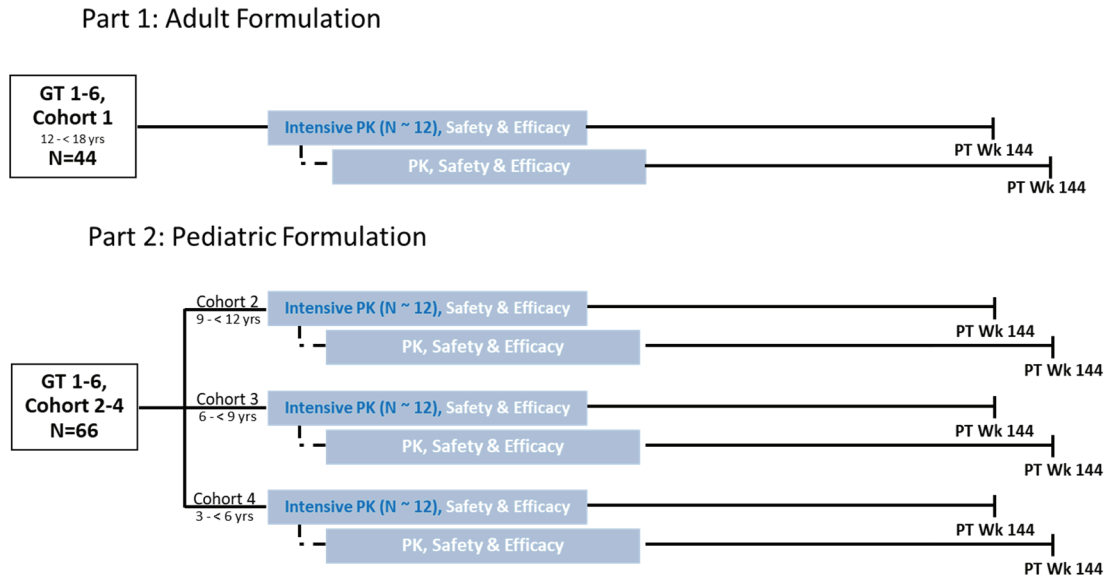
Has been changed to read:

Part 2 of the study allows for enrollment of approximately 81 HCV infected, GT1 – 6 pediatric subjects divided into the 3 to < 6, 6 to < 9 and 9 to < 12 years old age groups.

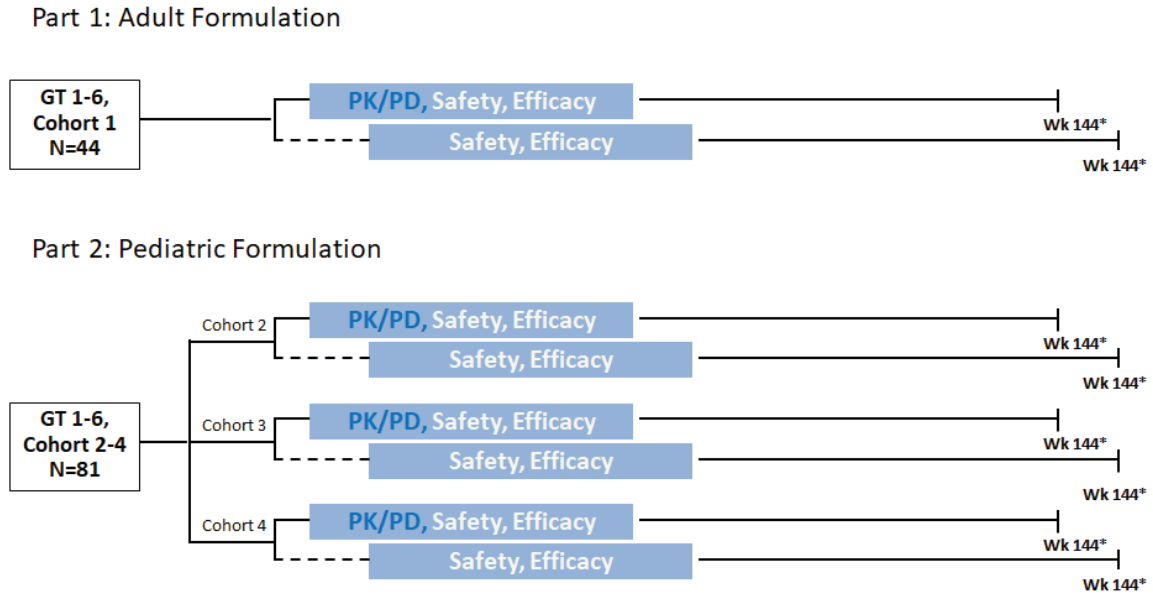
Section 5.1 Overall Study Design and Plan: Description
Second paragraph
Delete: last sentence

Enrollment into Part 2 may begin upon availability of the pediatric formulation.

Figure 1. Study Schematic
Previously read:



Has been changed to read:



Section 5.2.1 Inclusion Criteria
Criterion 9, first sentence previously read:

Subject co-infected with HIV-1 must be on a stable antiretroviral therapy (ART) for at least 8 weeks prior to screening, consisting of the qualifying ART regimens as outlined in Section 5.2.4 (Concomitant HIV-1 Antiretroviral Therapy).

Has been changed to read:

Subject co-infected with HIV-1 must be on a stable antiretroviral therapy (ART) for at least 8 weeks prior to screening, consisting of the qualifying ART regimens as outlined in Section 5.2.3.1 (Concomitant HIV-1 Antiretroviral Therapy).

Section 5.3.3 Efficacy Variables
Section title previously read:

Efficacy Variables

Has been changed to read:

Primary and Secondary Variables

Section 5.5.1 Treatments Administered
Subsection <u>Part 2 Pediatric Formulation:</u>
First paragraph, first sentence previously read:

Glecaprevir and Pibrentasvir (GLE/PIB) will be provided by the Sponsor as separate 15.67% and 8.25% film-coated pellets.

Has been changed to read:

Glecaprevir and Pibrentasvir (GLE/PIB) will be provided by the Sponsor as separate 15.67% and 8.25% film-coated pellets/granules.

Section 5.5.1 Treatments Administered
Subsection Part 2 Pediatric Formulation:
Second paragraph, first sentence previously read:

The film-coated pellets are packed in unit doses and are to be administered at once QD into a dosing vehicle.

Has been changed to read:

The film-coated pellets/granules are packed in unit doses and are to be administered at once QD into a dosing vehicle.

Table 11. Identity of Investigational Product
Add: Study Part "2"

Study Part	Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
2	GLE/PIB	AbbVie	Oral	Film-coated granules[a]	50 mg/20 mg unit dose

Table 11. Identity of Investigational Product
Add: new table note "a."

Film-coated pellets and granules are the same formulation, and the terminology is considered interchangeable. They are listed separately, however, to reflect the changes in the packaging and labeling from pellets in bottles to granules in sachets.

Section 5.5.2.2 Storage and Disposition of Study Drugs
Table previously read:

Study Drug	Storage Conditions
GLE/PIB film-coated Tablets	15° to 25°C (59° to 77°F)
GLE/PIB film-coated pellets	15° to 25°C (59° to 77°F), Protect from moisture

Has been changed to read:

Study Drug	Storage Conditions
GLE/PIB film-coated Tablets	15° to 25°C (59° to 77°F)
GLE/PIB film-coated pellets	15° to 25°C (59° to 77°F), Protect from moisture
GLE/PIB film-coated granules	2° to 25°C (36° to 77°F)[a]

a. Film-coated pellets and granules are the same formulation and terminology is considered interchangeable. They are listed separately, however, to reflect the changes in the packaging and labeling from pellets in bottles to granules in sachets.

Section 5.5.3 Method of Assigning Subjects to Treatment Groups
Fourth paragraph previously read:

In Part 2 of the study, caps on the number of subjects in each age group (3 to < 6, 6 to < 9, 9 to < 12 years of age) will be employed in IRT to ensure that approximately 22 subjects regardless of prior treatment experience and cirrhotic status are enrolled per age group.

Has been changed to read:

In Part 2 of the study, caps on the number of subjects in each age group (3 to < 6, 6 to < 9, 9 to < 12 years of age) will be employed in IRT to ensure that approximately 22 subjects on the final recommended dose regardless of prior treatment experience and cirrhotic status are enrolled per age group.

Section 5.6.4 Selection of Doses in the Study
Second paragraph previously read:

AbbVie has developed a separate pediatric formulation for GLE/PIB for use in Part 2 of the present study.

Has been changed to read:

AbbVie has developed a separate pediatric formulation for GLE + PIB for use in Part 2 of the present study.

Section 5.6.4 Selection of Doses in the Study
Third paragraph, last sentence previously read:

Given the wide therapeutic window of GLE and PIB, the updated initial doses will not anticipate to change the efficacy/safety profiles.

Has been changed to read:

Given the wide therapeutic window of GLE and PIB, the updated doses will not anticipate to change the efficacy/safety profiles.

Section 5.6.4 Selection of Doses in the Study
Fourth paragraph previously read:

For the present study, the proposed doses by weight band range are shown in Table 12.

Has been changed to read:

For the present study, the final proposed doses by weight band range are shown in Table 11.

Table 12. Proposed Glecaprevir and Pibrentasvir Doses for the Pediatric Population Previously read:

Formulation	Age Group (yrs) & Weight Band (kg)	Doses (mg)	
		Glecaprevir	Pibrentasvir
Pediatric formulation	3 to < 6 yr 12 to < 20 kg	120	45
	6 to < 9 yr ≥ 20 to < 30 kg	160	60
	9 to < 12 yr ≥ 30 to < 45 kg	200	75
Adult formulation	12 to < 18 yr ≥ 45 kg	300	120

Has been changed to read:

Formulation	Age Group (yrs) & Weight Band (kg)	Final Proposed Doses (mg)	
		Glecaprevir	Pibrentasvir
Pediatric formulation	3 to < 6 yr 12 to < 20 kg	150	60
	6 to < 9 yr ≥ 20 to < 30 kg	200	80
	9 to < 12 yr ≥ 30 to < 45 kg	250	100
Adult formulation	12 to < 18 yr ≥ 45 kg	300	120

Section 5.6.4 Selection of Doses in the Study
Fourth and fifth paragraph previously read:

The doses of the pediatric formulation may be adjusted dependent upon the intensive pharmacokinetic analysis of the first approx. 6 subjects of each of the ≥ 3 to < 12 year old age cohorts. Once final dosing of an age cohort has been confirmed, further drug dose changes for an age cohort will be included into a protocol amendment if the final dose differs from the current proposed dosing.

For Part 1, enrollment will start with pediatric subjects ≥ 12 to < 18 years old who are ≥ 45 kg and willing to swallow the adult formulations. Part 2 enrollment will start in pediatric subjects ≥ 3 to < 12 years old with the pediatric formulation. Based on current modeling and available PK data, the above proposed doses of the pediatric formulation are the target doses for use in children < 12 years of age. The pharmacokinetic and clinical data will be used to confirm appropriate exposure in each of the ≥ 3 to < 12 years old age groups. Dose adjustments will be made if necessary to ensure safe and efficacious exposures, but not to exceed the adult dose of 300/120 mg of GLE/PIB.

Has been changed to read:

The doses of the pediatric formulation were adjusted based upon the intensive pharmacokinetic analysis of the first approx. 17 subjects enrolled across the age cohorts.

The final proposed dosing for each age cohort has been confirmed by additional IPK analysis. These drug dose changes are included in this protocol amendment. Dose adjustments were made as necessary to ensure safe and efficacious exposures, but did not exceed the adult dose of 300/120 mg of GLE/PIB.

For Part 1, enrollment commenced with pediatric subjects ≥ 12 to < 18 years old who are ≥ 45 kg and willing to swallow the adult formulation. Part 2 enrollment initiated in pediatric subjects ≥ 3 to < 12 years old with the pediatric formulation. Based on current modeling and available PK data at the completion of the IPK portion of Part 2, the above proposed doses of the pediatric formulation are the target doses for use in children < 12 years of age. The pharmacokinetic and clinical data will be used to confirm appropriate exposure in each of the ≥ 3 to < 12 years old age groups.

Section 6.1.5 Adverse Event Reporting
Last paragraph previously read:

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.

Has been changed to read:

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

Section 6.1.7.2 Management of ALT Elevations
Second bullet, sub-bullet previously read:

If the subject is found to have an active hepatitis B infection, additional evaluation with a Hepatitis B Questionnaire should be performed by the investigator.

Has been changed to read:

If the subject is found to have an active hepatitis B infection, additional evaluation by completion of the eCRF Transaminase Elevations Questionnaire should be performed by the investigator.

Section 7.0 Protocol Deviations
"Primary Contact:" previously read:

[redacted]
Study Management Associate
Medical Department
Avenida de Burgos, 91
28050 Madrid, Spain

Office: [redacted]
Fax:

Has been changed to read:

[redacted]
Study Management Associate
[redacted]
One North Waukegan Road
North Chicago, IL 60064

Office: [redacted]

Section 8.1.2 Efficacy
Section title previously read:

Efficacy

Has been changed to read:

Primary, Secondary, and Efficacy Analyses

Section 8.1.2 Efficacy
Add: new first paragraph

The primary and secondary analyses of PK parameters will be performed on subjects in the ITT population with available PK samples, unless otherwise specified.

Section 8.1.2.1 Primary Efficacy Endpoint
Section title previously read:

Primary Efficacy Endpoint

Has been changed to read:

Primary Endpoints

Section 8.1.2.2 Secondary Efficacy Endpoints
Section title previously read:

Secondary Efficacy Endpoints

Has been changed to read:

Secondary Endpoints

Section 8.1.2.2 Secondary Efficacy Endpoints
First paragraph previously read:

The secondary efficacy endpoints are:

Has been changed to read:

The secondary endpoints are:

Section 8.1.2.3 Additional Efficacy Endpoint
Section title previously read:

Additional Efficacy Endpoint

Has been changed to read:

Additional Efficacy Endpoints

Section 8.1.7 Pharmacokinetic and Exposure-Response Analyses
First paragraph previously read:

Plasma concentrations of GLE and PIB will be tabulated and summarized for subjects in Part 1 and Part 2 by age group and overall.

Has been changed to read:

Plasma concentrations of GLE and PIB will be tabulated and summarized for subjects in Part 1 and Part 2 by age group, actual dose administered, and overall.

Section 8.1.7 Pharmacokinetic and Exposure-Response Analyses
Third paragraph, first sentence previously read:

Values for the pharmacokinetic parameters of GLE and PIB including the C_{max}, C_{trough}, and AUC will be tabulated and summarized for subjects by age group and overall.

Has been changed to read:

Values for the pharmacokinetic parameters of GLE and PIB including the C_{max}, C_{trough}, and AUC will be tabulated and summarized for subjects by age group, actual dose administered, and overall.

Section 8.2 Determination of Sample Size
First paragraph, first sentence previously read:

It is planned to enroll a total of approximately 110 subjects into this study.

Has been changed to read:

It is planned to enroll a total of approximately 125 subjects into this study.

Section 8.2 Determination of Sample Size
Last paragraph previously read:

Additional subjects will be enrolled to reach the proposed total of 110 subjects to provide safety and efficacy information.

Has been changed to read:

Additional subjects will be enrolled to reach the proposed total of 125 subjects to provide safety and efficacy information.

Section 15.0 Reference List
Add: new Reference 30

HCV in Children. IDSA. Available from: https://www.hcvguidelines.org/unique-populations/children. Updated on: 2018 May 24.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Clinical Program Development
		Protocol Author Clinical Program Development
		Therapeutic Area Infectious Disease
		Data and Statistical Sciences
		Pharmacokinetics

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical Program Development
		Protocol Author Clinical Program Development
		Therapeutic Area Infectious Disease
		Data and Statistical Sciences
		Pharmacokinetics

Appendix C. Study Activities
Subsection Treatment Period
Table note "h." previously read:

Non-cirrhotic subjects: Coagulation panel performed only at Day 1 and as clinically indicated.

Cirrhotic subjects: Coagulation panel is required at all treatment visits.

Has been changed to read:

For non-cirrhotic subjects: Coagulation panel performed only at Day 1, at EOT/premature D/C, and as clinically indicated.

For cirrhotic subjects: Coagulation panel is required at all treatment visits, including the EOT/premature D/C visit.

Appendix C. Study Activities
Subsection Treatment Period
Table note "j." first sentence previously read:

Subjects with no history of cirrhosis who have not had a liver biopsy or Fibroscan within 24 months prior to screening, will have a screening FibroTest and APRI to determine the presence or absence of cirrhosis for the purpose of treatment assignment.

Has been changed to read:

Subjects with no history of cirrhosis who have not had a liver biopsy within 24 months prior to screening, or Fibroscan within 6 months prior to screening will have a screening FibroTest and APRI to determine the presence or absence of cirrhosis for the purpose of treatment assignment.

Appendix C. Study Activities
Subsection Post Treatment Period
Activity "Hematology/Chemistry/Urinalysis[b]/Coagulation Panel" previously read:

Hematology/Chemistry/Urinalysis[b]/Coagulation Panel

Has been changed to read:

Hematology/Chemistry/Urinalysis[b]/Coagulation Panel[b]

Appendix C. Study Activities
Subsection Post Treatment Period
Table note "b."
Add: new third and fourth sentence

The coagulation panel will be obtained at PTW4 for all patients. For non-cirrhotic subjects: Perform the coagulation panel at visits only if clinically indicated after post treatment Week 4.

Appendix C. Study Activities
Subsection Post Treatment Period
Table note "f." previously read:

Resistance samples are only collected for patients that meet virologic failure criteria.

Has been changed to read:

Resistance samples are only collected for patients that meet virologic failure criteria and should be drawn at the confirmatory visit, and if confirmed, at all subsequent visits.

Appendix D. Estimated Blood Loss for Pediatric Subjects
Subsection Post-Treatment Period – Part 1: Excluding Subjects in Japan
Previously read:

	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wk 96 and 144	Premature D/C
Estimated Whole Blood Drawn (mL) for standard tubes	24.3	19.0	8.5	6	15.5	15.5	18.3

An HCV resistance sample may be obtained per protocol in addition to the above blood drawn. The estimated whole blood drawn for the HCV Resistance sample is 6.0 mL.

Has been changed to read:

	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wk 96 and 144	Premature D/C
Estimated Whole Blood Drawn (mL) for standard tubes	24.3	20.8	8.5	6	17.3	17.3	18.3

An HCV resistance sample may be obtained per protocol in addition to the above blood drawn. The estimated whole blood drawn for the HCV Resistance sample is 6.0 mL.

Appendix D. Estimated Blood Loss for Pediatric Subjects
Subsection Post-Treatment Period – Part 1: Subjects in Japan
Previously read:

Estimated Whole Blood Drawn (mL) for standard tubes	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96 and 144	Premature D/C
	24.3	19.0	8.5	6	15.5	15.5	18.3

An HCV resistance sample may be obtained per protocol in addition to the above blood drawn. The estimated whole blood drawn for the HCV Resistance sample is 6.0 mL.

Has been changed to read:

Estimated Whole Blood Drawn (mL) for standard tubes	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96 and 144	Premature D/C
	24.3	20.8	8.5	6	17.3	17.3	18.3

An HCV resistance sample may be obtained per protocol in addition to the above blood drawn. The estimated whole blood drawn for the HCV Resistance sample is 6.0 mL.

Appendix D. Estimated Blood Loss for Pediatric Subjects
Subsection Post-Treatment Period – Part 2: Excluding Subjects in Japan
Previously read:

Estimated Whole Blood Drawn (mL)	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96 and 144	Premature D/C
for standard tubes	24.3	19.0	8.5	6	15.5	15.5	18.3
for pediatric tubes	20.1	13.4	5.1	4	8.5	8.5	11.3

An HCV resistance sample may be obtained per protocol in addition to the above blood drawn. The estimated whole blood drawn for the HCV Resistance sample is 6.0 mL.

Has been changed to read:

Estimated Whole Blood Drawn (mL)	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96 and 144	Premature D/C
for standard tubes	24.3	20.8	8.5	6	17.3	17.3	18.3
for pediatric tubes	20.1	14.8	5.1	4	9.9	9.9	11.3

An HCV resistance sample may be obtained per protocol in addition to the above blood drawn. The estimated whole blood drawn for the HCV Resistance sample is 6.0 mL.

Appendix D. Estimated Blood Loss for Pediatric Subjects
Subsection Post-Treatment Period – Part 2: Subjects in Japan
Previously read:

Estimated Whole Blood Drawn (mL)	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96 and 144	Premature D/C
for standard tubes	24.3	19	8.5	6	15.5	15.5	18.3
for pediatric tubes	21.3	16	6	4	12	12	14.3

An HCV resistance sample may be obtained per protocol in addition to the above blood loss. The estimated whole blood drawn for the HCV Resistance sample is 6.0 mL.

Has been changed to read:

Estimated Whole Blood Drawn (mL)	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96 and 144	Premature D/C
for standard tubes	24.3	20.8	8.5	6	17.3	17.3	18.3
for pediatric tubes	21.3	17.8	6	4	13.8	13.8	14.3

An HCV resistance sample may be obtained per protocol in addition to the above blood loss. The estimated whole blood drawn for the HCV Resistance sample is 6.0 mL.

Document Approval

Study M16123 - An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Subjects with Genotypes 1 – 6 Chronic Hepatitis C Virus (HCV) Infection (DORA) - Amendment 3 - EudraCT 2016-004102-34 - 22Mar2019

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Signed by:	Date:	Meaning Of Signature:
[redacted]	22-Mar-2019 09:30:02 PM	Approver
	23-Mar-2019 01:08:35 AM	Approver
	23-Mar-2019 06:35:33 AM	Approver
	25-Mar-2019 03:11:17 P	Approver
	25-Mar-2019 04:04:44 PM	Approver