1.0 Title Page

Clinical Study Protocol M14-491

An Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Treatment-Naïve and Treatment-Experienced Asian Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Compensated Cirrhosis

AbbVie Investigational Product:	ABT-450/r/ABT-267, ABT-333
Date:	11 February 2015
Development Phase:	3
Study Design:	This is an open-label combination drug study.
Investigator:	Multicenter. Investigator information is on file at AbbVie
Sponsor:	AbbVie
Sponsor/Emergency Contact:	[redacted]

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

1.1 Synopsis

AbbVie Inc.	**Protocol Number:** M14-491
Name of Study Drug: ABT-450, ritonavir, ABT-267, ABT-333	**Phase of Development:** 3
Name of Active Ingredient: ABT-450 ritonavir ABT-267 ABT-333	**Date of Protocol Synopsis:** 11 February 2015
Protocol Title: An Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Treatment-Naïve and Treatment-Experienced Asian Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Compensated Cirrhosis	
Objectives: The primary objectives of this study are to assess the safety and to compare the percentage of subjects achieving SVR_{12} rate (the percentage of subjects achieving a 12 week sustained virologic response, SVR_{12}, [HCV ribonucleic acid (RNA), < lower limit of quantification (LLOQ), 12 weeks following therapy] and the percentage of subjects achieving SVR_{24} [HCV RNA < LLOQ, 24 weeks following therapy] (SVR_{24} for China only) following 12 weeks of treatment with co-formulated ABT-450, ritonavir and ABT-267 (ABT-450/r/ABT-267) and ABT-333 coadministered with ribavirin to the historical SVR rate of telaprevir plus pegIFN and RBV therapy in HCV genotype 1b-infected cirrhotic adults. The secondary objectives of this study are to demonstrate the effect of the DAA combination regimen on HCV RNA levels during and after treatment as measured by on-treatment virologic failure and post-treatment relapse, respectively.	
Investigator: Multicenter trial: Investigator information is on file at AbbVie.	
Study Sites: Approximately 18 sites.	
Study Population: Treatment-naïve and previous IFN (alpha, beta or pegIFN) with RBV therapy treatment-experienced HCV genotype 1b Chinese, Korean, and Taiwanese adults with compensated cirrhosis, aged 18 to 70 years of age, inclusive.	
Number of Subjects to be Enrolled: Approximately 100 subjects; 60 from China, 20 from South Korea and 20 from Taiwan.	
Methodology: This is a Phase 3, open-label, multicenter study evaluating the efficacy and safety of ABT 450/r/ ABT-267 and ABT-333 coadministered with ribavirin for 12 weeks in HCV genotype 1b, treatment-naïve and IFN (alpha, beta or pegIFN) plus RBV treatment-experienced Asian adults with compensated cirrhosis. Treatment will consist of: ABT-450/r/ABT-267 150/100/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) + RBV* for 12 weeks.	

Methodology (Continued):

* RBV will be administered weight-based 1000 – 1200 mg divided to twice daily.

Subjects meeting the eligibility criteria will be enrolled and begin the 12-week treatment period. Approximately 100 subjects are will be enrolled. A minimum of 35 treatment-naïve and 35 treatment-experienced subjects will be enrolled.

The treatment-experienced subjects are defined as follows:

- Non-responder: Received at least 12 weeks of IFN (alpha, beta or pegIFN) with RBV therapy for the treatment of HCV and failed to achieve undetectable HCV RNA (HCV RNA < LLOD) at the end of treatment, or
- Relapser: Received IFN (alpha, beta or pegIFN) with RBV therapy for the treatment of HCV and was undetectable at or after the end of treatment, but subsequently had detectable HCV RNA within 24 weeks of treatment follow-up; or
- IFN (alpha, beta or pegIFN) with RBV therapy Intolerant: treatment of HCV was discontinued during the treatment period due to intolerance to any of the components of the IFN based therapy.

This study will consist of a Treatment Period and a Post-Treatment (PT) Period. All subjects dosed with study drug who complete or prematurely discontinue study drug will be followed for 48 weeks in the Post-Treatment Period, to monitor safety, HCV RNA level, the emergence and persistence of viral variants and assessment of patient reported outcomes (PROs).

Visits will occur during the treatment period at Day 1, Weeks 1, 2, 4, 6, 8, 10, and 12 and Post-Treatment Weeks 2, 4, 8, 12, 24, 36, and 48 for all subjects on study.

The safety data will be reviewed by the sponsor, as this is an open-label study, and by an independent Data Monitoring Committee (DMC) during the Treatment Period of the study.

Virologic Failure Criteria – The following criteria will be considered evidence of virologic failure.

- 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;
- Failure to achieve HCV RNA < LLOQ by Week 6; or
- Confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point after HCV RNA < LLOQ during treatment.

Confirmatory testing should be completed as soon as possible. If any of the above criteria are met for a subject in the Treatment Period, study drug will be discontinued.

The Sponsor will evaluate efficacy throughout the Treatment and Post-Treatment Periods in this open-label study.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female of Chinese, South Korean, and Taiwanese descent with full Chinese, South Korean, and Taiwanese parentage between the ages of 18 and 70 years, inclusive, at the time of Screening.
2. Chronic HCV-infection prior to study enrollment. Chronic HCV-infection is defined as one of the following:

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

Main Inclusion (Continued):

- Positive for anti-HCV antibody (Ab) or HCV RNA > 1000 IU/mL at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or
- Positive for HCV RNA > 1000 IU/mL at the time of Screening with a liver biopsy consistent with chronic HCV-infection (or a liver biopsy performed prior to enrollment with evidence of chronic hepatitis C disease).

3. Screening laboratory result indicating HCV genotype 1b-infection.
4. Compensated cirrhosis defined as a Child-Pugh Score of ≤ 6 at Screening.
5. Per local standard practice, documentation of cirrhosis by one of the following methods:
   - Diagnosis on previous liver biopsy or liver biopsy conducted during screening e.g., Metavir Score of > 3 (including 3/4 or 3 – 4), Ishak score of > 4 or,
   - FibroScan score ≥ 14.6 kPa within 6 months of Screening or during the Screening Period.

Main Exclusion:

1. HCV genotype performed during screening indicating unable to genotype or infection with any other HCV genotype.
2. Positive test result at Screening for Hepatitis B surface antigen (HBsAg), or HBV DNA > LLOQ if HBsAg negative, or anti-Human Immunodeficiency virus antibody (HIV Ab).
3. Use of known strong inducers of cytochrome P450 3A (CYP3A) or strong inhibitors of CYP2C8 within 2 weeks or within 10 half-lives, whichever is longer, of the respective medication/supplement prior to study drug administration.
4. Any current or past clinical evidence of Child-Pugh B or C classification or clinical history of liver decompensation including ascites (noted on physical exam), variceal bleeding, or hepatic encephalopathy.
5. Serum Alpha-Fetoprotein (sAFP) > 100 ng/mL at Screening.
6. Confirmed presence of hepatocellular carcinoma (HCC) 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 (a positive ultrasound result should be confirmed with CT scan or MRI.)
7. Any primary 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
   - Drug-related liver disease

   Steatosis and steatohepatitis on a liver biopsy coincident with HCV-related changes would not be considered exclusionary unless the steatohepatitis is considered to be the primary cause of the liver disease.

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

Main Exclusion (Continued):

8. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - Alanine aminotransferase (ALT) > 7 × upper limit of normal (ULN)
   - Aspartate aminotransferase (AST) > 7 × ULN
   - Estimated Glomerular filtration rate adjusted for the Asian population (eGFR) < 50 mL/min/1.73m2 as estimated by the C-MDRD method, modified for the Asian population, according to the following formula: eGFR = 175 × (Serum Creatinine) $^{-1\ 234}$ × (Age) $^{-0\ 179}$ × (0.79 if Female)
   - Albumin < 2.8 g/dL
   - International normalized ratio (INR) > 2.3. Subjects with a known inherited blood disorder and INR > 2.3 may be enrolled with permission of the AbbVie Study Designated Physician
   - Hemoglobin < LLN
   - Platelets < 60,000 cells per mm^3
   - Absolute neutrophil count (ANC) < 1200 cells/µL
   - Total bilirubin ≥ 3.0 mg/dL

Investigational Products:	• ABT-450/Ritonavir/ABT-267 75 mg/50 mg/12.5 mg tablet • ABT-333 250 mg tablet • Ribavirin 200 mg tablet (for Korea and Taiwan) • Ribavirin 100 mg tablet (for China)
Doses:	• ABT-450/Ritonavir/ABT-267 150/100/25 mg QD • ABT-333 250 mg BID • Ribavirin weight-based dosing 1000 to 1200 mg divided twice daily
Mode of Administration:	Oral

Duration of Treatment:

Subjects will receive ABT-450/Ritonavir/ABT-267 and ABT-333 co-administered with RBV for 12 weeks.

Criteria for Evaluation:

Efficacy:

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

Patient Reported Outcomes (PROs):

The change in general and disease-specific Health Related Quality of Life (HRQoL) will be assessed using the SF-36v2 (Short Form 36-Version 2) and HCV Patient Reported Outcomes (HCVPRO) instruments, respectively. Health State Utility will be measured using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L).

Criteria for Evaluation (Continued):

Resistance:

For subjects receiving study drugs who experience virologic failure, the amino acid variants at signature resistance-associated amino acid positions by population nucleotide sequencing at baseline compared to the prototypic reference sequence, the amino acid variants by population nucleotide sequencing at available post-baseline time points compared to baseline, and the amino acid variants at signature resistance-associated positions by population nucleotide sequencing compared to the prototypic reference sequence will be tabulated and summarized. In addition, a listing of amino acid variants that emerge in isolates from at least 2 subjects will be provided, and the persistence of viral resistance-associated amino acid variants will be summarized.

Pharmacokinetic:

Plasma concentrations for ABT-450, possible ABT-450 metabolites, ritonavir, ABT-267, ABT-267 metabolites ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites and RBV will be determined at each study visit up to the end of treatment.

Values for the pharmacokinetic parameters of ABT-450, ABT-267, ritonavir, ABT-333, ABT-333 M1 metabolite, and ribavirin including the C_{max}, T_{max}, C_{trough}, and AUC will be determined by non-compartmental methods using data from subjects who participate in intensive pharmacokinetic sampling in the study. Additional parameters or summaries may be determined if useful in the interpretation of the data.

Safety:

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

Statistical Methods:

Efficacy:

For South Korea and Taiwan, the primary efficacy endpoint is:

A1. SVR_{12}: Superiority to the historical SVR rate for telaprevir plus pegIFN and RBV therapy – lower confidence bound of 2-sided 95% confidence interval (LCB) for the percentage of subjects with SVR_{12} must exceed 67% to achieve superiority.

For China, the primary efficacy endpoints are as follows. In order to control the Type 1 error rate of 0.05, a fixed-sequence testing procedure will be used to proceed through the primary endpoints in the order numbered below.

B1. SVR_{12}: Superiority to the historical SVR rate for telaprevir plus pegIFN and RBV therapy – lower confidence bound of 2-sided 95% confidence interval (LCB) for the percentage of subjects with SVR_{12} must exceed 67% to achieve superiority.

B2. SVR_{24}: Superiority to the historical SVR rate for telaprevir plus pegIFN and RBV therapy – lower confidence bound of 2-sided 95% confidence interval (LCB) for the percentage of subjects with SVR_{24} must exceed 67% to achieve superiority.

To test each hypothesis that the percentage of treatment-naïve and IFN based treatment experienced HCV genotype 1b-infected Asian subjects with compensated cirrhosis treated with ABT 450/r/ABT 267 + ABT-333 + RBV for 12 weeks who achieve SVR_{12}/SVR_{24} is superior to a clinically meaningful threshold based on historical SVR rates for the HCV genotype 1b-infected population treated with telaprevir plus pegIFN and RBV.

Statistical Methods (Continued):

Efficacy (Continued):

The percentage of subjects with SVR_{12}/SVR_{24} will be calculated with a 2-sided 95% CI using Wilson score method, and the LCB will be compared to the defined threshold. The LCB of the 95% CI of SVR_{12}/SVR_{24} must be greater than 67% in order for the regimen to be considered superior.

The secondary endpoints are:

- The percentage of subjects with on treatment virologic failure (defined as confirmed HCV RNA ≥ the lower limit of quantitation (LLOQ) (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point during treatment after HCV RNA < LLOQ, confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment or HCV RNA ≥ LLOQ persistently during treatment with at least 6 weeks (≥ 36 days) of treatment
- The percentage of subjects with relapse by Post-Treatment Week 12 (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drugs among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment) and,
- The percentage of subjects with relapse by Post-Treatment Week 24 (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 24 weeks after the last dose of study drugs among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment).

The percentages (with 2-sided 95% confidence intervals using the Wilson Score method to the binomial distribution) of the subjects with on treatment virologic failure and post-treatment relapse will be calculated and summarized.

Resistance:

The following resistance information will be provided for subjects receiving active study drugs who experience virologic failure (who have HCV RNA ≥ 1000 IU/mL): 1) the amino acid variants at baseline at signature resistance-associated positions identified by population nucleotide sequencing and comparison to the prototypic reference sequence, 2) the amino acid variants in available post-baseline samples identified by population nucleotide sequencing and comparison to the baseline sequence, and 3) the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by population nucleotide sequencing and comparison to the prototypic reference sequence.

In addition, a listing of amino acid variants that emerge in isolates from at least 2 subjects will be provided, and the persistence of viral resistance-associated amino acid variants will be summarized.

Pharmacokinetic:

Plasma concentrations for ABT-450, possible ABT-450 metabolites, ritonavir, ABT-267, ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites and RBV will be tabulated and summarized at each study visit through the end of the Treatment Period.

Values for the pharmacokinetic parameters of ABT-450, ABT-267, ritonavir, ABT-333, ABT-333 M1 metabolite, and ribavirin including the C_{max}, T_{max}, C_{trough}, and AUC will be summarized and tabulated.

Statistical Methods (Continued):

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. The number and percentage of subjects with serious treatment-emergent adverse events and the number and percentage of subjects with treatment-emergent adverse events leading to study drug discontinuation will also be provided.

Tabulations will also be provided in which the number of subjects reporting an adverse event (MedDRA preferred term) is presented by grading and relationship to study drug(s).

Change from baseline in laboratory tests and vital sign measurements to each time point of collection will be summarized descriptively. Laboratory test and vital sign values that are potentially clinically significant, according to predefined criteria, will be identified and the number and percentage of subjects with potentially clinically significant values during treatment will be calculated.

1.2 List of Abbreviations and Definition of Terms

Abbreviations

Ab	Antibody
ABT-450/r/ABT-267	ABT-450 co-formulated with ritonavir and ABT-267
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area Under the Concentration Curve
BID	Twice Daily
BMI	Body mass index
BOC	Boceprevir
BUN	Blood urea nitrogen
CL/F	Apparent Oral Clearance
CR/CL	Creatinine clearance
CRF	Case report form
CT	Computed Tomography
CYP2C8	Cytochrome P450 2C8
CYP3A	Cytochrome P450 3A
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
eGFR	Estimated Glomerular Filtration Rate
EOT	End of treatment
EOTR	End of treatment response
EU	European Union

EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Health State Instrument
GCP	Good Clinical Practice
GCSF	granulocyte colony stimulating factor
GGT	Gamma-glutamyl transferase
GT	Genotype
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HCVPRO	Hepatitis C Virus Patient Reported Outcomes Instrument
Hemoglobin A1c	Glycated hemoglobin
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
HRQoL	Health Related Quality of Life
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon
IL28B	Interleukin 28B
IMP	Investigational Medical Product
INR	International normalized ratio
IP-10	Interferon gamma-induced protein 10
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to Treat
IU	International units
IUD	Intrauterine device
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimally Important Difference
MRI	Magnetic Resonance Imaging

NS3A	Nonstructural viral protein 3A
NS4A	Nonstructural viral protein 4A
NS5A	Nonstructural viral protein 5A
NS5B	Nonstructural viral protein 5B
PCR	Polymerase Chain Reaction
PCS	Physical Component Summary
PegIFN	Pegylated-interferon alfa-2a or alfa-2b
PK	Pharmacokinetic
POR	Proof of Receipt
PRO	Patient Reported Outcomes
PT	Post-Treatment
QD	Once daily
QTc	QT interval corrected for heart rate
QTcF	QTc using Fridericia's correction formula
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
ROC	Receiver Operating Characteristic
RT-PCR	Reverse transcriptase PCR
RVR	Rapid virologic response
SAE	Serious adverse event
sAFP	Serum Alpha-Fetoprotein
SAS	Statistical Analysis System
SD	Standard Deviation
SF-36 V2	Short Form 36-Version 2
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
SVR_4	Sustained virologic response 4 weeks post dosing
SVR_{12}	Sustained virologic response 12 weeks post dosing
SVR_{24}	Sustained virologic response 24 weeks post dosing
TP	Treatment Period

TVR	Telaprevir
ULN	Upper limit of normal
VAS	Visual analogue scale
V/F	Apparent Volume of distribution
WBC	White blood cells

Definition of Terms

Non-responder	Received at least 12 weeks of IFN (alpha, bet or pegIFN) with RBV therapy for the treatment of HCV and failed to achieve undetectable HCV RNA (HCV RNA < LLOD) at the end of treatment
Relapser	Received IFN-based therapy (IFN [alpha, beta or pegIFN] with RBV therapy) for the treatment of HCV and was undetectable at or after the end of treatment, but subsequently had detectable HCV RNA within 24 weeks of treatment follow-up
IFN-based therapy (IFN [alpha, beta, or pegIFN] with RBV therapy) Intolerant	Treatment of HCV was discontinued during the treatment period due to intolerance to any of the components of the IFN RBV therapy.
Study Drug	ABT-450/r/ABT-267, ABT-333, RBV
Study Day 1	First day of study drug dosing
Treatment Period	Baseline/Day 1 through the day of last dose of study drug
Post-Treatment Period	Day after the last dose of study drug through Post-Treatment Week 48 or the day of Post-Treatment Discontinuation

2.0 Table of Contents

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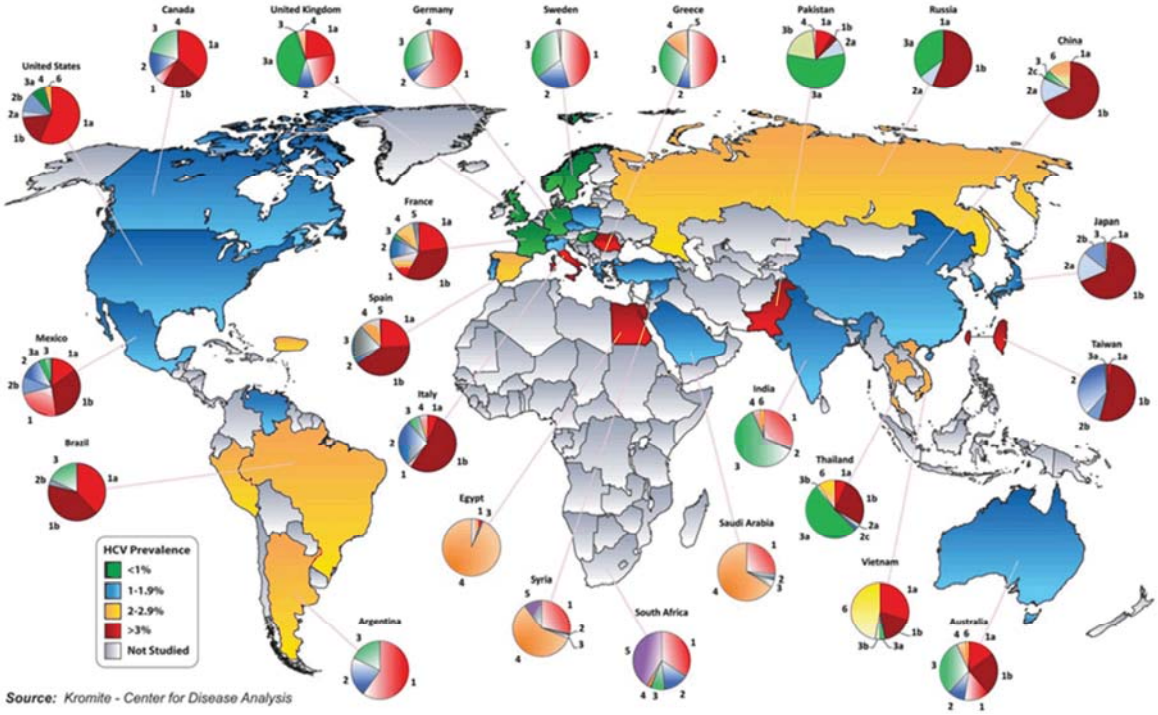
3.0 Introduction

Hepatitis C viral (HCV) infection is a global health problem, with over 170 million individuals chronically infected worldwide.[1] Cirrhosis is a common sequelae of HCV infection occurring in approximately 20% of patients.[2] Complications of cirrhosis include hepatic decompensation (ascites, encephalopathy, variceal hemorrhage, hepatorenal syndrome, or hepatic synthetic dysfunction) and hepatocellular carcinoma ensue at a rate of about 3% per year.[3-6] Without liver transplantation, decompensated cirrhosis leads to death in 50% to 72% of patients after 5 years.7 As a result of the high prevalence of HCV infection and resultant complications, HCV is the leading indication for liver transplantation in the United States and the world as a whole.[8]

World Geographical Distribution of HCV Genotypes

HCV can be classified into 6 major genotypes based on sequence divergence of 30%. In North America and Western Europe, HCV genotype 1 (subgenotypes 1a and 1b) is the most prevalent, causing > 75% of all infections in some countries (Figure 1).[9] In Asia, genotypes 1 (subgenotype 1b), 2, 3, and 6 are the most common types of HCV infections.[10]

Figure 1. Worldwide Distribution of HCV Genotypes



Epidemiology of HCV in China

Chronic HCV infection is recognized as an important cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma in China.[11] Epidemiological studies in the mid-1990s reported a national prevalence of 3.2%,[12] but other reports suggested a prevalence ranging from 0.29% to 9.6%.[13]

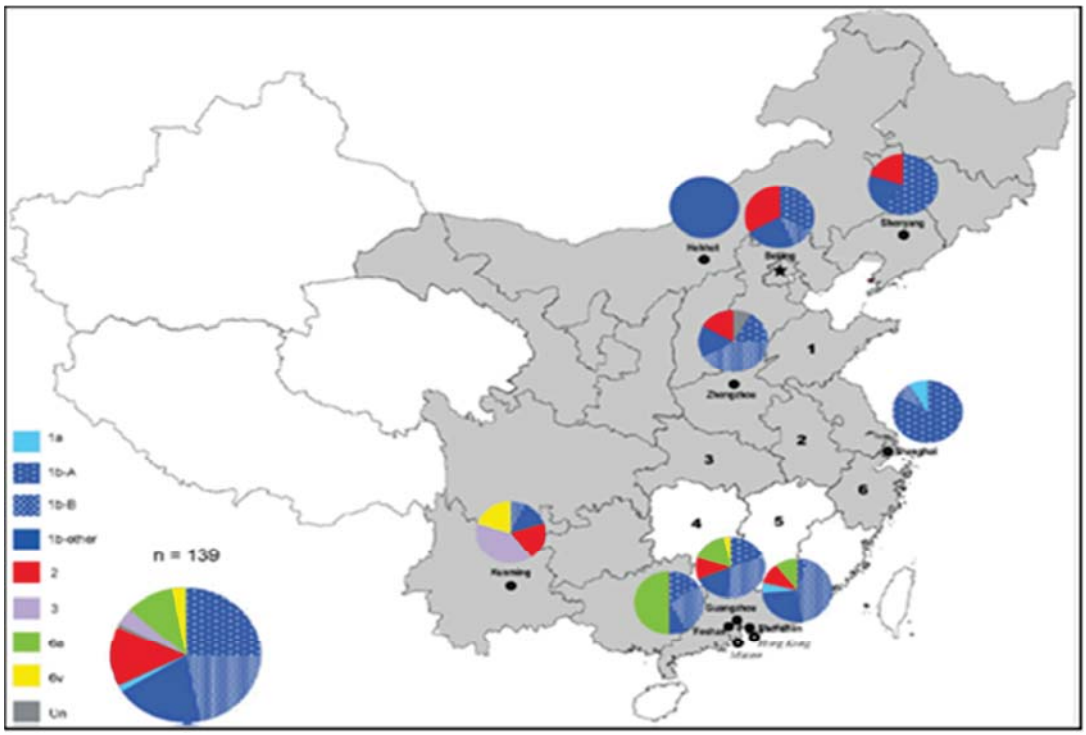
These studies showed that the frequency of HCV infection in China varied by geographical region within the country, age, and population groups and also between rural and metropolitan areas. With the Yangtze River as the boundary, the prevalence rate in northern China (3.6%) was higher than southern China (2.9%).[12] Anti-HCV positive rates were reported to increase gradually with age, from 2% in 1 year old to 3.9% in 50 to 59 year old groups, respectively.[12] A study of individuals > 55 years old in the rural

Henan province found a prevalence of 9.6%,[14] while Liu et al., documented a prevalence of 0.9% in persons 25 to 65 years old in Anyang.[15]

In 2006, the National Nutritional Survey estimated that the overall national prevalence is approximately 0.43%, which represents approximately 5.1 million Chinese infected with HCV.[16] A recent study reported that 25 million Chinese were infected with HCV chronically and advance liver diseases were frequently detected.[17] Among human immunodeficiency virus (HIV)-positive Chinese patients, it is estimated that 60% to 90% are coinfected with HCV.[16] Among patients with chronic hepatitis B, it is estimated that 11% to 15% are coinfected with HCV.[18,19] In addition, 50% of the patients receiving dialysis in China are reported to be infected with HCV.[16] Together, these data suggest that a significant number of Chinese patients are at risk for the morbidity and mortality associated with HCV infection.

An important epidemiologic feature of HCV infections in China is the distribution of genotypes (Figure 2). HCV subgenotype 1b is the most common genotype in China with a prevalence of 66%,[20] but it has been reported to be as high as 90% in some areas of southern China.[16] HCV genotype 2 is the second most common genotype, with a prevalence of 14%,[20] increasing gradually from southern to northern China (Figure 2).[16] Other HCV genotypes include genotype 6, which is detected in approximately 10% of cases, especially in the south region of China; and genotype 3 which is reported in approximately 4.3% of the cases in China (Study M14-491).[20] Majority of these chronic HCV-infected patients in China have IL28B CC genotype.[17]

Figure 2. HCV Genotypes Distributions in China



In summary, the current epidemiology data indicate that HCV infections are an important public health problem in China and that the most prevalent genotypes in the general population countrywide are HCV subgenotype 1b and genotype 2. HCV genotypes 3 and 6 are detected in the southern region of China, but their frequency is reported to be increasing in recent years.

Epidemiology of HCV in South Korea

South Korea is a relatively low prevalence area for HCV, while known as a high prevalence area for HBV infection. For this reason less attention has been given to HCV related liver diseases and few studies have been focused in the analyses of clinical and epidemiological characteristics of HCV-infection in Korea.[21] A recent nationwide seroprevalence survey showed that the age, sex, and area-adjusted prevalence of

anti-HCV antibody in Korean adults in 2009 was 0.78%,[22] whereas the nationwide seroprevalence of HBsAg in persons aged > 10 years in 2009 was 3.2% according to the results of the National Health and Nutrition Examination Survey.[23] In Korea, chronic liver disease is caused by HCV in approximately 10 – 15% of patients and by HBV in 65% to 75% of patients. Few studies have reported the prevalent HCV genotypes in Korea.[24,25] An assessment of anti-HCV antibodies detection performed in blood donor revealed that genotype 1b and 2a/c are dominant in Korea and genotypes 4 and 6 were identified in a small proportion of the tested population.[26]

However, after the launch of new therapeutics such as DAA in 2011, the importance of HCV infection as a cause of liver disease has been increasingly recognized in South Korea.

A recent evaluation of a large multicenter cohort of 1,173 anti-HCV antibody positive adult patients shown that the mean age of the HCV patients is around 55 years old, and half of the infected people were women.[27] The large majority presented with chronic hepatitis (66%) as the clinical diagnosis, followed by cirrhosis of the liver (15%), and HCC (10%). In patients with HCC, cirrhosis was present in 87% of the patients. The proportion of patients with Child class B or C decompensated liver cirrhosis was 8.1%. Comparison of clinical and epidemiological characteristics between patients with subgenotype 1b and those with non-1b genotypes (genotypes 2, 3, 4, and 6) showed that advanced liver disease such as cirrhosis of the liver or HCC was more prevalent in the subgenotype 1b group than in non-1b genotypes (29.4% versus 22.5%, respectively; $P = 0.02$).[27]

Antiviral therapy was initiated in 43% of patients, which is a higher proportion than that reported in studies conducted in the US and Europe.[27-29] The patients who had received antiviral therapy included those with chronic hepatitis (73.2%), cirrhosis of the liver (15.2%), HCC (8.0%), and acute hepatitis (3.6%). Currently, most HCV patients were treated with a combination of pegIFN/RBV (65%), and the remainder were treated with conventional interferon (15%), or a combination of conventional interferon alpha and RBV (17%), or pegIFN alone (3%). The duration of treatment is 48 weeks.[27]

Epidemiology of HCV in Taiwan

Similar to the case in China, the frequency of HCV infection in Taiwan varied by geographical region within the country, age, and population groups. There is a wide geographic variation in HCV seroprevalence in Taiwan. The seroprevalence of anti-HCV varied from 1.7% to 57.9% in different townships in different studies reported over the period from 1992 to 2003. In the HCV hyperendemic areas, transmission may partly be related to the iatrogenic routes. People acquired HCV infection when they received medical or dental procedures, blood transfusion, medical injections, hemodialysis, acupuncture, and similar procedures.[30,31]

In Taiwan, the prevalence of HCV is estimated at 4% to 10% in the general population,[30,32] however increases dramatically in some subpopulations. The prevalence of HCV goes up to 30% to 56% in HIV-positive patients in studies that included different proportions of injecting drug users (IDUs)[31,33,34] and up to 90% in hemophilic patients.[35] After an outbreak of HIV infection occurred among IDUs in Taiwan between 2003 and 2007, HCV seropositivity was 95% to 97% among HIV-positive IDUs.[36] A seroprevalence of anti-HCV positivity also increases gradually with age, from 4.3% in subjects with 60 to 69 years old, 6.3% in subjects with 70 to 79 years old, and 8.8% in subjects with > 80 years old group.[30,37]

In regards to HCV subtype distribution, a difference is observed between the north and south regions. The most common subtype in the south are 1b and genotype 2, while 1b alone is the most common genotype observed in the north regions.[38]

HCV infection is highly associated to mortality due progressive liver diseases (liver cancer, and cirrhosis). However, chronic hepatitis C has been also associated with an increased mortality from extra-hepatic diseases, including circulatory diseases renal diseases, and extra-hepatic cancers.[39] Currently, the local standard of care treatment has been pegINF/RBV for 24 – 48 weeks pending on patients' clinical and virological characteristics.

In summary, the prevalence of HCV in China, South Korea, and Taiwan varies depending on the research and region from less that 1% to 10%. Most patients with Chronic HCV are middle-age. Subgenotype 1b is the predominant serotype detected in more than 60% of the patients followed by genotype 2. The current standard of care (SoC) for the treatment of chronic HCV infection in these countries is pegIFN combined with RBV. SVR rates vary from 50% to 70% among subgenotype 1b, however the pegIFN-RBV regimen carries a well described burden of toxicity (e.g., severe anemia, and depression) and cumbersome weekly injections. Therefore, the treatment for chronic HCV in Asian could be improved by a regimen that requires shorter treatment duration, provides higher SVR rates and a convenient all oral PegIFN-free regimen.

Treatment in HCV Patients with Cirrhosis

Patients with compensated cirrhosis who receive treatment and achieve an SVR (sustained virologic response) essentially eliminate their subsequent risk of decompensation, may achieve histologic regression, and decrease their risk of hepatocellular carcinoma by two-thirds.[40-42]

While the introduction of the protease inhibitors, telaprevir (TVR) or boceprevir (BOC), have increased SVR rates, current treatment is less than optimal as the protease inhibitors must be used in combination with pegIFN/RBV, two agents with considerable treatment limiting toxicities and treatment may extend for up to 48 weeks. Furthermore, regardless of a patient's treatment history, treatment of HCV infected patients with underlying cirrhosis with either telaprevir or boceprevir in combination with pegIFN/RBV results in lower rates of SVR when compared to overall response rates: treatment-naïve patients treated with TVR (62% response rate in cirrhotics versus 79% overall response rate in the ADVANCE study),[43,44] prior partial responders treated with TVR (34% response rate in cirrhotics versus 59% overall response rate in the REALIZE study),[45,46] prior null responders treated with TVR (14% response rate in cirrhotics versus 32% overall response rate in the REALIZE study),[45,46] treatment-naïve patients treated with BOC (31% to 42% response rate in cirrhotics versus 62% to 66% overall response in the SPRINT-2 study),[47]

and treatment-experienced patients treated with BOC (35% response in cirrhotics versus 59% overall response rate in the RESPOND-2 study).[47]

Combinations of multiple DAAs (direct-acting antiviral agent) have the potential of further improving HCV treatment by increasing SVR rates, eliminating interferon (IFN), increasing the safety and tolerability of treatment, shortening duration of therapy and simplifying the treatment algorithm. In addition, wider application of DAA therapy and better responses with combination DAA regimens could significantly reduce the public health burden of this disease.

Promising short-term antiviral efficacy results have been reported from IFN-free combinations (either with or without RBV) of a protease inhibitor with a nucleoside polymerase inhibitor,[48] a non-nucleoside polymerase inhibitor,[49] or a nonstructural protein 5A (NS5A) inhibitor.[50] Twelve-week SVR (SVR_{12}) rates of 36% (4/11) in HCV genotype 1-infected null responders and 90% (9/10) in HCV genotype 1b-infected null responders have been observed in subjects treated with the combination of a protease inhibitor and NS5A inhibitor (BMS 650032 and BMS-790052) for 24 weeks.[51,52] Additionally, a recent descriptive sub-analysis from the SOUND-C2 study, a Phase 2b study evaluating IFN-free treatment with BI 201335 and BI 207127 plus RBV, reported SVR_{12} rates of 54% (20/37) in genotype 1, treatment-naive patients with compensated liver cirrhosis, regardless of IL 28B allele status.[53] Recently, preliminary data from ELECTRON Phase 2 study revealed that sofobuvir/ledipavir combination with or without ribavirin for 12 weeks delivered 100% (11/11) and 70% (7/10) SVR_{12} in cirrhotic genotype 1 HCV patients respectively.[54] LONESTAR trial also demonstrated 100% (11/11) and 91% (11/11) SVR_{12} in sofobuvir/ledipavir with or without RBV in treatment-experienced cirrhotic HCV genotype 1 patients.[55]

Together, these safety and efficacy data suggest that interferon-free DAA combinations may address patient's needs and further advance HCV therapy by increasing SVR rates even in difficult-to-treat populations, improving safety and tolerability of treatment, reducing duration, and simplifying treatment.

AbbVie IFN-Free Regimen

AbbVie's IFN-free regimen for the treatment of chronic HCV genotype 1 infection includes 3 DAAs targeting different steps in HCV replication. ABT-450 is a nonstructural protein 3/nonstructural protein 4A (NS3/NS4A) protease inhibitor coadministered with the pharmacokinetic enhancer, ritonavir (ABT-450/r); ABT-267 is a NS5A inhibitor, and ABT-333 is a NS5B non-nucleoside polymerase inhibitor. The 3-DAA regimen has been studied with and without ribavirin in over 2,300 patients in Phase 3 trials across a variety of patient populations including compensated cirrhosis. Based on Phase 3 data, the regimen with or without RBV is safe, well tolerated and efficacious in treatment-naïve and treatment-experienced HCV genotype 1-infected subjects. The overall efficacy results (intent-to-treat) from the Phase 3 studies are listed in Table 1.

Table 1. SVR_{12} Rates (Intent-to-Treat, Missing = Failure) in Phase 3 by Subpopulation of Subtype, Prior Treatment History, and Presence or Absence of Cirrhosis

Subpopulation	3-DAA 12 Weeks SVR_{12}	3-DAA + RBV 12 Weeks SVR_{12}	3-DAA + RBV 24 Weeks SVR_{12}
Genotype 1b non-cirrhotics			
Naïve	99.0	98.0, 99.5	--
Null	100	93.5, 94.9	--
Partial	100	96.0, 100	--
Relapser	100	97.2, 100	--
Genotype 1a non-cirrhotics			
Naïve	90.2	95.3, 97.0	--
Null	--	95.4	--
Partial	--	100	--
Relapser	--	94.0	--
Genotype 1b cirrhotics			
Naïve	--	100	100
Null	--	100	100
Partial	--	85.7*	100
Relapser	--	100	100
Genotype 1a cirrhotics			
Naïve	--	92.2	92.9
Null	--	80.0	92.9
Partial	--	100	100
Relapser	--	93.3	100

* Based on N = 7; 6/7 achieved SVR.

Phase 3 Placebo-Controlled Studies: Studies M11-646 and M13-098

Study M11-646 and Study M13-098 are randomized, placebo-controlled studies to assess the safety and efficacy of 12 weeks therapy with 3-DAA + RBV in HCV genotype 1-infected treatment-naïve (Study M11-646) and prior pegIFN/RBV non-responders (Study M13 098) without cirrhosis. ABT-450/r/ABT-267 with ABT-333 was given for

12 weeks of treatment in combination with RBV. Subjects randomized to the placebo arm received placebo for 12 weeks, after which they received open-label ABT-450/r/ABT-267 with ABT-333 in combination with RBV for 12 week.

In Study M11-646, treated subjects (N = 631) had a median age of 52 years (range: 18 to 70); 54.5% of the subjects were male; 5.4% were black and 5.1% were Hispanic or Latino; 16.2% had a body mass index (BMI) greater than or equal to 30 kg/m^2; 79.1% had baseline HCV RNA levels ≥ 800,000 international units (IU)/mL; 8.7% had bridging fibrosis (F3); 67.7% had HCV GT1a; 32.3% had HCV GT1b, and 69.3% had IL28B non-CC genotype.

The SVR_{12} rate for treatment-naïve subjects receiving 3-DAA + RBV for 12 weeks in Study M11-646 was 96.2%. Virologic failure was noted in 7/322 (2.2%) GT1a subjects (on-treatment virologic failure: n = 1; relapse: n = 6) and 1/151 (0.7%) GT1b subjects (relapse).

In Study M13-098, treated subjects (N = 394) had a median age of 54 years (range: 19 to 71); 57.6% of the subjects were male; 8.1% were black and 6.3% were Hispanic or Latino; 19.8% had a BMI greater than or equal to 30 kg/m^2; 87.1% had baseline HCV RNA levels ≥ 800,000 IU/mL; 14.5% had bridging fibrosis; 58.4% had HCV GT1a; 41.4% had HCV GT1b; 89.6% had IL28B non-CC genotype; 49.0% were prior pegIFN/RBV null responders; 21.9/% were prior pegIFN/RBV partial responders, and 29.2% were prior pegIFN/RBV relapsers. The SVR_{12} rate for treatment-experienced subjects receiving 3-DAA + RBV for 12 weeks was 96.3% in Study M13-098. Virologic failure (all relapse) was noted in 5/173 (2.9%) GT1a subjects and 2/123 (1.6%) GT1b subjects.

Phase 3 Regimen-Controlled Studies: Studies M13-389, M13-961, and M14-002

Studies M13-389, M13-961, and M14-002 are randomized, regimen-controlled studies to assess the safety and efficacy of 12 weeks of treatment with 3-DAA + RBV versus 3-DAA without RBV. Study M13-961 and Study M14-002 are placebo-controlled

studies, while Study M13-389 is an open-label study. The patient population was different in each of the 3 studies. Study M13-389 enrolled G1b-infected subjects with prior non-response to PegIFN/RBV, Study M13-961 enrolled G1b-infected subjects who were treatment-naïve, and Study M14-002 enrolled G1a-infected subjects who were treatment naïve. All three studies excluded subjects with cirrhosis.

In Study M13-389, treated subjects (N = 186) had a median age of 57 years (range: 26 to 70); 54.8% of the subjects were male; 4.8% were black and 3.2% were Hispanic or Latino; 21.5% had a BMI greater than or equal to 30 kg/m^2; 87.6% had baseline HCV RNA levels ≥ 800,000 IU/mL; 14.5% had bridging fibrosis; 90.9% had IL28B non-CC genotype; 34.9% were prior pegIFN/RBV null responders; 28.5% were prior pegIFN/RBV partial responders, and 36.6% were prior pegIFN/RBV relapsers.

The SVR_{12} rates were 96.6% in the 3-DAA + RBV arm and 100% in the 3-DAA without RBV arm in Study M13-389. The 3-DAA regimen without RBV demonstrated noninferiority in SVR_{12} rates compared to 3-DAA + RBV, as the lower bound of the 95% confidence interval for the difference in response rates was 3.4%, which was above the prespecified noninferiority threshold of –10.5%. No subject in either arm experienced on treatment virologic failure or post-treatment relapse.

In Study M13-961, treated subjects (N = 419) had a median age of 50 years (range: 19 to 70); 45.8% of the subjects were male; 4.8% were black and 1.7% were Hispanic or Latino; 16.5% had a BMI greater than or equal to 30 kg/m^2; 73.3% had baseline HCV RNA ≥ 800,000 IU/mL; 10.0% had bridging fibrosis; and 79.0% had IL28B non-CC genotype.

The SVR_{12} rates for treatment-naïve subjects with HCV GT1b infection who received either 3-DAA + RBV or 3-DAA without RBV for 12 weeks in Study M13-961 were 99.5% and 99.0%, respectively. The 3-DAA regimen demonstrated noninferiority in SVR_{12} rates compared to 3-DAA + RBV, as the lower bound of the 95% confidence interval for the difference in response rates was –2.1%, which was above the prespecified

noninferiority threshold of –10.5%. One of the 419 treated subjects (3-DAA + RBV arm) experienced on-treatment virologic failure.

In Study M14-002, treated subjects (N = 305) had a median age of 54 years (range: 19 to 70); 65.2% of the subjects were male; 11.8% were black and 9.2% were Hispanic or Latino; 19.7% had a BMI greater than or equal to 30 kg/m^2; 86.6% had baseline HCV RNA levels ≥ 800,000 IU/mL; 17.7% had bridging fibrosis; and 69.2% had IL28B non-CC genotype.

The SVR_{12} rates for treatment-naïve subjects with HCV GT1a infection who received either 3-DAA + RBV or 3-DAA without RBV for 12 weeks in Study M14-002 were 97.0% and 90.2%, respectively. The SVR_{12} rate in the 3-DAA arm did not achieve noninferiority to the 3-DAA + RBV arm since the lower bound of the 95% confidence interval for the difference between arms was –12.0%, below the prespecified –10.5% noninferiority margin. Virologic failure was noted in 2/100 (2.0%) subjects (on treatment virologic failure: n = 1; relapse: n = 1) in the RBV-containing regimen and 16/205 (7.8%) subjects (on treatment virologic failure: n = 6; relapse: n = 10) in the RBV-free regimen. The difference between arms demonstrates that RBV contributes to the efficacy in GT1a-infected patients and suggests that 3-DAA + RBV is the optimal regimen for these patients.

A Phase 3 Study in Cirrhotics: Study M13-099

Study M13-099 is a randomized, multicenter, open-label trial in treatment-naïve subjects or subjects previously treated with pegIFN/RBV with chronic HCV GT1-infection with compensated (Child-Pugh A, score ≤ 6) cirrhosis. ABT-450/r/ABT-267 with ABT-333 in combination with RBV was administered for either 12 or 24 weeks of treatment.

Treated subjects (N = 380) had a median age of 58 years (range: 21 to 71); 70.3% of the subjects were male; 3.2% were black and 11.8% were Hispanic or Latino; 28.4% had a BMI greater than or equal to 30 kg/m^2; 14.7% had platelet counts of < 90,000 × 10^9/L, 86.1% had baseline HCV RNA levels of 800,000 IU/mL or greater; 68.7% had HCV

GT1a, 31.3% had HCV GT1b, 81.8% had IL28B non-CC genotype; 42.1% were treatment-naïve, 36.1% were prior pegIFN/RBV null responders; 8.2% were prior pegIFN/RBV partial responders, and 13.7% were prior pegIFN/RBV relapsers.

The SVR_{12} rates for subjects with compensated cirrhosis treated with 3-DAA + RBV for 12 or 24 weeks were 91.8% and 95.9%, respectively. Virologic failure was noted in 13/208 (6.3%) subjects (on treatment virologic failure: n = 1; relapse: n = 12) receiving the 12-week regimen and 4/172 (2.3%) subjects (on treatment virologic failure: n = 3; relapse: n = 1) receiving the 24-week regimen.

Analyses of subgroups suggest that the overall difference in SVR_{12} rates was driven largely by lower SVR_{12} rate among genotype 1a prior null responders who received. The SVR_{12} for the treatment-naïve and treatment-experienced genotype 1b patients were both 99%. Therefore, a 12-week treatment regimen is recommended for all patients with cirrhosis with the exception of GT1a prior null responders for whom 24 weeks of treatment provides a higher SVR.

Integrated Safety Results

A summary of treatment-emergent adverse events from the pooled analyses of data from the Phase 3 studies is presented in Table 2. A majority of subjects experienced at least one event, but most subjects experienced events that were mild in severity. Rates of severe adverse events and adverse events leading to discontinuation were low across studies but numerically higher in the study of subjects with cirrhosis.

Table 2. Overview of Treatment-Emergent Adverse Events (AE)

	Placebo-Controlled		Regimen-Controlled		Cirrhotics	
	12-Week 3-DAA + RBV	12-Week PBO	12-Week 3-DAA + RBV	12-Week 3-DAA	12-Week 3-DAA + RBV	24-Week 3-DAA + RBV
Events, %	N = 770	N = 255	N = 401	N = 509	N = 208	N = 172
Subjects ≥ 1 AE	89.0	76.9	82.8	75.0	91.8	90.7
Severe AE	3.5	0.4	1.0	1.2	6.7	7.6
Grade 3 or 4 AE	3.9	0.8	3.0	2.0	7.7	8.1
Serious AE	2.1	0.4	2.2	1.4	6.3	4.7
AE leading to discontinuation	0.8	0.4	0.5	0.4	1.9	2.3
Deaths	0.1[a]	0	0	0	0.5[b]	0

PBO = Placebo

a. Lung cancer.

b. Metformin toxicity, lactic acidosis, multi-organ system failure.

The most common adverse events regardless of causality are listed in Table 3. Adverse events that occurred at a ≥ 5% incidence in the 3-DAA + RBV regimen versus the placebo were considered to be adverse drug reactions related to the study treatment. These include fatigue, nausea, pruritus, insomnia, asthenia, and anemia. These events were mostly attributable to ribavirin as the rates were lower in the RBV-free arm, and were similar to the placebo rates observed in the placebo-controlled cohorts. In general, rates of adverse events were similar in patients with cirrhosis versus patients without cirrhosis. Patients with cirrhosis had a higher frequency of bilirubin elevations.

Table 3. Treatment-Emergent Adverse Events with ≥ 10% Frequency in at Least One Arm of the Analysis and Rates of Key Post-Baseline Lab Abnormalities

	Placebo-Controlled		Regimen-Controlled		Cirrhotics	
	12-Week 3-DAA + RBV	12-Week PBO	12-Week 3-DAA + RBV	12-Week 3-DAA	12-Week 3-DAA + RBV	24-Week 3-DAA + RBV
Treatment-emergent Adverse Events, %	N = 770	N = 255	N = 401	N = 509	N = 208	N = 172
Headache	34.3	29.8	24.4	25.1	27.9	30.8
Fatigue	34.2	26.3	29.9	26.5	32.7	46.5
Nausea	22.3	14.9	15.7	8.4	17.8	20.3
Pruritus	15.7	4.3	12.0	6.1	18.3	19.2
Insomnia	14.0	7.5	12.2	5.1	15.4	18.0
Diarrhea	13.5	9.0	8.7	11.4	14.4	16.9
Asthenia	13.5	6.7	9.0	3.9	13.9	12.8
Rash	10.0	5.9	6.2	3.7	11.1	14.5
Cough	8.7	5.1	6.7	4.7	11.5	11.0
Irritability	5.3	4.7	3.2	3.1	7.2	12.2
Anemia	5.3	0	7.5	0.2	7.7	10.5
Dyspnea	9.7	5.5	4.7	2.2	5.8	12.2
Laboratory Events, %	N = 765	N = 254	N = 401	N = 509	N = 208	N = 172
Hemoglobin						
< 10 g/dL (Gr 2)	5.5	0	6.2	0	7.2	11.0
< 8.0 g/dL (Gr 3)	0.1	0	0.5	0	1.4	0.6
ALT						
> 5 × ULN (Gr 3)	1.2	3.9	0.7	0.2	2.9	0
Bilirubin						
> 3 × ULN (Gr 3)	2.6	0	5.7	0.4	13.5	5.2

PBO = Placebo

Note: Percentages of laboratory events are based on the number of subjects with at least one post-baseline value.

Transient elevations in total (predominantly indirect) bilirubin may occur due ABT-450 inhibition of OATP1B1, an enzyme involved in bilirubin transport, accentuated by RBV-induced hemolysis. The elevations generally peaked by Weeks 1 – 2 and declined

after wards. Rates of hyperbilirubinemia were lower in subjects treated with 3-DAA without RBV. Rates and degree of hyperbilirubinemia were higher in patients with cirrhosis, but the temporal pattern of elevation followed by resolution was similar and few were symptomatic (jaundice). All bilirubin elevations resolved completely after treatment was discontinued.

Rates of ≥ grade 2 hemoglobin reductions were 5% to 7% across the 12-week arms among subjects who received the RBV-containing regimen, and 11% with the 24-week arm. Grade 3 hemoglobin events were rare. Anemia observed during the clinical trials was attributable to the presence of RBV as it was not observed when the 3-DAA regimen was administered without RBV.

Transient asymptomatic post baseline serum ALT elevations of > 5 × ULN occurred at a frequency of 1% across active treatment arms and were evaluated by an external hepatic panel. The ALT elevations were asymptomatic, usually occurred within the first 4 weeks of treatment and typically declined with ongoing treatment. A disproportionate number of the cases were in women on concurrent estrogen-containing therapy (i.e., contraceptives or hormone replacement) and discontinuation of the hormonal therapy with continuation or brief interruption of the DAA regimen led to resolution in serum ALT elevation. Among the cases of serum ALT elevation thought to be related to the DAA regimen, none resulted in hepatic dysfunction and they resolved or improved with ongoing treatment. All cases had resolved completely in the post-treatment follow-up.

Thirty Asian subjects were enrolled in these Phase 3 studies. Overall, no data in the 37 Asian subjects suggest a difference in efficacy or safety.

In summary, the 3-DAA regimen, with or without RBV, was well tolerated with a low discontinuation rate. Adverse events were typically mild, and the main adverse events and laboratory abnormalities observed were mainly due to the presence of RBV. Transient, asymptomatic serum ALT elevations were observed at a low rate, were not associated with hepatic dysfunction and generally resolved with ongoing treatment.

Study M12-536 is an ongoing Phase 2, multicenter, randomized, dose and duration ranging, open-label study evaluating the antiviral activity, safety and pharmacokinetics of two doses of ABT450/r (100/100 mg or 150/100 mg) with ABT 267 25 mg for 12 or 24 weeks for treatment-experienced HCV subgenotype 1b-infected Japanese subjects and for 12 weeks for treatment-experienced HCV genotype 2-infected Japanese subjects. A preliminary analysis shows that among subjects infected with HCV subgenotype 1b, SVR_{24} rates from 88.9% to 100% were achieved in the 12 week treatment arms, and SVR_{12} rates of 100% were achieved in the 24-week treatment arms. The most common treatment-emergent adverse events (AEs) were nasopharyngitis, headache, back pain, hypertension, gastroenteritis, pruritus, and rash. One serious AE (fluid retention) was deemed as having a reasonable possibility of being related to study drug; this AE led to study drug discontinuation.

The current study is intended to examine the safety and efficacy of the combination of ABT-450/r/ABT-267 and ABT-333 coadministered with ribavirin for 12 weeks in treatment-naïve and pegIFN-containing regimen treatment experienced Asian adults with chronic HCV GT1b infection and compensated cirrhosis.

3.1 Differences Statement

The combination of ABT-450/r, ABT-267 and ABT-333 coadministered with RBV for 12 and 24 weeks was explored in treatment-naïve and treatment-experienced genotype 1 HCV subjects with compensated cirrhosis in Study M13-099 globally except in Asia. This is a study to evaluate ABT 450/r/ABT 267 and ABT-333 coadministered with RBV for 12 weeks in HCV genotype 1b-infected Asian subjects with compensated cirrhosis.

3.2 Benefits and Risks

This is a single arm study with ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks to treat HCV genotype 1b-infected patients with compensated cirrhosis in an Asian population.

The likelihood of successfully demonstrating high SVR_{12} in an Asian cirrhotic population in the current study is high. Based on data from Study M13-099, the SVR_{12} rates for the same regimen in treatment-naïve and treatment-experience genotype 1b patients with compensated cirrhosis were 100% and 98%, respectively. The regimen was well tolerated with < 2% treatment discontinuation rate due to adverse events.

Risks associated with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV, including the risks of toxicity and virologic failure, appear limited and manageable based on the results of the ongoing Phase 3 trials discussed above. Given the potential high rate of cure in this population of HCV-infected subjects, the risk-benefit comparison is favorable.

4.0 Study Objectives

4.1 Primary Objectives

The primary objectives of this study are to assess the safety and to compare SVR_{12} (the percentage of subjects achieving a 12-week sustained virologic response, SVR_{12}, [HCV ribonucleic acid {RNA},< lower limit of quantification {LLOQ}, 12 weeks following therapy]) and SVR_{24} (the percentage of subjects achieving a 24-week sustained virologic response, SVR_{24} [HCV RNA < LLOQ, 24 weeks following therapy]) of 12 weeks of treatment with co-formulated ABT-450, ritonavir and ABT-267 (ABT-450/r/ABT-267) and ABT-333 coadministered with ribavirin to the historical SVR rate of telaprevir plus pegIFN and RBV therapy in HCV genotype 1b-infected cirrhotic adults.

4.2 Secondary Objectives

The secondary objectives of this study are to demonstrate the effect of the DAA combination regimen on HCV RNA levels during and after treatment as measured by on treatment virologic failure and post-treatment relapse, respectively.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, open-label, multicenter study evaluating the efficacy and safety of ABT-450/r/ABT-267 and ABT-333 coadministered with ribavirin for 12 weeks in HCV genotype 1b, treatment-naïve and IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment-experienced adults with compensated cirrhosis.

Treatment will consist of: ABT-450/r/ABT-267 150/100/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) + RBV* for 12 weeks.

* RBV will be administered weight-based 1000 – 1200 mg divided to twice daily.

Approximately 100 subjects will be enrolled (approximately 60 subjects from sites in China and 20 subjects each from sites in S. Korea and Taiwan). At least 35 treatment-naïve and 35 treatment-experienced subjects will be enrolled.

This study will consist of a Treatment Period and a Post-Treatment (PT) Period.

During the Treatment Period, subjects will receive treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV for 12 weeks.

Upon completing the Treatment Period or premature discontinuation of the Treatment Period, subjects will enter the 48-week Post-Treatment Period. Safety evaluations will also occur by a Data Monitoring Committee (DMC); see Section 5.5.5.1.

As this is an open-label study, safety and efficacy evaluations will occur throughout the Treatment and Post-Treatment Periods. Safety evaluations will also occur by a Data Monitoring Committee (DMC); see Section 5.5.5.1.

A primary analysis will occur after all subjects have completed the Treatment Period through Post-Treatment Week 24 of the Post-Treatment Period or prematurely discontinued from the study. An interim analysis will occur after all subjects at sites in

South Korea and Taiwan have completed the Treatment Period through Post-Treatment Week 12 of the Post-Treatment Period or prematurely discontinued from the study. This interim analysis is planned to also support regulatory submission activities in S. Korea and Taiwan.

5.1.1 Screening

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study specific procedures, will receive a unique subject number via the Interactive Response Technology (IRT) system and will undergo the study procedures identified in Section 5.3.1.1 associated with the Screening Visit. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through Study Day 1 prior to dosing and record the results of this assessment and the details of the informed consent process in the subject's medical records. Eligible subjects have up to 35 days following the Screening Visit to enroll into the study.

Subjects who meet all eligibility criteria with the exception of their initial non-invasive assessment of liver cirrhosis by FibroScan may undergo a liver biopsy.

Liver biopsy should only be performed during the Screening Period if all inclusion criteria and none of the exclusion criteria are met (see Section 5.3.1.1 for exception regarding FibroScan).

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

5.1.1.1 Rescreening

Subjects who meet all eligibility criteria with the exception of up to three exclusionary laboratory parameters may rescreen once within the 35-day screening period without prior

AbbVie approval. However, subjects with any of the following exclusionary values will not be allowed to rescreen: exclusionary HCV genotype, a positive hepatitis B surface antigen, positive human immunodeficiency virus (HIV) antibody, confirmed pregnancy, or positive drug screening results without a prescription nor medical justification confirmed by the investigator on over the counter medication. Subjects with more than three exclusionary laboratory results will require approval from the AbbVie Study Designated Physician prior to rescreening. Subjects being rescreened because of exclusionary laboratory parameter(s) must have the related panel(s) repeated (e.g., exclusionary ALT requires a repeat chemistry panel) within the same screening period.

Subjects who otherwise meet all eligibility criteria, but have a positive urine alcohol screen, may have only the urine alcohol screen repeated. If the repeat urine alcohol screen is negative, the subject may be considered eligible.

Subjects who fail to enroll within 35 days of Screening, regardless of the reason for falling outside the 35-day screening window, may be allowed to rescreen only once without approval of the AbbVie Study Designated Physician. These subjects must be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary at the first screening attempt (with the exception of HCV genotype, IL28B genotype, FibroTest, FibroScan, liver biopsy, Follicle stimulating hormone [FSH], and hemoglobin Apolipoprotein A1 [AIC] which do not need to be repeated).

For subjects who do not meet the study eligibility criteria, 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 the eligibility criteria, approximately 100 treatment-naïve and IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment-experienced subjects will be enrolled via IRT and assigned to 12 weeks of treatment. Approximately 100 subjects will be enrolled (approximately 60 subjects at sites in China and 20 subjects each at sites in

South Korea and Taiwan). At least 35 treatment-naïve subjects and 35 treatment-experienced subjects will be enrolled. Subjects will be administered study drugs at the site on Study Day 1. Subjects will receive instructions about the study drugs and the dosing schedule at the Day 1 Visit. ABT-450/r/ABT-267 will be administered orally once daily and ABT-333 and RBV will be dosed orally twice daily as described in Section 5.5.1. The doses are as follows:

- ABT-450/r/ABT-267 150/100/25 mg QD
- ABT-333 250 mg BID
- RBV weight based, 1000 mg to 1200 mg daily divided BID per local label (e.g., < 75 kg = 1000 mg daily divided BID or ≥ 75 kg = 1200 mg daily divided BID)

Subjects will be administered the first doses of study drugs at the site on Study Day 1 (ABT-450/r/ABT-267, ABT-333, and RBV). Plasma samples for pharmacokinetic analysis and HCV RNA analysis will be collected on Study Day 1 prior to dose and at 2 hours post dose and at the additional visits detailed in Table 5 and Table 6.

All subjects will continue to return to the site on an outpatient basis up to 12 weeks for the study procedures identified in Section 5.3.1.1. Sites should ensure that subjects adhere to the study visits listed in Table 5. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

Safety and tolerability of the treatments will be assessed throughout the study. Laboratory testing will include chemistry, hematology, and urinalysis (Section 5.3.1.1). Blood samples for optional pharmacogenetic analysis, will be collected as detailed in Section 5.3.1.3. Patient Reported Outcomes (PROs) will also be assessed at the visits listed in Table 5 and Table 6. Virologic failure criteria will be evaluated and applied by the Investigator as detailed in Section 5.4.1.1 and ongoing review of the data is planned in order to determine if subjects meet the virologic failure criteria (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 and as described in Section 5.4.1.

Ideally, this should occur on the day of study drug discontinuation, but should 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. Subjects who complete or discontinue treatment will be monitored for safety, HCV RNA, the emergence and persistence of resistant viral variants and assessment of PROs in the 48-week Post-Treatment Period as detailed in Section 5.4.1.

5.1.3 Post-Treatment (PT) Period

All subjects who receive at least one dose of DAA in the Treatment Period and either complete treatment or prematurely discontinue study drug will be monitored in the Post-Treatment Period for safety, HCV RNA, the emergence and persistence of resistant viral variants and assessment of PROs for an additional 48 weeks following the last dose of study drug.

The Post-Treatment Period will begin the day following the last dose of study drug treatment. Subjects with HCV RNA < LLOQ at the end of treatment and who have a confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point in the Post-Treatment Period will be considered to have relapsed. Confirmation of an HCV RNA ≥ LLOQ in the Post-Treatment Period should be completed as soon as possible.

Subjects who prematurely discontinue the Post-Treatment Period should return to the site for a Post-Treatment discontinuation visit as outlined in Table 6.

All subjects who receive at least one dose of DAA and who do not achieve and maintain virologic suppression (HCV RNA < LLOQ), or who relapse post DAA therapy, should discuss the future treatment options with the investigators.

5.2 Selection of Study Population

The study population consists of HCV genotype 1b-infected adult subjects with compensated cirrhosis who are either treatment-naïve or (IFN [alpha, beta or pegIFN] with RBV) based treatment-experienced adults. Refer to Section 5.2.1 for details regarding required documentation for prior IFN-based treatment failures.

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 of Chinese, South Korean, and Taiwanese descent with full Chinese, South Korean, and Taiwanese parentage between the ages of 18 and 70 years of age, inclusive, at time of screening.
2. Chronic HCV-infection prior to study enrollment. Chronic HCV-infection is defined as one of the following:
   - Positive for anti-HCV antibody (Ab) or HCV RNA > 1000 IU/mL at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or
   - Positive HCV RNA > 1000 IU/mL at the time of Screening with a liver biopsy consistent with chronic HCV-infection (or a liver biopsy performed prior to enrollment with evidence of chronic hepatitis C disease).
3. Screening laboratory result indicating HCV genotype 1b-infection.
4. Per local standard practice, documentation of cirrhosis by one of the following methods:
   - Diagnosis on previous liver biopsy or liver biopsy conducted during screening, e.g., Metavir Score of > 3 (including 3/4 or 3-4), Ishak score of > 4 or,
   - FibroScan score ≥ 14.6 kPa within 6 months of Screening or during the Screening Period.

   Subjects with a non-qualifying FibroScan result may only be enrolled if they have a qualifying liver biopsy diagnosis.

5. Compensated cirrhosis defined as Child-Pugh score of ≤ 6 at Screening.

6. Subject has never received antiviral treatment including IFN based therapy (IFN [alpha, beta or pegIFN] with or without RBV) for hepatitis C infection (treatment-naïve subject), or subject must have documentation that they meet the definition of one of the following categories (treatment-experienced subject):

   - Non responder: received at least 12 weeks of IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) for the treatment of HCV and failed to achieve undetectable HCV RNA (HCV RNA < LLOD) at the end of treatment; or
   - Relapser: Received IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) for the treatment of HCV and was undetectable (HCV RNA < LLOD) at or after the end of treatment, but subsequently had detectable HCV RNA within 24 weeks of treatment follow-up; or
   - IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) Intolerant: treatment of HCV was discontinued during the treatment period due to intolerance to any of the components of the IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) therapy.

   HCV RNA levels that serve as documentation to support the type of prior non-response should have been obtained in relation to the previous IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment. IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) must have been completed no less than 2 months prior to the Screening visit.

7. Female who is:

   - practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle)
   - sexually active with female partners only
   - not of childbearing potential and sexually active with male partner(s);
     - postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle stimulating hormone [FSH] level indicating a postmenopausal state) or

- surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s)

- of childbearing potential and sexually active with male partner(s):
  - currently using at least one effective method of birth control at the time of screening and
  - agree to using two effective methods of birth control while receiving study drugs (as outlined in the subject information and consent form or other subject information documents), starting with Study Day 1 and for 7 months after stopping study drug or as **directed by the local ribavirin label**.

8. Males who are not surgically sterile who are sexually active with female partner(s) of childbearing potential must agree to practice two effective forms of birth control (as outlined in the subject informed consent or other subject information documents) throughout the course of the study, starting with Day 1 and for 7 months after stopping study drug or **as directed by the local ribavirin label**.
9. Body Mass Index (BMI) is from ≥ 18 to < 38 kg/m^2 at the time of screening. BMI is calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m).
10. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements and must voluntarily sign and date an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to the initiation of any screening or study specific procedures.

Rationale for Inclusion Criteria

1 – 6	To select the appropriate subject population with sufficient disease severity for evaluation
7, 8	For the safety of study subjects
10	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

1. HCV genotype performed during screening indicating unable to genotype or subtype infection with any other HCV genotype or subtype.
2. Positive test result at Screening for hepatitis B surface antigen (HBsAg), or HBV-DNA > LLOQ if HBsAg negative, or anti-human immunodeficiency virus antibody (HIV Ab).
3. Any current or past clinical evidence of Child-Pugh B or C Classification or clinical history of liver decompensation including ascites (noted on physical exam), variceal bleeding or hepatic encephalopathy.
4. Serum Alpha-Fetoprotein (sAFP) > 100 ng/mL at Screening.
5. 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 (a positive ultrasound result should be confirmed with CT scan or MRI.)
6. Any primary 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
   - Drug-related liver disease

   Steatosis and steatohepatitis on a liver biopsy coincident with HCV-related changes would not be considered exclusionary unless the steatohepatitis is considered to be the primary cause of the liver disease.
7. Screening laboratory
   - ALT > 7 × upper limit of normal (ULN)

- Aspartate aminotransferase (AST) > 7 × ULN
- Estimated Glomerular filtration rate adjusted for the Asian population (eGFR) < 50 mL/min/1.73 m^2 as estimated by the C-MDRD method, modified for the Asian population, according to the following formula: eGFR = 175 × (Serum Creatinine) $^{-1.234}$ × (Age) $^{-0.179}$ × (0.79 if female)
- Albumin < 2.8 g/dL
- International normalized ratio (INR) > 2.3. Subjects with a known inherited blood disorder and INR > 2.3 may be enrolled with permission of the AbbVie Study Designated Physician
- Hemoglobin < LLN
- Platelets < 60,000 cells per mm^3
- Absolute neutrophil count (ANC) < 1200 cells/µL
- Total bilirubin ≥ 3.0 mg/dL

8. Females who are pregnant or plan to become pregnant, or breastfeeding, or males whose partners are pregnant or planning to become pregnant within 7 months (or per local RBV label) after their last dose of study drug/RBV.
    - Female subjects with a borderline hCG at Screening and/or Day 1 may enroll into the study if they either:
        - Have a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy; or
        - Are confirmed to be postmenopausal defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone (FSH) level indicating a postmenopausal state at Screening.
9. Use of known strong inducers of cytochrome P450 3A (CYP3A) (e.g.,phenobarbital, rifampin, carbamazepine, St. John's Wort), or strong CYP2C8 inhibitors within 2 weeks or within 10 half-lives, whichever is longer, of the respective medication/supplement, prior to the initial dose of study drug.
10. Use of any medication listed below, as well as those that are contraindicated for ritonavir and RBV, within 2 weeks or 10 half-lives of the medication whichever is longer, to study drug administration including but not limited to:

Table 4. Medications Contraindicated for Use with the Study Drug Regimen

Alfuzosin	Estazolam	Pimozide
Amiodarone	Flecainide	Piroxicam
Astemizole	Flurazepam	Propafenone
Bepredil	Fusidic acid	Propoxyphene
Carbamazepine	Gemfibrozil	Quindine
Cisapride	Hormonal contraceptives	Rifabutin
Clorazepate	Lovastatin	Rifampin
Clozapine	Midazolam (oral)	Sildenafil*
Diazepam	Pethidine	Simvastatin
Efavirenz	Phenobarbital	St. John's Wort
Encainide Ergot	Phenytoin	Terfenadine
Derivatives		Triazolam
(ergotamine, dihydroergotamine, ergonovine, methylergonovine)		Voriconazole

* When used for the treatment of pulmonary arterial hypertension.

Note: Not all medications contraindicated with ritonavir and ribavirin are listed above. Refer to the most current package inserts or product labeling of ritonavir and ribavirin for a complete list of contraindicated medications.

11. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% at the Screening Visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or carcinoma in situ) in the past 5 years.
12. History of solid organ transplant.
13. Clinical significant abnormal ECG, or ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 470 msec at Screening or Study Day 1 (Baseline, prior to dosing).
14. Clinically significant abnormalities or comorbidities, other than HCV-infection, that make the subject an unsuitable candidate for this study in the opinion of the investigator.
15. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol.

16. Positive result of a urine drug screen at the Screening Visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, propoxyphene, or alcohol, with the exception of a positive result associated with documented short term use or chronic stable use of a prescribed or over-the-counter medication. In the case of a positive urine drug screen attributed to an over-the-counter medication, there must be documented medical justification for its use confirmed by the Investigator. Single positive results on urine screen for alcohol are discussed in Section 5.1.1.1, Rescreening.
17. Current enrollment in another interventional clinical study, previous enrollment in this study, or previous use of any protease inhibitor, non-nucleoside polymerase inhibitor, or Ns5A inhibitor, either investigational or experimental (including previous exposure to ABT-450, ABT-267 or ABT333). Receipt of any investigational produce within 6 weeks prior to study drug administration.

Rationale for Exclusion Criteria

1 – 8, 11 – 13, 15	To ensure safety of the subjects throughout the study
9, 10, 16	To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications
14, 17	To avoid bias for the evaluation of efficacy and safety

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, traditional medicines, and/or herbal supplements) that the subject is receiving from the time of signing the consent through the Treatment Period and 30 days after study drugs are stopped, must be recorded in the electronic case report form (eCRF) along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency. The investigator should review all concomitant medications for any potential interactions.

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

The AbbVie Study Designated Physician should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prior HCV Therapy

Treatment-naïve subjects must not have prior or current use of any investigational or commercially available anti-HCV agents, including IFN, pegIFN, telaprevir, boceprevir or RBV. Subjects who previously participated in trials of direct-acting antiviral agents for treatment of HCV may be enrolled with the approval of the AbbVie Study Designated Physician if they can provide documentation that they received placebo.

Treatment-experienced subjects must have previously received IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) and failed treatment. These subjects should have documentation of IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment history, including start and stop dates and HCV RNA levels to document the type of non-response or the reason for discontinuation of therapy to document intolerance in the source document.

Treatment-experienced subjects must have discontinued IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) at least 2 months prior to the Screening Visit and IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) was the last therapy received in order to be eligible for the study.

5.2.3.2 Concomitant Therapy

The investigator should confirm that concomitant medication can be administered with DAAs (including ritonavir). Some medications may require dose adjustments due to potential for drug-drug interactions. The investigator should also review the label(s) for the concomitant medication(s) for additional information.

The use of hepatoprotective medication (e.g., Sho-saiko-to, Milk thistle, ursodeoxycholic acid, glycyrrhizin acid, SAMe, etc.) is allowed, provided that the drug does not meet any other exclusion criterion. While the subject is using hepatoprotective medication, the dose should be kept stable.

During the Post-Treatment Period, investigators should reassess concomitant medications and subjects may resume previously prohibited medications or revert to pre-study doses, 2 weeks following discontinuation of study drugs, if applicable.

5.2.3.3 Prohibited Therapy

In addition to the medications listed above in Table 4, use of known strong inducers of CYP3A or strong inhibitors of CYP2C8 are prohibited within 2 weeks or within 10 half-lives, whichever is longer, prior to the initial dose of study drugs and through the first 2 weeks after the subject has completed active study drugs in the Treatment Period.

Refer to the ritonavir and RBV labeling for a list of prohibited medications. Anti-HCV medications other than those specified in the protocol will not be allowed during the Treatment Period of the study.

Hormonal contraceptives (including oral, topical, injectable or implantable varieties) may not be used from 2 weeks prior to the first dose of study drug until 2 weeks after the end of study drug dosing. Post-menopausal hormone replacement therapy may be used at the discretion of the Investigator.

Management of hematologic growth factor therapy is the responsibility of the Investigator; growth factors will not be provided by AbbVie, and AbbVie will not reimburse for the expense of growth factors or their use.

Investigators should refer to the package inserts for erythropoiesis stimulating agents for additional information regarding their use.

5.3 Efficacy, Pharmacokinetic, Optional Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Table 5. Study Activities – Treatment Period (TP)

Activity	Treatment Period (TP)									
	Treatment Visits – All Subjects									
	Screening	Day1/ Baseline[a]	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12 (EOT)[b]	Premature D/C[b]
Informed Consent[c]	X									
Provide RBV Medication Guide[d] and Partner Risk Fact Sheet	X									
Medical History	X	X[e]								
Physical Exam	X	X							X	X
Vital Signs, Weight, Height	X[f]	X	X	X	X	X	X	X	X	X
ECG	X	X[g]							X	X
Hematology/Chemistry/Urinalysis/ Coagulation Panel	X	X	X	X	X	X	X	X	X	X
Pregnancy Test (serum [s] urine [u])[h]	X (s, u)	X (s, u)			X (u)		X (u)		X (u)	X (u)
Urine Albumin[i]		X								
FSH (all females), HbA1c	X									
HBsAg, Anti-HCV Ab, Anti-HIV Ab, HBV-DNA if HBsAg Negative	X									
Drug/Alcohol Screen	X									
Total Insulin		X							X	X
HCV Genotype and Subgenotype	X									
IL28B Sample		X								

Table 5. Study Activities – Treatment Period (TP) (Continued)

Activity	Treatment Period (TP)									
	Treatment Visits – All Subjects									
	Screening	Day1/ Baseline[a]	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12 (EOT)[b]	Premature D/C[b]
Screening: Liver Biopsy or Fibroscan[j]	X									
Longitudinal FibroTest		X[k]								
Child-Pugh Score	X								X	X
Clinical Assessment of Hepatic Decompensation		X[l]								
HCC Screening: Liver Ultrasound and Alpha Fetoprotein[m]	X									
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X
Patient Reported Outcomes Instruments (PROs)[n]		X			X		X		X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X
Study Drugs Dispensed		X			X		X			
HCV RNA Samples	X	X[o]	X	X	X	X	X	X	X	X
HCV Resistance Sample		X	X	X	X	X	X	X	X	X
Pharmacokinetic Sample		X[p]	X	X	X	X	X	X	X	X
Archive Plasma Sample	X	X	X	X	X	X	X	X	X	X

Table 5. Study Activities – Treatment Period (TP) (Continued)

Activity	Treatment Period (TP)									
	Treatment Visits – All Subjects									
	Screening	Day1/ Baseline[a]	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12 (EOT)[b]	Premature D/C[b]
Archive Serum Sample	X	X	X	X	X	X	X	X	X	X
Interferon Gamma-Induced Protein 10 (IP-10) Sample		X			X		X		X	X
Pharmacogenetic Sample (optional)[q]		X								

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

a. All procedures, including pharmacokinetic sample collection, to be performed prior to first dose with the exception of the 2-hour post-dose pharmacokinetic and HCV RNA samples.

b. Subjects should begin the Post-Treatment Period after the subject completes study drug treatment or prematurely discontinues Treatment Period.

c. Subjects will need to sign an informed consent for the study (prior to performing any screening or study-specific procedures) and the optional Pharmacogenetic sample(s), if applicable.

d. Where applicable/locally available.

e. Medical history will be updated at the Day 1 Visit. This updated medical history will serve as the Baseline for clinical assessment.

f. Height will be measured at Screening only.

g. Evaluate the Day 1 ECG prior to dosing to determine eligibility.

h. Urine pregnancy testing is not required after the Screening Visit for female subjects with a documented history of bilateral tubal ligation, bilateral oophorectomy or hysterectomy or who are confirmed to be post-menopausal. A positive urine pregnancy test requires a confirmatory serum test. (Refer to Section 5.3.1.1 [Pregnancy Test] for additional details.)

i. Done at Day 1/Baseline and collected for decrease in eGFR as defined in Section 5.3.1.1.

j. Subjects who do not have a qualifying historical liver biopsy, but who otherwise meet all of the inclusion criteria and none of the exclusion criteria will undergo a liver biopsy.

k. Longitudinal FibroTest measured for exploratory analysis of fibrosis over time. Day 1 results will be blinded to the investigator/site.

Table 5. Study Activities – Treatment Period (TP) (Continued)

l. Clinical assessment of Hepatic encephalopathy and ascites at Day 1 prior to dosing.

m. Liver Ultrasound and alpha fetoprotein to be performed at Screening. Subjects with a historical negative Liver Ultrasound, CT or MRI (within 3 months prior to screening) are not required to have a screening Ultrasound performed. If additional Liver Ultrasound testing is required it should be completed as an unscheduled visit. A positive Ultrasound result suspicious for HCC will be confirmed with CT scan or MRI.

n. SF-36v2, EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L), and Hepatitis C Virus Patient Reported Outcomes Instrument (HCVPRO), should be administered before any study procedures and in the following order: SF-36v2, EQ-5D-5L and HCVPRO.

o. HCV RNA will be collected at 0-hour (immediately prior to the morning dose) and at 2 hours post-dose.

p. Blood Sample(s) for pharmacokinetic assay as described in Section 5.3.2.1 will be collected as follows:

- Day 1: 0-hr (immediately prior to the morning dose), and at 2 hours post-dose.
- A single pharmacokinetic sample will be collected at all other Treatment Study Visits without regard to the time of dosing as detailed in Section 5.3.2.1 above. Additional intensive PK samples will be collected at a single visit on or after the Week 2 study visit. Samples will be collected at predose and approximately 2, 4, 6 and at 24 hours post DAA dose. Subjects may opt out of intensive PK sampling. On the day of intensive blood sampling, subjects will take their morning dose of DAAs and ribavirin onsite in the presence of study site personnel and the time of administration will be noted.

q. If the optional pharmacogenetic sample is not collected at Day 1, it may be collected at any other visit during the study.

Table 6. Study Activities – Post-Treatment (PT) Period

Activity	PT Wk 2	PT Wk 4	PT Wk 8	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48 or PT D/C[a]
Vital Signs and Weight	X	X	X	X	X	X	X
Hematology/Chemistry/Urinalysis/Coagulation Panel	X	X	X	X	X	X	X
Monthly Pregnancy Test (females)[b]		X	X	(Weeks 12, 16, 20, 24, 28)			
Longitudinal FibroTest				X			X
Child-Pugh Score				X			
HCC Screening: Liver Ultrasound and Alpha Fetoprotein[c]				X		X	
PRO Instruments[d]		X		X	X		X
Concomitant Medication Assessment[e]	X	X	X	X	X	X	X
Adverse Event Assessment[f]	X	X	X	X	X	X	X
HCV RNA[g]	X	X	X	X	X	X	X
HCV Resistance Sample	X	X	X	X	X	X	X
Archive Plasma Sample	X	X	X	X	X	X	X
Archive Serum Sample	X	X	X	X	X	X	X
IP-10 Sample					X		X

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

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

b. Urine pregnancy testing is not required after TP Day 1 visit for female subjects with a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy, or who are confirmed post-menopausal. At PT Weeks 16, 20 and 28, subjects may have an unscheduled office visit for pregnancy testing or elect to perform the tests at home with test kits provided by the site. Additional testing may be required per local RBV label.

Table 6. Study Activities – Post-Treatment (PT) Period (Continued)

c. Liver ultrasound and alpha fetoprotein to be performed at PT Week 12 and PT Week 36. A positive Ultrasound result suspicious for HCC will be confirmed with CT scan or MRI.

d. PRO instruments should be administered before any study procedures and in the order listed below.
   - **PT Week 4:** SF-36v2, EQ-5D-5L and HCVPRO
   - **PT Week 12:** SF-36v2, EQ-5D-5L and HCVPRO
   - **PT Week 24:** SF-36v2, EQ-5D-5L and HCVPRO
   - **PT Week 48 or D/C:** SF-36v2, EQ-5D-5L and HCVPRO

e. Only medications related to the treatment of HCV and medications prescribed in association with a SAE will be collected after 30 days post-dosing.

f. Only SAEs will be collected after 30 days post-dosing.

g. Confirmation of an HCV RNA ≥ LLOQ in the post-treatment period should be completed as soon as possible per Section 5.1.3.

5.3.1.1 Study Procedures

The study procedures outlined in Table 5 and Table 6 are discussed in detail in this section with the exception of the assessment of concomitant medications (Section 5.2.3.3), the collection of blood samples for optional pharmacogenetic analysis (Section 5.3), the collection of blood samples for pharmacokinetic analysis (Section 5.3.2), the monitoring of treatment compliance (Section 5.5.6), 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 individual laboratorie(s).

Informed Consent and RBV Information

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. All subjects will be given the RBV Medication Guide (where applicable/locally available). Male subjects will be given an additional copy of the RBV Medication Guide (where applicable/locally available) and a RBV Partner Risk Fact Sheet to share with their female partner(s). Details about how informed consent will be obtained and documented are provided in Section 9.3.

Medical History

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

Physical Examination

A complete physical examination will be performed at visits indicated in Table 5, or upon subject discontinuation. A symptom-directed physical examination may be performed at any other visit, when necessary.

The physical examination performed on Day 1 of the Treatment Period 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

Body temperature (oral or tympanic), blood pressure, pulse, and body weight will be measured at the visits indicated in Table 5 and Table 6. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes. The vital signs performed on Day 1 will serve as the baseline for clinical assessment. The subject should wear lightweight clothing and no shoes during weighing. Height will only be measured at Screening; the subject will not wear shoes.

12-lead Electrocardiogram

A 12-lead resting ECG will be obtained at the visits indicated in Table 5 or upon subject discontinuation from the Treatment Period (or as clinically needed). The Day 1 (Treatment Period) reading will serve as the baseline assessment. The ECG should be performed prior to blood collection.

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 all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

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

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

The QT interval measurement (corrected by Fridericia formula, QTcF) will be documented in the eCRF only if the local reader's assessment is "prolonged QT."

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 7 at the visits indicated in Table 5 and Table 6.

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

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

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study. The certified laboratory chosen for this study is Covance. Information on the location of the lab where samples will be sent will be found in the lab manual.

Table 7. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Additional Tests
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands, if detected Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable) ANC Prothrombin Time/INR[a] Activated partial thromboplastin time (aPTT) Reticulocyte count	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin[a,b] Direct and indirect bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin[a] Chloride Bicarbonate Magnesium Gamma-glutamyl transferase (GGT)[b] Creatinine clearance (Cockcroft Gault calculation) eGFR[e] Alpha2-macroglobulin[b] Haptoglobin[b] Apolipoprotein A1[b] Alpha fetoprotein	HBV DNA[g] HBsAg[c] Anti-HCV Ab[c] Anti-HIV Ab[c] FSH (all females)[c] Opiates[c] Barbiturates[c] Amphetamines[c] Cocaine[c] Benzodiazepines[c] Alcohol[c] Phencyclidine[c] Propoxyphene[c] Methadone[c] Urine and Serum Human Chorionic Gonadotropin (hCG) females)[d] Total insulin HCV RNA Hepatitis B Panel[f] Hepatitis A Antibody, Total[f] Hepatitis E Virus IgG[f] Hepatitis E Virus IgM[f] Hemoglobin A1C[c] IP-10 IL28B[c] HCV genotype and subtype[c] Pharmacogenetic sample (optional)
Urinalysis		
Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocyte esterase Microscopic (reflex) Albumin[i] Urine Archive Specimen[h]		

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

b. Also a component of FibroTest.

c. Performed only at Screening.

d. Urine pregnancy testing is not required after Day 1 of the Treatment Period for female subjects who are confirmed to be post-menopausal or who have a documented history of prior bilateral tubal ligation, bilateral oophorectomy or hysterectomy.

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

f. Performed for management of transaminase elevations. See Section 6.7.4 for details.

g. Only performed if HBsAg is negative.

h, Performed if eGFR level is < 50 mL/minute. See Section 6.7.5 Management of eGFR decreases for details.

i. Collected at Day 1 and if eGFR level < 50 mL/minute. See Section 6.7.5 Management of eGFR decreases for details.

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

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

The management of laboratory abnormalities that may occur during the study is described in Section 6.7.

Pregnancy Test

A urine pregnancy test will be performed for all female subjects at all the visits indicated in Table 5 and Table 6 except for those female subjects with a documented history of bilateral tubal ligation, bilateral oophorectomy or hysterectomy or who are confirmed to be post-menopausal. In addition, a serum pregnancy test will be performed at Screening and Day 1 and analyzed by the central laboratory. All urine pregnancy tests will be performed on-site during the study visit if there is a scheduled visit, as indicated in Table 5 and Table 6 and monthly for a minimum of 7 months after the discontinuation of RBV, or according to the local RBV label and/or local treatment guidelines for RBV. A positive urine pregnancy test requires a confirmatory serum test. Urine pregnancy tests are not required after Day 1 for female subjects with a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy, or for subjects who are confirmed to be postmenopausal. Confirmation of postmenopausal status will be determined during the Screening period, based on the subject's history and on the FSH level.

During post-treatment where there is not a scheduled study visit, female subjects of childbearing potential may either have pregnancy testing performed at the site as an unscheduled study visit using an unscheduled test kit or a urine pregnancy test may be conducted by the subject at home with a pregnancy test kit provided by the site; site

personnel should contact these female study subjects to capture the results of any study related pregnancy tests performed at home. The at home pregnancy test results will only be recorded in the subject's source records.

If the subject elects to return to the study site for an unscheduled visit for pregnancy testing, the results of the urine pregnancy test will be captured in the eCRF, unless serum pregnancy is elected. Serum pregnancy testing will be completed by the central laboratory.

Hepatitis and HIV Screen

HBsAg (hepatitis B surface antigen), anti-HCV Ab, anti-HIV Ab and HBV-DNA (only if HBsAg is negative) will be performed at Screening. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report these results per local regulations, if necessary. The HBsAg and/or HBV DNA results will be reported by the central laboratory to the clinical database.

Urine Screens for Drugs of Abuse

Urine specimens will be tested at the Screening Visit for the presence of drugs of abuse. The panel for drugs of abuse will minimally include the drugs listed in Table 7. A positive screen is exclusionary, with the exception of a positive screen associated with documented short-term use or chronic stable use of a prescribed medication in that class.

Subjects who otherwise meet all eligibility criteria, but have a positive urine alcohol screen, may have only the urine alcohol screen repeated as described in Section 5.1.1. If the repeat urine screen is negative, and all other eligibility criteria have been met, the subject may be considered eligible for study participation.

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

Screening: Liver Biopsy or FibroScan

To be eligible, subjects must have a diagnosis of cirrhosis by **one** of the following methods, per local standard practice:

- Diagnosis on liver biopsy, e.g., Metavir Score of > 3 (including 3/4), Ishak score of > 4; or
- FibroScan score ≥ 14.6 kPa within 6 months of Screening or during the Screening Period;
- Subjects with a non-qualifying FibroScan result may only be enrolled if they have a qualifying liver biopsy.

Longitudinal FibroTest

In addition to the assessments of cirrhosis performed during the Screening Period, all subjects will have FibroTest performed at baseline (Day 1) and throughout the Post-Treatment Period as indicated in Table 5 and Table 6 for the purpose of assessing changes in liver fibrosis over time. Day 1 results will be blinded to the investigator/site.

Child-Pugh Score and Category

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 visits indicated in Table 8.

Table 8. Child-Pugh Classification of Severity of Cirrhosis

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

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

** Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.
Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

Clinical Assessment of Hepatic Decompensation

A clinical assessment of hepatic encephalopathy and ascites will be performed at Day 1 prior to dosing to confirm the subject has not progressed to hepatic decompensation since Screening.

Hepatocellular Carcinoma Screening: Liver Ultrasound and Alpha Fetoprotein

In order to monitor for the presence of hepatocellular carcinoma (HCC), alpha fetoprotein will be assayed and an ultrasound of the liver will be performed as indicated in Table 5 and Table 6.

A positive Ultrasound result suspicious for HCC at screening will be confirmed with CT scan or MRI during the screening period. Suspicious ultrasound lesions confirmed by CT or MRI are exclusionary.

A positive Ultrasound result suspicious for HCC during the treatment or Post-Treatment Period will be confirmed with CT scan or MRI. Confirmatory results should be discussed with the AbbVie Study Designated Physician as appropriate.

Concomitant Medication Assessment

Use of medications (prescription or over-the-counter, including vitamins and herbal supplements) from the time of signing the consent through 30 days after last dose of study drug will be recorded in the eCRF at each study visit indicated in Table 5.

During the Post-Treatment Period, antiviral therapies related to the treatment of HCV and medications prescribed in association with an SAE will be recorded in the eCRF at the visits indicated in Table 6.

Assignment of Subject Numbers

All screening activities must be completed and reviewed prior to enrollment. Subjects who meet the eligibility criteria will proceed to enrollment via the IRT system on Day 1 (Treatment Period).

Subject numbers will be unique 4-digit numbers and will begin with 1001 with the first two digits representing the investigative site, and the last two digits representing the subjects at that site. Enrolled subjects will keep their subject number assigned at the Screening Visit.

Study Drug Diary

Subjects will be provided self-administration instructions and study drug diaries to record the exact date, time and number of tablets of study drug administration. On Study Day 1 , the time of dosing will be recorded to the nearest minute by the site staff. The exact date, time and number of tablets of study drug taken will be recorded daily by the subjects between study visits. In the event the study drug diary is not available, the site may obtain dosing information via patient interview and record this information in the source notes.

Patient Reported Outcomes (PRO) Instruments (Questionnaires)

Subjects will complete the self-administered PRO instruments (where allowed per local regulatory guidelines) on the study days indicated in Table 5 and Table 6. Subjects will be instructed to follow the instructions provided with each instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read or understand any of the instruments may have site personnel read the questionnaires to them. Site personnel will encourage completion of each instrument at all visits and will ensure that a response is entered for all items.

In this study, PRO instruments should be consistently presented so that subjects complete the SF-36v2 instrument first, followed by the EQ-5D-5L and followed by the HCVPRO. PRO instruments should be completed prior to drug administration (on Day 1) and prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels.

Short Form 36 – Version 2 Health Status Survey

The SF-36v2 is a general Health Related Quality of Live (HRQoL) instrument with extensive use in multiple disease states. The SF-36v2 instrument comprises 36 total items (questions) targeting a subject's functional health and well-being in 8 dimensions (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). Scoring is totaled into a Physical Component Summary and a Mental Component Summary. Higher SF-36v2 scores indicate a better state of health. Completion of the SF-36v2 should require approximately 10 minutes to complete.

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

The EQ-5D-5L is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-5L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on

5 levels of severity. Responses to the 5 items encode a discrete health state which is mapped to a preference (utility) using country-specific based weights, where available. Subjects also rate their perception of their overall health on a separate visual analogue scale (VAS). The EQ-5D-5L should require approximately 5 minutes to complete.

HCV Patient Report Outcomes (HCVPRO) Instrument

The HCVPRO has been developed specifically to capture the function and wellbeing impact of HCV conditions and treatment. This instrument has been preliminarily validated and further validation is ongoing. The HCVPRO contains 16 items important to HCV patients; items are totaled to a summary score. Higher HCVPRO score indicates a better state of health. Completion of the HCVPRO should require approximately 5 minutes.

Study Drug Compliance for Kits

Study drug compliance will be recorded per kit in the IRT system. Study drugs will be collected at each drug dispensation visit after Day 1, as indicated Section 5.5.6. The number of tablets of ABT-450/r/ABT-267, ABT-333, and of RBV remaining in each bottle will be recorded in the source and transferred to the IRT system along with the date of reconciliation.

HCV Genotype and Subgenotype

Plasma samples for HCV genotype and subgenotype will be collected at Screening. Genotype and subgenotype will be assessed using the Versant® HCV Genotype Inno LiPA Assay, Version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY).

HCV RNA Levels

Plasma samples for HCV RNA levels will be collected as indicated in Table 5 and Table 6. Plasma HCV RNA levels will be determined for each sample collected by the

central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v. 2.0. For this assay, the lower limit of quantification (LLOQ) is 15 IU/mL.

HCV Resistance Testing Sample

A plasma sample for HCV resistance testing will be collected at 0-hour (prior to dose) and 2 hours post dose on Day 1 and at the study visits, indicated in Table 5 and Table 6. Specific instructions for preparation and storage of HCV RNA and HCV resistance samples will be provided by the central laboratory, the Sponsor, or its designee.

Archive Plasma Sample

Archive plasma samples will be collected at the study visits, indicated in Table 5 and Table 6. Archive plasma samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, viral load, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by the Sponsor.

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

Archive Serum Sample

Archive serum samples will be collected at the study visits, indicated in Table 5 and Table 6. Archive serum samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, viral load, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by the Sponsor.

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

Interferon Gamma-Induced Protein 10 (IP-10) Levels

A plasma sample for IP-10 testing will be collected at the study visits indicated in Table 5 and Table 6. Specific instructions for preparation and storage of IP-10 samples will be provided by the central laboratory, the Sponsor, or its designee.

5.3.1.2 Meals and Dietary Requirements

All study drugs should be dosed together and administered with food, i.e., the AM dose of ABT-450/r/ABT-267, ABT-333 and RBV should be taken together with food and the PM dose of ABT-333 and RBV should be taken together with food.

5.3.1.3 Blood Samples for Pharmacogenetic Analysis

IL28B Sample

One (required) whole blood sample for DNA isolation will be collected from each subject Day 1 for Interleuken 28B (IL28B) pharmacogenetic analysis. This sample will not be used for any testing other than IL28B genotypes.

Optional Sample for Pharmacogenetic Analysis

A separate (optional) whole blood sample for DNA isolation will be collected on Day 1 (Treatment Period) from each subject who consents to provide the optional sample for pharmacogenetic analysis. If the optional pharmacogenetic sample is not collected at Day 1, it may be collected at any other visit during the study. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

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

Samples will be stored in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABT-450, ABT-267 and ABT-333 (or drugs for the treatment of HCV) continues but no longer than 10 years.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic assay of ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, as well as ritonavir and RBV will be collected by venipuncture at each study visit, including at Day 1, for the 0-hour and 2-hour PK sample collection. Intensive PK samples will be collected from at least 30 subjects at a visit on or after 2 weeks of the beginning of the treatment with DAAs. Samples will be collected at predose and approximately 2, 4, 6, and at 24 hours post DDA dose. Subjects may opt out of intensive PK sampling.

The date and time of the first dose of each drug will be recorded in the source documents and the eCRF. The time that each blood sample is collected will be recorded to the nearest minute.

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 ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ritonavir and RBV 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 ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ritonavir, RBV and archive plasma samples will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory. Specific instructions for shipping to the analytical lab from the central laboratory will be provided by the central laboratory, the Sponsor, or its designee.

5.3.2.4 Measurement Methods

Plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, and RBV will be determined using validated assay methods under the supervision of the Drug Analysis Department at AbbVie. Plasma concentrations of possible metabolites of ABT-450 and ABT-267, and other metabolites of ABT-333 may also be determined using non-validated methods.

5.3.3 Efficacy Variables

Virologic response will be assessed by HCV RNA in IU/mL at various time points from Day 1 through 48 weeks after completion of treatment.

5.3.3.1 Primary Variable

The primary endpoints are the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) and the percentage of subjects with SVR_{24} (HCV RNA < LLOQ 24 weeks after the last actual dose of study drug).

5.3.3.2 Secondary Variable(s)

The secondary endpoints are:

- The percentage of subjects with on-treatment virologic failure;
- The percentage of subjects with relapse by post treatment Week 12;
- The percentage of subjects with relapse by post treatment Week 24.

5.3.3.3 Resistance Variables

The following resistance analyses will be performed for subjects receiving study drugs who experience virologic failure (who have HCV RNA ≥ 1000 IU/mL):

1. the amino acid variants at baseline at signature resistance-associated positions identified by population nucleotide sequencing and comparison to the prototypic reference sequence,

2. the amino acid variants in available post-baseline samples identified by population nucleotide sequencing and comparison to the baseline sequence,
3. the amino acid variants in available post-baseline samples at signature resistance associated positions identified by population nucleotide sequencing and comparison to the prototypic reference.

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

Values for the pharmacokinetic parameters of ABT-450, ABT-267, ritonavir, ABT-333, ABT-333 M1 metabolite, and RBV including the C_{max}, T_{max}, C_{trough}, and AUC will be determined by noncompartmental methods using data from subjects who participate in the intensive pharmacokinetic sampling. Additional parameters or summaries may be determined if useful in the interpretation of the data.

Individual plasma concentrations and pharmacokinetic parameters of ABT-450, ABT-267, ritonavir, ABT-333, ABT-333 M1 metabolite, ribavirin and possible metabolites of ABT-450, ABT-267, and ABT-333 (other than ABT-333 M1) will be tabulated and summarized.

5.3.6 Pharmacogenetic Variables

IL28B genotypes are associated with response to pegIFN/RBV. IL28B status will be determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. These IL28B genotype results may be analyzed as part of a multi-study assessment of IL28B and response to ABT-450, ABT-267, ABT-333, or drugs of these classes. The results may also be used for the development of diagnostic

tests related to IL28B and study treatment, or drugs of these classes. The results of additional pharmacogenetic analyses may not be reported with the clinical study report.

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

DNA samples from subjects who separately consent for additional pharmacogenetic analysis may be analyzed for genetic factors contributing to the subject's response to study treatment, in terms of pharmacokinetics, pharmacodynamics, efficacy, tolerability and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related to drug response (including IL28B). Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. Pharmacogenetic analyses will be limited to studying response to HCV therapy; no other analyses will be performed.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

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

If, during the course of study drug administration, the subject prematurely discontinues during the Treatment Period or the Post-Treatment Period, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Table 5 and Table 6. Ideally this should occur on the day of study drug discontinuation, but no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in

accordance with the Investigator's best clinical judgment. The last dose of any study drug and reason for discontinuation from the Treatment Period will be recorded in the EDC (electronic data capture) system. The subject should then begin the Post-Treatment Period where the subject will be monitored for 48 weeks for safety, HCV RNA, the emergence and persistence of resistant viral variants and PROs.

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

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the Treatment Period, the administration of study drug (including RBV) to that subject must be discontinued immediately. Specific instructions regarding subject pregnancy can be found in Section 6.6. Subjects will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3. The Investigator is also encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry.

5.4.1.1 Virologic Failure Criteria

The following criteria will be considered evidence of virologic failure. Subjects demonstrating any of the following will be discontinued from study drug:

- 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;
- Failure to achieve HCV RNA < LLOQ by Week 6 (≥36 days of treatment); or
- Confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point after HCV RNA < LLOQ during treatment.

Confirmatory testing should be completed as soon as possible. Subjects should remain on study treatment until the virologic failure has been confirmed.

If any of the above criteria are met for subjects on DAA therapy, the subject will discontinue study treatment (Section 5.4.1). Subjects with HCV RNA < LLOQ at the end of treatment and who have a confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point in the Post-Treatment Period will be considered to have relapsed. Confirmation of an HCV RNA ≥ LLOQ in the Post-Treatment Period should be completed as soon as possible.

5.4.2 Discontinuation of Entire Study

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

5.5 Treatments

5.5.1 Treatments Administered

Each dose of study drug (ABT-450/r/ABT-267, ABT-333 and RBV) will be dispensed in the form of tablets at the visits listed in Table 6.

ABT-450/r/ABT-267 will be provided by the Sponsor as 75 mg/50 mg/12.5 mg tablets. ABT 450/r/ABT-267 will be taken orally as 2 tablets once daily which corresponds to a 150 mg ABT-450/100 mg ritonavir/25 mg ABT-267 dose QD.

ABT-333 will be provided by the Sponsor as 250 mg tablets. ABT-333 will be taken orally as 1 tablet twice daily, which corresponds to a 250 mg dose BID.

RBV will also be provided by the Sponsor to the Investigator for use in this study. RBV will be provided as 200 mg tablets for Korea and Taiwan sites. RBV will be provided as 100 mg tablets for China sites. RBV has weight-based dosing 1000 to 1200 mg divided twice daily per local label. (For example, for Korea and Taiwan subjects weighing less than 75 kg, 200 mg RBV may be taken orally as 2 tablets in the morning and 3 tablets in the evening which corresponds to a 1000 mg total daily dose. Or for subjects weighing 75 kg or more, 200 mg RBV may be taken orally as 3 tablets in the morning and 3 tablets in the evening which corresponds to a 1200 mg total daily dose. For example, for Chinese subjects weighing less than 75 kg, RBV 100 mg tablets may be taken orally as five 100 mg tablets in the morning and five 100 mg tablets in the evening which corresponds to a 1000 mg total daily dose. Or for Chinese subjects weighing 75 kg or more, RBV 100 mg tablets may be taken orally as six 100 mg tablets in the morning and six 100 mg tablets in the evening which corresponds to a 1200 mg total daily dose.)

At Day 1 subjects will be administered study drugs by the study site personnel and receive instructions for self-administration of all study drugs from Study Day 2 through Study Week 12 of the Treatment Period.

On the day of intensive PK subjects will take their morning dose of DAAs and RBV onsite in the presence of study site personnel and the time of administration will be noted.

Subjects will be instructed to take study medication at the same time(s) every day. All compounds should be taken with food.

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

All subjects who receive at least one dose of DAA and who fail to achieve virologic suppression, or who experience virologic breakthrough on DAA therapy will be discontinued from treatment. Resistance monitoring will continue in the Post-Treatment Period regardless whether subjects opt for alternative post-study treatment.

5.5.2 Identity of Investigational Product

Information about the study drugs to be used in this study is presented in Table 9.

Table 9. Identity of Investigational Products

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
ABT-450/ Ritonavir/ABT-267	AbbVie	Oral	Tablet	75 mg/50 mg/ 12.5 mg
ABT-333	AbbVie	Oral	Tablet	250 mg
Ribavirin for Korea and Taiwan	Roche or Generic Manufacturer	Oral	Tablet	200 mg
Ribavirin for China	Shanghai Sine Tianping Pharmaceutical Co., Ltd.	Oral	Tablet	100 mg

5.5.2.1 Packaging and Labeling

ABT-450/r/ABT-267 tablets will be supplied in bottles containing 64 tablets. ABT-333 will be supplied in bottles containing 64 tablets. Ribavirin 200 mg will be supplied in bottles containing 168 tablets each for Korea and Taiwan. Ribavirin 100 mg will be supplied in cartons for China. Each Ribavirin 100 mg carton will contain a blister pack of 24 tablets for China.

Each bottle or carton will be labeled as required per country requirements.

The labels must remain affixed to the bottles or cartons. 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
ABT-450/Ritonavir/ABT-267 bottles	15° to 25°C (59° to 77°F)
ABT-333 bottles	15° to 25°C (59° to 77°F)
Ribavirin 200 mg bottles Ribavirin 100 mg cartons	15° to 25°C (59° to 77°F) 15° to 25°C (59° to 77°F)

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to the Sponsor. Upon receipt of study drugs, the site will acknowledge receipt within the IRT system.

5.5.3 Method of Assigning Subjects to Treatment

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

Subjects who are enrolled will retain their subject number, assigned at the Screening Visit, throughout the study. For enrollment of eligible subjects into the study, the site will utilize the IRT system in order to receive unique study drug kit numbers. The study drug kit numbers will be assigned according to schedules computer-generated before the start of the study by the AbbVie Statistics Department. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each 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. Study drug dosing will be initiated at the Study Day 1 Visit.

ABT-450/r/ABT-267 will be dosed QD; ABT-333 and RBV will be dosed BID. Thus with normal dosing, 2 ABT-450/r/ABT-267 tablets, 1 ABT-333 tablet, should be taken in the morning, and 1 ABT-333 tablet should be taken in the evening.

RBV should be dosed BID, e.g., 2 to 3 tablets taken in the morning, and 3 RBV tablets taken in the evening for subjects in Korea and Taiwan, or 5 to 6 tablets taken in the morning and 5 to 6 tablets taken in the evening for subjects in China.

All study drugs should be dosed together and administered with food i.e., the AM dose of ABT-450/r/ABT-267, ABT-333 and RBV should be taken together with food and the PM dose of ABT-333 and RBV should be taken together and with food.

5.5.5 Blinding

This is an open-label study.

5.5.5.1 Data Monitoring Committee

An independent DMC will review safety data and provide recommendations to the Sponsor as per the DMC charter. The charter also describes DMC membership, which will include individuals with experience in the management of patients with chronic HCV infection, and member responsibilities. The DMC will receive interim summaries of safety data according to a schedule and format specified in the charter. After each review, the DMC will communicate its recommendations to the Sponsor. The Sponsor will retain sole responsibility for study management, communication with study sites and regulatory authorities.

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 should receive counseling regarding the importance of dosing adherence with the treatment regimen with regard to virologic response and potential development of resistance. Subjects will be administered study drugs at the site at the Day 1 Visit. The start and stop dates of all study drugs will be recorded in the source documents and eCRFs. Subjects will be provided self-administration instructions and study drug diaries to record the exact date, time and number of tablets of study drug administration each day between study visits.

Subjects will be instructed to return all bottles of ABT-450/r/ABT-267 and ABT 333 (full, partial, or empty) and bottles and/or blister packs or cartons of RBV (full, partial or empty) to the study site at each visit indicated in Table 3. At every study visit, during the Treatment Period, study site personnel will inspect the contents of the bottles and record the status of each one as well as the exact number of remaining tablets of ABT-450/r/ABT-267 and ABT-333 or tablets of RBV in IRT at the dispensing visits and in the source at all other Treatment Period visits (Weeks 1, 2, 6, and 10). Study drugs may be re-dispensed at Treatment Period Weeks 1, 2, 6 and 10 therefore, Reconciliation in IRT should occur only when the bottles are returned to the site at the dispensation visits during the Treatment Period in Table 2. If poor adherence is noted, the subject should be counseled and this should be documented in the subject's source.

Study drugs should not be interrupted for toxicity management or any other reason for more than 7 days consecutively. If study drugs need to be interrupted for more than 7 days consecutively, the Study Designated Physician should be contacted and consideration should be given to discontinue the subject.

At Day 1, for the 0-hour and 2-hour PK sample collection, the date and time of the first dose of each drug will be recorded in the source documents and the eCRF. The date of last dose of all study drugs will be recorded in the source documents and the appropriate eCRF.

5.5.7 Drug Accountability

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

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

Upon completion of or discontinuation from the Treatment Period, all original study drug bottles (containing unused study 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. The number of tablets of each type of study drug returned in each bottle will be noted in the IRT system or on a drug accountability log (if appropriate). Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The Phase 3 Study M13-099 demonstrated a high SVR_{12} of 99% with ABT-450/r/ ABT-267 + ABT-333 with ribavirin for 12 weeks treatment in subjects infected with HCV genotype 1 and with compensated cirrhosis except those with HCV genotype 1a who were prior null responders. Study M13-099 was conducted globally except Asia. The current single arm study is evaluating the safety and efficacy of the same regimen in Asian subjects infected with HCV genotype 1b and with compensated cirrhosis. No control arm is required per design.

The regulatory requirements for the primary endpoint differ for countries participating in this trial. Currently SVR_{12} is accepted as the primary endpoint by health authorities in S. Korea and Taiwan but not in China. Therefore, for S. Korea and Taiwan, superiority of the SVR_{12} rate to the historical SVR rate for telaprevir plus pegIFN/RBV therapy is specified as a primary endpoint. For China, superiority of the SVR_{12} and SVR_{24} rates to the historical SVR rate for telaprevir plus pegIFN/RBV therapy in genotype 1 HCV infected patients with cirrhosis is specified as the primary endpoints.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study. HCV RNA assays are standard and validated. Clonal and population sequencing methods are experimental. The SF-36v2 and EQ 5D 5L instruments are standard in the literature and thoroughly validated. The HCVPRO is preliminarily validated and has demonstrated excellent responsiveness in patients with HCV.

5.6.3 Justification of Primary Endpoint Success Criteria

The current study is a Asian study examining the combination of ABT-450/r/ABT-267 and ABT-333 administered with RBV for 12 weeks in treatment-naïve and IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment-experienced HCV genotype 1-infected subjects with compensated cirrhosis. This is a similar trial design as in AbbVie

Study M13-099. In Study M13-099, the SVR_{12} rate for each treatment arm was compared to an historical SVR rate for telaprevir plus pegIFN and RBV (54%, see Table 10). A weighted average of the corresponding SVR rates among treatment-naïve and treatment-experienced (prior relapsers, partial responders and null responders) in HCV genotype 1 infected cirrhotic subjects was calculated to reflect the population expected to enroll in Study M13-099. The historical rate of 54% was defined conservatively as the upper bound of the 95% confidence interval for the telaprevir-based rate.

Table 10. Estimated SVR Rates for Telaprevir Plus PegIFN and RBV in Cirrhotic Subjects

	Telaprevir-Treated Subjects with Cirrhosis n/N (%)	Projected Enrollment in Study M13-099 (%)	Population-Based Weighted Average % [95% CI]
Meta Analysis of ADVANCE[57] and ILLUMINATE[57] Studies			
Naïve Subjects	(56)	53	
REALIZE[57]			
Prior relapsers	48/57 (84)	12	47 [41, 54]
Prior partial responders	11/32 (34)	12	
Prior null responders	7/50 (14)	23	

Consistent with Study M13-099, the SVR_{12} and SVR_{24} rates from the current study will be compared to a clinically relevant threshold based on historical SVR rates for telaprevir plus pegIFN/RBV. However, since the historical SVR rate used in Study M13-099 is based on a population that included HCV genotype 1a-infected cirrhotic subjects as well as HCV genotype 1b-infected cirrhotic subjects, a higher threshold will be used in this study to account for a genotype 1b only population.

Because data are not available on the subpopulation of HCV genotype 1b-infected subjects with cirrhosis treated with telaprevir plus pegIFN/ RBV, the SVR rates in HCV genotype 1a and genotype 1b-infected, non-cirrhotic subjects treated with telaprevir plus pegIFN/RBV were used to determine an appropriate adjustment factor to increase the historical rate used in Study M13-099. An appropriate adjustment factor was determined based on the relative failure rate between the HCV genotype 1b and genotype 1a

populations in the telaprevir ADVANCE, ILLUMINATE, and REALIZE studies Table 11 and Table 12). For treatment-naïve subjects, the SVR failure rate in genotype 1b subjects was reduced by a relative 29% (from 28% to 20%) from the SVR rate for genotype 1a subjects (Table 11). For treatment-experienced subjects, the SVR failure rate in genotype 1b was also reduced by a relative 29% (from 41% to 29%) from the SVR rate for genotype 1a subjects (Table 12). Since the SVR rate for the genotype 1a cirrhotic subjects is not available and SVR rate for all cirrhotic patients would be higher than that for genotype 1a cirrhotic subjects, it would be more conservative to estimate the SVR rate for the genotype 1b cirrhotic subjects by taking 29% reduction from the combined data from genotype 1a + genotype 1b cirrhotic subjects together. Therefore, to account for the exclusion of HCV genotype 1a-infected subjects in the current study, the historical SVR failure rate of 46% used in Study M13-099 for genotype 1 was reduced by a relative 29%, resulting in a 33% failure rate (or 67% SVR rate) for genotype 1b. The rate of 67% should be conservative because the 54% was based on a population that was a mix of genotype 1a and 1b and the expectation is that the SRV rate for genotype 1a subjects would be lower than the SVR rate for the mix population of genotype 1a and 1b subjects.

Hence, for this current study, for a regimen to be considered superior to a clinically meaningful threshold based on SVR rates for telaprevir plus pegIFN/RBV, the lower confidence bound of the SVR rate must exceed 67%. The value of 67% used for the superiority comparison represents the 54% historical genotype 1 SVR rate plus a relative 29% adjustment factor for the exclusion of genotype 1a subjects.

Table 11. SVR Rates for Telaprevir Plus pegIFN and RBV Therapy in Treatment-Naïve Subjects by Subgenotype

	ADVANCE	ILLUMINATE	Meta Analysis
Telaprevir Studies	**T12/PR n/N (%)**	**T12/PR n/N (%)**	**T12/PR % [95% CI]**
Treatment-naïve GT1a subjects	162/217 (75)[57]	273/388 (70)[58]	72 [68, 75]
Treatment-naïve GT1b subjects	119/142 (84)[57]	112/149 (75)[59]	80 [75, 84]

GT1a = genotype 1a; GT1b = genotype 1b

Table 12. Estimated SVR Rates for Telaprevir-Based Therapy in Treatment Experienced Subjects by Subgenoytpe

	REALIZE†‡				
	GT1a (Pooled T12/PR48) n/N (%)	**With Increase for Excluding Cirrhotics (%)**	**GT1b (Pooled T12/PR48) n/N (%)**	**With Increase for Excluding Cirrhotics (%)**	**Population-Based Weighted Average* % [95% CI]**
Relapsers	119/142 (83.8)	84.3	123/140 (87.9)	88.4	GT1a 59 [53, 65] GT1b 71 [64, 77]
Partial responders	26/55 (47.3)	59.3	27/40 (67.5)	79.5	
Null responders	24/88 (27.3)	36.5	22/59 (37.3)	46.5	

GT1a = genotype 1a; GT1b = genotype 1b

† US Prescribing Information for INCIVEK™ (telaprevir). Vertex Pharmaceuticals Incorporated; Cambridge, MA.

‡ Zeuzem S, Andreone P, Pol S, et al. REALIZE trial final results: telaprevir-based regimen for GT1 hepatitis c virus infection in patients with prior null response, partial response or relapse to peginterferon/ribavirin. J Hepatol. 2011;54Suppl:S3.

* Based on a population of 30% relapsers, 35% partial responders, 35% null responders.

5.6.4 Suitability of Subject Population

This study plans to enroll both HCV treatment-naïve and treatment-experienced (pegIFN/RBV) subjects with genotype 1b chronic HCV and compensated cirrhosis.

The selection of subject population is based on the results from the Phase 3 trial Study M13-099. Study M13-099 demonstrated high SVR_{12} 100% and 98% with a 12-week regimen of ABT-450/r/ABT-267 + ABT-333 with ribavirin in the treatment of naïve and treatment-experienced subjects infected with HCV genotype 1b and with compensated cirrhosis. Study M13-099 was conducted globally except Asia and Russia. The goal of the current study is to confirm the results form Study M13-099 in Asian subjects infected with genotype 1b chronic HCV and compensated cirrhosis.

5.6.5 Selection of Doses in the Study

Doses of the three DAAs to be used in this study have shown significant antiviral activity and have been shown to be generally safe and well tolerated both as monotherapy, in combination with pegIFN + RBV, and in combination with each other and RBV in western studies. Of note, coadministration of ABT-450/r, ABT-267 and ABT-333 at the doses planned for use in this study do not clinically significantly impact plasma exposures compared to administration as single agents thus dose adjustments based on drug interactions are not required.

ABT-450/r

An ABT-450 dose of 150 mg QD using the ABT-450/r/ABT-267 co-formulated tablet has been selected to for Phase 3 studies. The same dose and formulation was used in western Phase 3 studies.

The ABT-450/r doses of 100/100 and 150/100 mg evaluated in the western Phase 2 studies using the ABT-450 SDD tablet provided high ITT SVR_{12} rates in treatment-naïve (100% and 95%, respectively) and treatment-experienced (91% and 95.5%, respectively) subjects when dosed with ABT-333 and ABT-267 + RBV. The higher ABT-450 dose of 150 mg, administered with 100 mg ritonavir has been selected to advance into western

Phase 3 studies as it provides an optimal balance between safety and suppression of resistant variants.

In combination with other DAAs ± RBV, the highly fit, moderately resistant R155K viral variant was observed in a lower fraction of patients who had virologic failure at the 150/100 and 200/100 mg ABT-450/r dose (SDD tablet of ABT-450) compared to the 100/100 mg ABT-450/r dose. This finding is consistent with monotherapy data for ABT-450/r where the higher 200/100 mg dose of ABT-450/r selected fewer resistant variants including R155K as compared to the lower 50/100 and 100/100 mg doses of ABT-450/r. Higher doses were also associated with higher SVR_{24} rates when combined with pegIFN and RBV. Thus based on resistance profile and SVR_{24} data with pegIFN + RBV, higher doses provide better efficacy. However, ABT-450 doses of 200/100 and 250/100 mg (SDD tablet) were associated with a greater incidence of grade 3+ ALT elevations (4% to 5% at doses ≥ 200/100 versus 0.3% to 0.5% at lower doses) suggesting that doses ≤ 200/100 mg SDD tablet might have a more favorable safety profile. In western subjects, the ABT-450 150 mg dose from the ABT-450/r/ABT-267 co-formulated tablets planned for this study has a ~60% higher exposure compared to the 150/100 mg SDD tablet but the exposure is ~50% lower than that from the 200/100 mg SDD formulation. The 150 mg ABT-450 dose from the co-formulation will hence provide a good balance between minimize the incidence of asymptomatic, transient grade 3 ALT elevations while maximizing virologic suppression.

ABT-450 exposures from the ABT-450/r/ABT-267 co-formulated tablets are comparable between Chinese and Western subjects. Thus, same dose of ABT-450 is hence recommended in Western and Chinese subjects.

ABT-333

An ABT-333 dose of 250 mg BID using the optimized tablet formulation that is expected to provide exposures comparable to the 400 mg BID dose used in Phase 2 studies has been selected to for Phase 3 studies. The same dose and formulation was used in western Phase 3 studies. This is based on comparable efficacy and better safety profile compared

to exposures at higher ABT-333 doses. Comparable viral load decline following monotherapy (approximately 1 $\log_{10}$ IU/mL) was observed at exposures greater than that achieved with the 400 mg BID dose evaluated in western Phase 2 studies. Additionally, the 400 and 800 mg BID doses resulted in identical SVR rates (63%) when combined with pegIFN and RBV for 12 weeks followed by 36 weeks of pegIFN + RBV, indicating that increasing ABT-333 dose > 400 mg BID did not improve efficacy. Furthermore, available data from the Phase 2b study indicates that when ABT-333 400 mg BID dose is combined with ABT-450, ABT-267 and RBV for 12 weeks, very high SVR_{12} rates were observed in treatment-naïve and treatment-experienced subjects (> 90%). While both the 400 mg BID and 800 mg BID doses of ABT-333 in combination with pegIFN and RBV were well tolerated by HCV-infected subjects for 12 weeks, the 800 mg BID dose was associated with a greater mean hemoglobin reduction compared to the 400 mg BID dose and compared to placebo plus pegIFN and RBV. Therefore, 400 mg ABT-333 in tablet formulation is favored.

In the western subjects, the 250 mg optimized tablet used in the current study has comparable bioavailability to the 400 mg tablet formulation used in western Phase 2 studies. Hence, the ABT-333 250 mg optimized tablet dosed BID was selected as the Phase 3 formulation as it provides exposures that maximizes efficacy and a superior safety profile compared to higher ABT-333 doses.

The ABT-333 250 mg optimized tablet, alone or in combination, has not been evaluated in Chinese subjects. However, ABT-333 400 mg tablet (which is bioequivalent to the ABT-333 250 mg optimized tablet) was evaluated as a part of the 3-DAA regimen, ABT-450/r + AB-267 + ABT-333, in Chinese and Western subjects (Study M12-221). Following administration of the 3-DAA combination (ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID) for 21 day, ABT-333 exposures in Chinese subjects were comparable to Caucasian subjects with this 400mg tablet formulation. Thus, same dose of ABT-333, 250 mg optimized tablet, can be used in Chinese and Western subjects.

ABT-267

An ABT-267 dose of 25 mg QD using the ABT-450/r/ABT-267 co-formulated tablet has been selected to for Phase 3 studies. The same dose and formulation was used in Western Phase 3 studies.

Compared to higher doses, the 25 mg QD dose provided comparable viral load decline following monotherapy and lower potential to decrease ABT-450 exposures. In Western subjects, following 2 to 3 days of ABT-267 monotherapy at doses of 1.5 mg to 200 mg QD, the 25 mg dose of ABT-267 showed viral load decline comparable to higher doses with none of the rebound between doses seen at lower doses. Resistance analysis following monotherapy suggests that doses significantly greater than 25 mg would be needed to improve the resistance profile as a variety of NS5A resistant mutants were observed following monotherapy with doses of 5 mg to 200 mg. In addition, higher ABT-267 doses have been associated with decreases in ABT-450 exposures; the ABT-267 200 mg dose resulted in ~80% lower ABT-450 exposures when ABT-450 250 mg was dosed with 100 mg ritonavir. Hence, doses > 25 mg could decrease the exposures of the "anchor" molecule ABT-450, without providing significant benefit in terms of improved efficacy. Additionally, available data from the Phase 2b study indicates that when ABT-267 25 mg QD dose is combined with ABT-450, ABT-333 and RBV for 12 weeks, very high SVR_{12} rates were observed in treatment-naïve and treatment experienced subjects (> 90%).

In Western subjects, the co-formulated ABT-450/r/ABT-267 formulation used in the current study has ABT-267 bioavailability comparable to the ABT-267 25 mg tablet used in Phase 2 studies. In addition, ABT-450 exposures from the ABT-450/r/ABT-267 co-formulated tablets are comparable between Chinese and Western subjects. Thus, same dose of ABT-450 can be used in Chinese and Western subjects.

Hence, the ABT-267 dose in the current study is the 25 mg dose, as it provides exposures that maximizes efficacy without compromising ABT-450 exposures.

RBV

The daily dose of RBV selected in Western Phase 2 and 3 studies is 1000 mg to 1200 mg, divided twice daily, and based on subject weight. This dose was chosen as it was the approved dose for treatment of adult patients with chronic hepatitis C infection in combination with pegIFN. The same dose is selected for this study because its safety profile has been well characterized when administered with pegIFN, including the incidence of hemolytic anemia, and there are well-defined dose reduction criteria in the event of RBV-induced anemia. In addition, this dose was studied in the absence of pegIFN in subjects with chronic hepatitis C infection in Studies M12-267, M12-746, M12-998 and M11-652 and was found to be generally safe and well-tolerated and resulted in high SVR rates.

In Chinese subjects, the recommended dose of RBV with an IFN-based regimen is weight based, 1000 mg daily in subjects with a body weight of less than 75 kg, and 1200 mg daily in subjects with a body weight of greater than or equal to 75 kg, per the Chinese HCV Treatment Guidelines.[59] Hence, for the Regional Phase 3 studies, the proposed RBV dose is weight-based 1000 mg or 1200 mg.

Doses comparable to, and higher than, the DAA doses to be administered in this study have been studied in single- and multiple-dose healthy volunteer studies and administered to western HCV-infected subjects as monotherapy or in combination with pegIFN/RBV and found to be generally safe and well tolerated. In addition, the pharmacokinetics of ABT-450, ABT-267 and ritonavir when given in combination to western subjects with mild hepatic impairment were comparable to or slightly lower than in subjects with normal hepatic function. The area under the concentration curve (AUC) of ABT-450 and ABT-267 were comparable (≤ 30% change) in subjects with mild hepatic impairment compared to healthy controls. The AUC for ritonavir was 34% lower in subjects with mild hepatic impairment. Additionally, based on the package insert for RBV, dose adjustments are not required in subjects with mild hepatic impairment.

Based on these data, no dose adjustment is required for Chinese subjects with compensated cirrhosis taking the DAA combination in this study. The doses of ABT-267, ABT-333 and ABT-450/r chosen for this study in compensated cirrhotic subjects are the same that was used in Phase 3 studies for the IFN-free 3-DAA Study in Western subjects (Study M13-099).

The maximum dose of ABT-450/r/ABT-267 75 mg/50 mg/12.5 mg tablets will not exceed 150 mg/100 mg/25 mg per day for 12 weeks. The maximum dose of ABT-333 250 mg tablets administered in this study will not exceed 500 mg per day for 12 weeks. The maximum RBV dose administered in this study will not exceed 1200 mg, divided twice daily for 12 weeks.

6.0 Adverse Events

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 Definitions

6.1.1 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 6.7 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.

6.1.2 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.

6.2 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of DAAs (ABT-450/r/ABT-267 and ABT-333), and RBV:

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

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

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

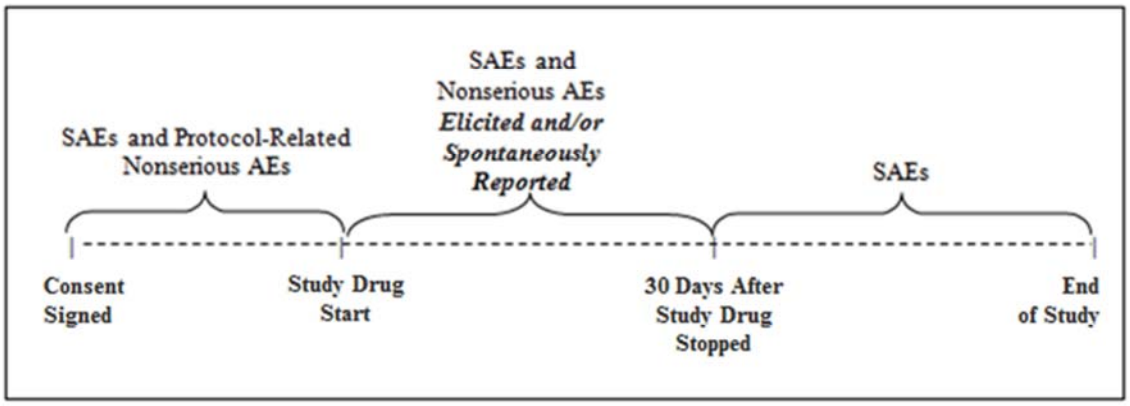
6.4 Adverse Event Collection Period

All serious adverse events as well as protocol-related nonserious adverse events 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 after last administration AEs and SAEs will be collected whether solicited or spontaneously

reported by the subject. From 30 days after last dose until the end of study, SAEs will be collected.

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection



6.5 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 s should use the SAE non-CRF paper forms and send them to Clinical Pharmacovigilance within 24 hours of the site being aware of the serious adverse event.

FAX to: [redacted]
Email: [redacted]

For safety concerns, contact the Antiviral Safety Team at:

[redacted]

For any subject safety concerns, please contact the Primary Study Designated Physician listed below:

[redacted]

In case of subject safety concerns or medical emergencies when the Primary Study Designated Physician is unavailable, please call the following central back-up number:

Phone: [redacted]

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

6.6 Pregnancy

Subjects and their partners should avoid pregnancy and males should avoid sperm donation throughout the course of the study, starting with Day 1 and for 7 months after the last dose of RBV (or per local RBV label) and/or consistent with local treatment guidelines for RBV.

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who report a positive pregnancy test during the Treatment Period must be notified to stop RBV immediately. Subjects will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3. Administration of DAAs may be continued at the investigator's discretion, if the benefit of continuing therapy is felt to outweigh the risk.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected for pregnancies occurring up to 7 months (or per local RBV label) after the last dose of RBV for treatment with DAAs plus RBV. The investigator is encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry, if RBV is included within the regimen.

Subjects who discontinue study medications due to pregnancy will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

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 the Sponsor within 24 hours of the site becoming aware of the event.

6.7 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. A table of Clinical Toxicity Grades for evaluating laboratory abnormalities is provided in Appendix C. This table should be used in determination of the appropriate toxicity management as discussed in Section 6.7.1 and Section 6.7.5.

A drug-related toxicity is an adverse event or laboratory value outside of the reference range that is judged by the Investigator or the Sponsor as having a "reasonable possibility" of being related to the study drug (Section 6.3). A toxicity is deemed "clinically significant" based on the medical judgment of the Investigator. Laboratory abnormalities will be managed as deemed clinically appropriate by the investigator until resolved.

Investigators should avoid interrupting study drugs for more than 7 consecutive days. The Investigator should ensure that any study drug interruptions or RBV dose modifications and associated adverse events are promptly entered into the appropriate eCRFs.

The toxicity management guidelines below should be followed throughout the Treatment Period of the study.

6.7.1 Grades 1 or 2 Laboratory Abnormalities and Mild or Moderate Adverse Events

Subjects who develop a mild or moderate adverse event or Grade 1 or 2 laboratory abnormality, other than those discussed separately in Section 6.7.4 and Section 6.7.5, may continue study drugs with follow-up per study protocol and in accordance with local standard of care.

6.7.2 Grades 3 or 4 Laboratory Abnormalities and Severe or Serious Adverse Events

Grade 3 – 4 Laboratory Abnormalities

With the exception of Grade 3 or higher abnormalities of total bilirubin, uric acid, phosphorus, total cholesterol, triglycerides, or glucose (in subjects with a history of diabetes), if a subject experiences a Grade 3 or greater abnormal laboratory parameter during the Treatment Period, the abnormal laboratory test should be repeated. If the Grade 3 or greater abnormality is confirmed, the investigator should assess whether the abnormality can be managed medically without interruption of study drug, or whether study drugs should be interrupted and the laboratory parameter followed until it improves. If study drugs are interrupted and restarted and the abnormality recurs, then study drugs should be permanently discontinued.

Decreases in serum hemoglobin or elevations of serum ALT should be managed according to the guidance in Section 6.7.4 and Section 6.7.5 below. Grade 3 or greater abnormalities of total bilirubin, uric acid, phosphorus, total cholesterol, triglycerides or glucose (in subjects with a history of diabetes) should be managed medically as appropriate and do not require confirmation or study drug interruption unless deemed necessary by the investigator.

Severe Adverse Event or Serious Adverse Events

If a subject experiences a severe adverse event or a serious adverse event that the investigator considers to be a reasonable possibility of relationship to study drug, investigator should assess whether the adverse event can be managed medically without interruption of study drug, or whether study drugs should be interrupted until it improves, or study drugs should be permanently discontinued. 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 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). If an interruption is required, it should not exceed 7 days.

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.

6.7.3 Management of Hemoglobin Decreases

Reductions in hemoglobin are a well characterized side effect of ribavirin exposure. If a subject experiences a hemoglobin decrease meeting one of the criteria outlined in Table 13, a confirmatory test should be performed. If the hemoglobin decrease is confirmed, the management guidelines in Table 13 should be followed. Management will be different for subjects without a history of known cardiac disease and subjects with known cardiac disease.

Use of hematologic growth factors (such as erythropoietin or filgrastim) or blood transfusions are permitted at the discretion of the Investigator. Management of hematologic growth factor therapy is the responsibility of the Investigator, and growth factors will not be provided by AbbVie.

Alternate management of hemoglobin decreases outside of these criteria requires approval of the AbbVie Study Designated Physician.

Table 13. Ribavirin Dose Modification Guidelines in Management of Hemoglobin Decreases

Hemoglobin Value	Intervention
All subjects	
< 10 g/L and ≥ 8.5 g/dL for subjects without cardiac disease < 12 g/L and ≥ 8.5 g/dL for subjects with cardiac disease	Reduce RBV dose*. Study drugs may be continued. If hemoglobin increases to ≥ 10 g/dL for subjects without cardiac disease or to 12g/dL for subjects with cardiac disease. RBV dose may be increased gradually in 200 mg increments towards original dose.
< 8.5 g/dL	Interrupt ribavirin. Manage the subject as medically appropriate. Investigator should evaluate if RBV discontinuation is warranted. If subsequent hemoglobin results are improved to ≥ 10 g/dL for subjects without cardiac disease or 12 g/dL for subjects with cardiac disease RBV, may be restarted.
Additional guidance for subjects with history of stable cardiac disease	
Hemoglobin decrease of ≥ 2 g/dL during any 4-week treatment period	Reduce RBV dose*. If a subsequent hemoglobin result is greater than the level that triggered the dose reduction, RBV dose may be increased gradually in 200 mg increments
< 12 g/dL after a 4-week RBV dose reduction	Interrupt ribavirin. Manage the subject as medically appropriate. Investigator should evaluate if RBV discontinuation is warranted. If subsequent hemoglobin results are improved to ≥ 12g/dL, RBV may be restarted.

* 1st dose reduction of ribavirin is to 600 mg/day. If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Subjects whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg tablet in the morning and two 200 mg tablets in the evening.

6.7.4 Management of Transaminase Elevations

Transient asymptomatic Grades 3 – 4 ALT elevations have been observed in approximately 1% of subjects receiving ABT-450/r-containing regimens. If a subject experiences an increase in ALT to > 10 × ULN, or to > 5 × ULN which was increased from previous measurement, the subject should have a confirmatory ALT measurement performed in a timely fashion. If the ALT increase is confirmed, the management guidelines in Table 14 should be followed. Subjects using an estrogen-containing product should discontinue use of that product. Alternate management of ALT increases is permitted with approval of the AbbVie Study Designated Physician.

Table 14. Management of Confirmed ALT Elevations

ALT ≥ 20 × ULN	• Permanently discontinue study drugs. • Manage the subject as medically appropriate.
ALT ≥ 10 × ULN or ALT ≥ 5 × ULN and increased from previous measurement with symptoms and signs of hepatitis present	• If using an estrogen-containing product: Discontinue estrogen-containing product and repeat ALT testing, preferably within 1 week. • Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and INR, preferably within 1 week. • Evaluate for alternative etiology of ALT elevation: update medical history and concomitant medications eCRF (if applicable), and obtain additional testing as appropriate. • Manage the subject as medically appropriate. • Permanently discontinue study drugs for any of the following: ALT level increases to 20 × ULN, increasing direct bilirubin, increasing INR, or new symptoms/signs of hepatitis.
ALT ≥ 5 × ULN and increased from previous measurement but < 10 × ULN and without symptoms or signs of hepatitis	• Continue study drugs. • As soon as possible, measure ALT, AST, total and fractionated bilirubin, alkaline phosphatase and INR. Repeat liver chemistries as indicated until resolution. Evaluate for alternative etiology of ALT elevation: update medical history and concomitant medications eCRF (if applicable), and obtain additional testing as appropriate. • Manage the subject as medically appropriate. • Permanently discontinue study drugs for any of the following: ALT level increases to 20 × ULN, increasing direct bilirubin, increasing INR, or symptoms/signs of hepatitis.

6.7.5 Management of eGFR Decreases

If calculated eGFR is confirmed to have decreased to < 50 mL/minute, medical evaluation should include a full review of current medications, including those taken on an as needed basis, those which are sold over the counter and any dietary and herbal supplements, and appropriate dose reduction or discontinuation based on impaired renal function should be done (if applicable). Ribavirin dose should be adjusted as in Table 15. Alternative management of RBV dose in the setting of reduced renal function will require approval of the AbbVie Study Designated Physician.

The investigator should also consider whether drug-drug interactions with concomitant medications may have contributed to the decrease in eGFR, and whether discontinuation of substitution of the possible interacting drug should be considered. For example, drug interactions between DAAs and some antihypertensive medications could potentially increase exposures of the antihypertensive and may reduce renal function. If anti-hypertensive medications are adjusted, vital signs must be monitored to ensure appropriate blood pressure control. Refer to Section 5.2.3.3 for additional information regarding drug-drug interactions.

If eGFR improves, the site should perform all necessary readjustment of any dose modifications that have been made.

The Investigator should ensure that any concomitant medication changes, RBV dose reductions, and study drug discontinuations, as well as consequent related adverse events are entered into the appropriate eCRFs.

Table 15. Dosing of RBV in Subjects with Renal Impairment

eGFR Value	RBV Dose
30 – 50 mL/min	Alternating doses of 200 mg with 400 mg every other day
< 30 mL/min	200 mg daily
Hemodialysis	200 mg daily

7.0 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the Independent Ethics Committee (IEC)/Independent Review Board (IRB) and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following AbbVie personnel:

Primary Contact:	Alternate Contact:

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

An interim analysis will occur after all enrolled subjects from S. Korea and Taiwan have completed the Treatment Period through Post-Treatment Week 12 of the Post-Treatment Period or prematurely discontinued from the study. This interim analysis is planned to support regulatory submission activities in S. Korea and Taiwan. The primary analysis will occur after all subjects have completed PT Week 24 or prematurely discontinued the study. All remaining data through PT Week 48 will be summarized in the end of study analysis.

SAS® (SAS Institute, Inc., Cary, NC) for the UNIX operating system will be used for all analyses. All confidence intervals will be 2-sided with an α level of 0.05. Descriptive statistics will be provided, such as the number of observations (N), mean, and standard deviation (SD) for continuous variables and counts and percentages for discrete variables.

Efficacy, safety, and demographic analyses will be performed on the intent-to-treat (ITT) population which will consist of all enrolled subjects who receive at least one dose of study drug. Additional summaries will be provided by geographic region (China, S. Korea, Taiwan).

No data will be imputed for any efficacy or safety analyses except for the PRO questionnaires and for analyses of the HCV RNA endpoints of RVR, EOTR, and all SVR endpoints. If a respondent answers at least 50% of the items in a multi-item scale of the SF-36v2, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing. The Mental and Physical Component Summary measures will not be computed if any domain is missing. If a respondent answers at least 12 of the 16 items on the HCVPRO, the missing items will be imputed with the mean score of the answered items. In cases where the respondent did not answer five or more items, the HCVPRO total score will be considered missing. For EQ-5D-5L index and VAS scores, no imputation will be performed for missing items.

HCV RNA values will be selected for the analyses of HCV RNA endpoints of RVR, EOTR, and all SVR endpoints based on the defined visit windows. When there is no HCV RNA value in a visit window based on defined visit windows, the closest values before and after the window, regardless of the value chosen for the subsequent and preceding window, will be used for the flanking imputation described below.

If a subject has a missing HCV RNA value at a post-baseline visit but with undetectable or unquantifiable HCV RNA levels at both the preceding value and succeeding value, the HCV RNA level will be considered undetectable or unquantifiable, respectively, at this visit for this subject. Subsequent to this flanking imputation, if a subject is missing a value for the visit window associated with the analysis, the subject will be imputed as a visit failure (i.e., not undetectable or unquantifiable). For SVR analyses (e.g., SVR_4, SVR_{12}, SVR_{24}) if after performing the flanking imputation there is no value in the appropriate window but there is an HCV RNA value after the window, then it will be imputed into the SVR window.

8.1.1 Demographics

Demographics and baseline characteristics will be summarized for the ITT population. Demographics include age, weight, and BMI, and the frequency of gender, race, ethnicity, age category ([< 55 years or ≥ 55 years] and [< 65 or ≥ 65 years]) and BMI category (< 30 kg/m2 or ≥ 30 kg/m^2). Baseline characteristics will include IL28B genotype ([CC, CT, or TT] and [CC or non-CC]), IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment history (treatment-naïve or treatment-experienced) non-responder {null responder, partial responder, or other non-responder} or relapser or IFN based therapy intolerant, baseline HCV RNA levels ([continuous] and [< 800,000 IU/mL or ≥ 800,000 IU/mL]), baseline IP-10 ([continuous] and [< 600 pg/mL or ≥ 600 pg/mL]), baseline HOMA-IR (< 3 mU × mmol/L^2 or ≥ 3 mU × mmol/L^2), Child-Pugh score at Screening (5 or 6), baseline Child-Pugh score (5, 6, or > 6), baseline longitudinal FibroTest score (continuous), baseline platelet counts [(continuous) and (< 60, 60 to < 90, 90 to < 120, or ≥ 120 × 10^9/L)],baseline albumin [(continuous) and (< 28, 28 to < 33, 33 to < 40, 40 to 49, and > 49 g/L), baseline alpha fetoprotein (continuous), presence of hepatic steatosis at baseline (yes, no), hepatoprotective drug use at baseline (yes, no), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, former injection drug user (yes, no, unknown), history of bleeding disorders (yes, no), history of diabetes (yes, no), history of depression or bipolar disorder (yes, no), and geographic region (China, S. Korea and Taiwan). Summary statistics (N, mean, median, Standard Deviation [SD], and range) will be generated for continuous variables (e.g., age and BMI). The number and percentage of subjects will be presented for categorical variables (e.g., gender and race).

8.1.2 Efficacy

All efficacy analyses will be performed on the ITT population.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT PCR) assay version 2.0. For this assay, the lower limit of detection (LLOD) is 15 IU/mL

and lower limit of quantification (LLOQ) is 25 IU/mL. HCV RNA results that are detectable but not quantifiable are reported as "< 25 IU/ML HCV RNA detected" and those that are undetectable are reported as "HCV RNA not detected" in the database.

8.1.2.1 Primary Efficacy Endpoints

For South Korea and Taiwan the primary endpoint is:

A1. SVR_{12}: Superiority to the historical SVR rate for telaprevir plus pegIFN/RBV therapy; the LCB of the 95% CI for the percentage of subjects with SVR_{12} must exceed 67% to achieve superiority.

For China, the primary endpoints are:

B1. SVR_{12}: Superiority to the historical SVR rate for telaprevir plus pegIFN/RBV therapy; the LCB of the 95% CI for the percentage of subjects with SVR_{12} must exceed 67% to achieve superiority.

B2. SVR_{24}: Superiority to the historical SVR rate for telaprevir plus pegIFN/RBV therapy; the LCB of the 95% CI for the percentage of subjects with SVR_{24} must exceed 67% to achieve superiority.

For China, in order to control the Type I error rate at 0.05, a fixed-sequence testing procedure will be used to proceed through the primary efficacy endpoints. That is, only if success has been demonstrated for the primary endpoint of superiority of SVR_{12} rate to the historical rate for telaprevir plus pegIFN and RBV therapy (B1) will the testing continue to the second primary endpoint of superiority of the SVR_{24} rate to the historical rate for telaprevir plus pegIFN and RBV therapy (B2).

To test the hypothesis that the percentage of treatment-naïve and IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment-experienced HCV genotype 1b infected Asian subjects with compensated cirrhosis treated with ABT-450/r/ABT-267 + ABT-333 + RBV for 12 weeks who achieve SVR_{12} is superior to a clinically meaningful threshold

based on the historical SVR rates for the HCV genotype 1 infected population treated with telaprevir plus pegIFN/RBV, the percentage of subjects with SVR_{12} will be calculated with a 2-sided 95% CI using Wilson score method, and the LCB will be compared to the defined threshold. The LCB of the 95% CI of SVR_{12} must be greater than 67% in order for the regimen to be considered superior.

Similarly, to test the hypothesis that the percentage of treatment-naïve and IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment-experienced HCV genotype 1b infected Asian subjects with compensated cirrhosis treated with ABT-450/r/ABT-267 + ABT-333 + RBV for 12 weeks who achieve SVR_{24} is superior to a clinically meaningful threshold based on historical SVR rates for the HCV genotype 1 infected population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with SVR_{24} will be calculated with a 2-sided 95% CI using Wilson score method, and the LCB will be compared to the defined threshold. The LCB of the 95% CI of SVR_{24} must be greater than 67% in order for the regimen to be considered superior.

The value of 67% used in the endpoints as the historical SVR rate for telaprevir plus pegIFN/RBV is described in Section 5.6.3.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The percentage of subjects with on-treatment virologic failure defined as the occurrence of at least one of the following:
  - confirmed HCV RNA ≥ the lower limit of quantitation (LLOQ) (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point during treatment after HCV RNA < LLOQ, or
  - confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment, or
  - Failure to achieve HCV RNA < LLOQ by Week 6 with ≥ 36 days of treatment.

- The percentage of subjects with relapse by Post-Treatment Week 12 (confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment).
- The percentage of subjects with relapse by Post-Treatment Week 24 (confirmed HCV RNA ≥ LLOQ between end of treatment and 24 weeks after the last dose of study drug among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment).

The percentages (with 2-sided 95% confidence intervals using the Wilson Score method to the binomial distribution) of the subjects with on treatment virologic failure and post-treatment relapse will be calculated and summarized.

8.1.2.3 Sensitivity Analyses for the Primary Endpoint

In addition to presenting the primary efficacy endpoints with HCV RNA and SVR_{12} and SVR_{24} imputed as described in Section 8.1, SVR_{12} and SVR_{24} will be presented using the following other methods to impute missing post-treatment virologic results:

- Imputing any missing HCV RNA values in the SVR_{12}/SVR_{24} window by carrying forward the last non-missing (post-baseline) HCV RNA value prior to the SVR_{12}/SVR_{24} window;
- Imputing as described in Section 8.1 but exclude the subjects who were categorized as "prematurely discontinued study drug with no on-treatment virologic failure" and "missing follow-up data in the PT Period."

For each of these, the simple percentage of subjects with SVR_{12}/SVR_{24} will be presented along with a 2-sided 95% CI using Wilson score method.

As a sensitivity analysis, comparisons of the SVR_{12} and SVR_{24} rates may be made to geographic region-specific SVR rates with IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment.

8.1.2.4 Subgroup Analysis

The percentage (with 2-sided 95% confidence intervals) of subjects with SVR_{12} and SVR_{24} will be presented for the following subgroups:

- Treatment-naïve versus previous IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment-experienced subjects;
  - For treatment-experienced subjects, type of response to previous IFN based therapy (non-responder, relapser, or (IFN based therapy intolerant);
  - For non-responders to previous IFN based therapy, type of response (null responder, partial responder, or other non-responder);
  - Geographic region/previous HCV treatment status (China/treatment-naïve, China/treatment-experienced, S. Korea/treatment-naïve, S. Korea/treatment-experienced, Taiwan/treatment-naïve, Taiwan/treatment-experienced).
- IL28B genotype (CC or non-CC), (CC, CT, or TT);
- Baseline HCV RNA level (< 800,000 IU/mL or ≥ 800,000 IU/mL);
- Baseline IP-10 (< 600 pg/mL or ≥ 600 pg/mL);
- Baseline HOMA-IR (< 3 or ≥ 3 mU × mmol/L^2);
- Sex (male versus female);
- Age (< 55 versus ≥ 55 years), (< 65 versus ≥ 65 years);
- BMI (< 30 or ≥ 30 kg/m^2);
- Subjects with RBV dose modifications (yes/no);
- Presence of hepatic steatosis at Baseline (yes/no);
- Hepatoprotective drug use at baseline (yes/no);
- History of Diabetes (yes/no);
- History of Bleeding Disorders (yes/no);
- History of Depression or Bipolar Disorder (yes/no);
- Former injection drug user (yes/no);
- Baseline Child-Pugh Score (5, 6, or > 6);
- Baseline platelets (< 90 or ≥ 90 × 10^9cells/L);

- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline alpha fetoprotein [AFP] (< 20 or ≥ 20 ng/mL).

8.1.2.5 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized and analyzed, as specified:

- The percentage of subjects with rapid virologic response (RVR) (HCV RNA < LLOQ at Week 4);
- The percentage of subjects with end of treatment response (EOTR) (HCV RNA < LLOQ at Week 12;
- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using only subjects with data in each visit window, i.e., no imputation for missing data);
- The number of subjects with virologic rebound at each protocol-specified visit (confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, or confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment. A single rebound value (≥ LLOQ or >1 $\log_{10}$ IU/mL above nadir) followed by lost to follow-up will be considered a rebound);
- The percentage of subjects who failed to have confirmed suppression of HCV RNA (never achieving HCV RNA < LLOQ) during the Treatment Period and have received at least 6 weeks of treatment (study drug duration ≥ 36 days);
- Time to suppression of HCV RNA (defined as the study day of the first occurrence of HCV RNA < LLOQ) during the Treatment Period;
- the percentage of subjects achieving SVR_4;
- The percentage of subjects who complete treatment (defined as a study drug duration ≥ 77 days) with HCV RNA < LLOQ at Final Treatment Visit who relapsed post-treatment within 4 weeks after the last actual dose of study drug (up to and including the SVR_4 assessment time point);
- The percentage of subjects who complete treatment (defined as a study drug duration ≥ 77 days) with HCV RNA < LLOQ at Final Treatment Visit who

relapsed between end of treatment and up to and including the last HCV RNA measurement collected in the PT Period;

- The percentage of subjects who achieved SVR_{24} who subsequently relapsed;
- Time to relapse at any time post-treatment for subjects who complete treatment with HCV RNA < LLOQ at Final Treatment Visit;
- The percentage of subjects with SVR_{12} weeks after the last planned dose of study drug ($SVR_{12planned}$);
- The percentage of subjects with SVR_{24} (South Korea and Taiwan);
- The percentage of subjects with SVR_{24} weeks after the last planned dose of study drug ($SVR_{24planned}$);
- Mean change from baseline in liver function tests (e.g., PT/INR, Fibrotest) to each applicable post-baseline time point.

In the above analyses for RVR, EOTR, and SVR, the percentage of responders and 2-sided 95% confidence intervals using Wilson score method will be calculated. From HCV RNA levels, the time to suppression on treatment and time to relapse post-treatment will be displayed graphically using Kaplan-Meier curves.

8.1.3 Patient Reported Outcomes

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

- mean change from baseline in HCVPRO total score to each applicable post-baseline time point;
- mean change from baseline in EQ-5D-5L health index score and VAS score to each applicable post-baseline time point;
- mean change from baseline in the SF-36v2 Mental Component Summary (MCS) and Physical Component Summary (PCS) scores to each applicable post-baseline time point.

Summary statistics (n, mean, SD, median, minimum and maximum) at each visit and for change from baseline to each visit will be provided for the HCVPRO total score, the EQ-5D-5L health index and VAS scores, and the SF-36v2 PCS and MCS scores.

For HCVPRO total score, a continuous plot by treatment arm will be provided with percent change from baseline on the horizontal axis and the cumulative percent of subjects experiencing up to that change on the vertical axis. These plots will be used to show change from Baseline to Final Treatment Visit, and change from Baseline to Post-Treatment Week 12 and change from Baseline to Post-Treatment Week 24.

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

8.1.4 Resistance Analyses

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo population sequence analysis in order to allow accurate assessment of the products of amplification. For subjects who experience virologic failure, the sample closest in time after failure with an HCV RNA level ≥ 1000 IU/mL will be used if the HCV RNA level at the time of failure is < 1000 IU/mL. The prototypic reference strain with its associated GenBank Accession ID for sequence analyses is 1b-Con1 (AJ238799).

For each DAA target, resistance-associated signature amino acid variants will be identified by AbbVie Clinical Virology. Amino acid positions where resistance-associated variants have been identified in vitro and/or in vivo in genotype 1b are 1) for ABT-450: 56, 155, 156, and 168 in NS3; 2) for ABT-267: 28, 29, 30, 31, 32, 58, and 93 in NS5A; and 3) for ABT-333: 316, 368, 411, 414, 445, 448, 553, 556, 558, and 559 in NS5B.

The following definitions will be used in the resistance analyses:

- Baseline sample: sample collected before the first dose of DAA study drug.
- Baseline variant: a variant (by population sequencing) in a baseline sample determined by comparison of the amino acid sequence of the baseline sample

to the appropriate prototypic reference amino acid sequence for a given DAA target (NS3, NS5A, or NS5B).

- Post-baseline variant by population sequencing: an amino acid variant in a post-baseline time point sample that was not detected at baseline in the subject and is detectable by population sequencing.
- Emerged variant by population sequencing: a post-baseline variant that is observed in 2 or more subjects of the same subgenotype by population sequencing.
- Linked variant by population sequencing: 2 or more signature or emerged amino acid variants identified within a sample by population sequencing where at least one of the variants is at a signature position, and no mixture of amino acids is detected at either position.

For those samples evaluated, a listing by subject of all baseline variants relative to the prototypic reference sequence at signature resistance-associated amino acid positions will be provided for each DAA target (NS3, NS5A, and/or NS5B). Furthermore, the HCV amino acid sequence at post-baseline time points with an HCV RNA level of ≥ 1000 IU/mL that are analyzed will be compared to the baseline and prototypic reference amino acid sequences. A listing by subject and time point of all post-baseline variants relative to the baseline amino acid sequences will be provided for each DAA target (NS3, NS5A, and/or NS5B). In addition, a listing by subject and time point of all post-baseline variants at signature resistance-associated amino acid positions relative to the prototypic reference amino acid sequences will be provided. Furthermore, the number and percentage of subjects with emerged variants by amino acid position and variant within a DAA target as compared to baseline will be summarized.

The number and percentage of subjects with linked variants by population sequencing within a DAA target will be summarized. In addition a listing of linked variants by subject and time point will be provided for each DAA target (NS3, NS5A, and NS5B).

The persistence of resistance-associated substitutions that emerged for each target (NS3, NS5A, and NS5B) will be assessed by population sequencing at selected post-treatment

time points. Listings by subject and time point of all post-baseline variants relative to the baseline amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B).

8.1.5 Safety

All subjects who receive at least one dose of study drug will be included in the safety analyses.

8.1.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (defined as any event that begins or worsens in severity after initiation of active study drugs through 30 days after the last dose of study drugs) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT). The tabulation of the number of subjects with treatment-emergent adverse events by severity rating and relationship to study drug will be provided. In addition, the number and percentage of subjects with serious treatment-emergent adverse events and the number and percentage of subjects with treatment-emergent adverse events leading to study drug discontinuation will also be provided.

Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe incident for the severity rating table and the most related for the relationship to study drug table. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC.

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.

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

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

Additional analyses will be performed if useful and appropriate.

8.1.5.3 Vital Signs Data

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each Post-Baseline Visit will be summarized. Frequencies and percentages of subjects with post-baseline values meeting pre-defined criteria for Potentially Clinically Significant vital signs values during treatment will be summarized.

8.1.6 Pharmacokinetic and Exposure-Response Analyses

Plasma concentrations and pharmacokinetic parameters of ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ritonavir and ribavirin will be tabulated and summarized and summary statistics will be computed for each time and visit.

In addition, plasma concentration data from this study may be combined with data from other studies and analyzed using the following general methodology:

Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (version VI, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. Apparent oral clearance (CL/F) and apparent

volume of distribution (V/F) of the PK analytes will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis. The evaluation criteria described below will be used to examine the performance of different models.

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

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

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

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

Where TVCLi = Typical value of clearance for an individual i1, Theta(1) is the intercept and Theta(2) – (4) are regression parameters relating the fixed effects (weight and age centered on the median value) to clearance.

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

The relationship between exposure (e.g., population pharmacokinetic model predicted concentrations over time or average concentrations or AUC or trough concentrations of the individual model-predicted pharmacokinetic profiles, or some other appropriate measure of exposure) and antiviral activity will be explored. Exposure response relationships will be explored using a semi-mechanistic viral dynamic model and/or logistic regression analyses.

Logistic regression analyses will explore the relationship between exposure and one or more virologic endpoints (e.g., RVR, EVR, SVR_4, SVR_{12}, relapse following end of treatment and breakthrough on treatment).

Additionally, relationship between exposure and safety endpoints of interest may also be explored.

Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

It is planned to enroll approximately 100 subjects (60 from China, 20 from South Korea and 20 from Taiwan). All subjects will receive ABT-450/r/ABT-267 + ABT-333 coadministered with RBV for 12 weeks. With a total sample size of about 100 subjects and assuming that 94% of the subjects will achieve SVR_{12}, this study has greater than

90% power to demonstrate SVR_{12} superiority with a 2-sided 95% lower confidence bound greater than 67% (based on the normal approximation of a single binomial proportion in a one-sample test for superiority using EAST 6.2). The SVR_{24} rate is anticipated to be very similar to the SVR_{12} rate and thus the power should still be at least 90%. No adjustment for dropout is applicable because subjects who do not have data at Post-Treatment Week 12 (after imputing) are counted as failures for SVR_{12} and SVR_{24}.

9.0 Ethics

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

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

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

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

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

Additional pharmacogenetic analyses will only be performed if the subject has voluntarily signed and dated the IRB/IEC approved pharmacogenetic informed consent after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The subject must provide consent specific to pharmacogenetic before the pharmacogenetic testing is performed. If the subject does not consent to the additional pharmacogenetic testing, it will not impact the subject's participation 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 on the appropriate source documents.

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

10.2 Case Report Forms

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

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

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

principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

11.0 Data Quality Assurance

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.

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

12.0 Use of Information

Any pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, neither the investigator, the subject, nor the subject's physician (if different from the investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie.

Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

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

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

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for ABT-450, ABT-267, ABT-333 and the product labeling for ritonavir and RBV.
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 Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Treatment-Naïve and Treatment-Experienced Asian Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Compensated Cirrhosis
Protocol Date:	11 February 2015

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 References

1. Weekly Epidemiological Record. No. 41, 07 October 2011, WHO.
2. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology. 2011;34 (4 Pt 1):809-16.
3. Sangiovanni A, Prati GM, Fasani P, et al. The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. Hepatology. 2006;43(6):1303-10.
4. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. Gastroenterology. 2004;127 (5 Suppl 1):S27-34.
5. Serfaty L, Aumaitre H, Chazouilleres O, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology. 1998;27(5):1435-40.
6. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology. 1997;112(2):463-72.
7. Fattovich G, Pantalena M, Zagni I, et al. Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. Am J Gastroenterol. 2002;97:2886-95.
8. Wasley A, Alter MJ. Epidemiology of hepatitis C: geographic differences and temporal trends. Semin Liver Dis. 2000;20(1):1-16.
9. Kromit. Center for Disease Analysis, International Conquer C Coalition (I-C3). 2010.
10. Sievert W, Altraif I, Razavi H, et al. A systemic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. Liver international: official journal of the International Association for the Study of the Liver. 2011;31 (Suppl 2):61-80.
11. Tao, Q, Wang Y, Wang, H, et al. Seroepidemiology of HCV and HBV infection in northern China. Gastroenterologia Japonica. 1991;26 (Suppl 3):156-8.

12. Expert Committee on Chronic Hepatitis C Antiviral Therapy. Expert Consensus for Antiviral Therapy for Chronic Hepatitis C. (Electronic Edition) Chin J Clin Infect Dis. 2009;3(3):343-52.

13. Zhao S, Jiang T, Li R, et al. HCV infection in voluntary donors and its influence on recruitment of donors in Chongqing area. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2008;16(3):676-80.

14. Zhang M, Sun X, Mark S, et al. Hepatitis C virus infection, Linxian, China. Emerg Infect Dis. 2005;11(1):17-21.

15. Liu, F, Chen K, He Z, et al. Hepatitis C seroprevalence and associated risk factors, Anyang, China. Emerg Infect Dis. 2009;15(11):1819-22.

16. Zhuo, H, Lu S, Wang T. Chronic hepatitis C and progress of anti-viral drugs research. Chemical Drugs, Division II-CDE/SFDA. 2012.

17. Wei L, Lopez-Talaver JC, et al. Prevalence of HCV viral and host IL28B genotypes in China. Poster Presented at: 62nd Annual Meeting of the American Association for the Study of Liver Disease (AASLD 2011).. November 4 – 8, 2011; San Francisco, CA. Poster 412.

18. Li W, Zhu Y, Hua Z. [Exploration on the association between the pattern of HBV markers and infection of HCV among population]. Zhonghua Liu Xing Bing Xue Za Zhi. 1994;15(4):212-4.

19. Chen X, Xuan M, Wu D. [Study of superinfection of HBV and HCV]. Zhonghua Liu Xing Bing Xue Za Zhi. 1999;20(3):141-3.

20. Lu L, Nakano T, He Y, et al. Heptitis C virus genotype distribution in China; predominance of closely related subtype 1b isolates and existence of new genotype 6 variants. J Med Virol. 2005;75(4):538-49.

21. Suh D, Jeong S. Current status of hepatitis C virus infection in Korea. Intervirology. 2006;49(1-2):70-5.

22. Kim do Y, Kim IH, Jeong SH, et al. A nationwide seroepidemiology of hepatitis C virus infection in South Korea. Liver Int. 2013;33(4):586-94.

23. Seong MH, Kil H, Kim YS, et al. Clinical and epidemiological features of hepatitis C virus infection in South Korea: a prospective, multicenter cohort study. J Med Virol. 2013;85(10):1724-33.

24. Han CJ, Lee HS, Kim HS, et al. Hepatitis C virus genotypes in Korea and their relationship to clinical outcome in type C chronic liver disease (in Korean). Korean J Intern Med. 1997;12(1)21-7.

25. Lee G. Distribution of hepatitis C virus genotypes determined by line probe assy in Korean patients with chronic HCV infection. Korean J Hepatol. 1998;4:244-253.

26. Oh DJ, Park YM, Seo YI, et al. Prevalence of hepatitis C virus infections and distribution of hepatitis C virus genotypes amount Korean blood donors. Ann Lab Med. 2012;32(3):210-5.

27. Kanwal F, Hoang T, Spiegel BM, et al. Predicotrs of treatment in patients with chronic hepatitis C infection – Role of patient versus nonpatient factors. Hepatology. 2007;46(6):1741-9.

28. Prasad L, Spicher VM, Zwahlen M, et al; Swiss Hepatitis C Cohort Study Group. Cohort Profile: the Swiss Hepatitis C cohort Study (SCCS). Int J Epidemiol. 2007;36(4):731-7.

29. Hansen N, Obel N, Christensen PB, et al; DANHEP group. Predictors of antiviral treatment initiation in hepatitis C virus-infected patients: a Danish cohort study. J Viral Hepat. 2009;16(9):659-65.

30. Chen CH, Yang PM, Huang GT, et al. Estimation of seroprevalence of hepatitis B virus and hepatitis C virus in Taiwan from a large-scale survey of free hepatitis screening participants. J Formos Med Assoc. 2007;106(2):148-55.

31. Lee HC, Ko NY, Lee NY, et al. Seroprevalence of viral hepatitis and sexually transmitted disease among adults with recently diagnosed HIV infection in Southern Taiwan, 2000 – 2005: upsurge in hepatitis C virus infections among injection drug users. J Formos Med Assoc. 2008;107(5):404-11.

32. Yang JF, Lin CI, Huang JF, et al. Viral hepatitis infections in southern Taiwan: a multicenter community-based study. Kaohsiung J Med Sci. 2010;26:461-9.

33. Chu FY, Chiang SC, Su FH, et al. Prevalence of human immunodeficiency virus and its association with hepatitis B, C, and D virus infections among incarcerated male substance abusers in Taiwan. J Med Virol. 2009;81:973-8.

34. Sun HY, Lee HC, Liu CE, et al. Factors associated with isolated anti-hepatitis B core antibody in HIV positive patients: impact of compromised immunity. J Viral Hepat. 2010;17:578-87.

35. Chen DS, Kuo GC, Sung JL, et al. Hepatitis C virus infection in an area hyperendemic for hepatitis B and chronic liver disease: the Taiwan experience. J Infect Dis. 1990;162(4):817-22.

36. Tseng YT, Sun HY, Chang SY, et al. Seroprevalence of hepatitis virus infection in men who have sex with men aged 18 – 40 years in Taiwan. J Formos Med Assoc. 2012;111(8):431-8.

37. Huang CF, Chuang WL, Yu ML. Chronic hepatitis C infection in the elderly. Kaohsiung J Med Sci. 2011;27(12):533-7.

38. Yu ML, Chuang WL, Chen SC, et al. Changing prevalence of hepatitis C virus genotypes: molecular epidemiology and clinical implications in the hepatitis C virus hyperendemic areas and a tertiary referral center in Taiwan. J Med Virol. 2001:65(1):58-65.

39. Lee MH, Yang HI, Lu SN, et al; R.E.V.E.A.L.-HCV Study Group. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. J Infect Dis. 2012;206(4):469-77.

40. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology. 2007;45(3):579-87.

41. Di Bisceglie AM, Everson GT, Linsay KL, et al. Prolonged antiviral therapy with peginterferon to prevent complications of advanced liver disease associated with hepatitis C: results of the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) trial. Hepatology. 2007;46:ALB1-ALB1.

42. Camma C, Di Bona D, Schepis F, et al. Effect of peginterferon alfa-2a on liver histology in chronic hepatitis C: a meta-analysis of individual patient data. Hepatology. 2004;39(2):333-42.

43. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir in combination with peginterferon and ribavirin in genotype 1 HCV treatment-naive patients: final results of phase 3 ADVANCE study. Hepatology. 2010;52:S427.

44. Jacobson IM, Catlett I, Marcellin P, et al. Telaprevir substantially improved SVR rates across all IL28B genotypes in the ADVANCE trial. J Hepatol. 2011a;54:S542-3.

45. Pol S, Aerssens J, Zeuzem S, et al. Similar SVR rates in IL28b cc, ct or tt prior relapser, partial- or null-responder patients treated with telaprevir/peginterferon/ribavirin: retrospective analysis of the REALIZE study. J Hepatol. 2011a;54:S6-S7.

46. Pol S, Roberts SK, Andreone P, et al. Efficacy and safety of telaprevir-based regimens in cirrhotic patients with HCV genotype 1 and prior peginterferon/ribavirin treatment failure: subanalysis of the REALIZE phase III study. Hepatology. 2011b;54:374A-5A.

47. Bruno S, Vierling JM, Esteban R, et al. Boceprevir in addition to standard of care enhanced SVR in hepatitis c virus (HCV) genotype-1 with advanced fibrosis/cirrhosis: subgroup analysis of SPRINT-2 and RESPOND-2 studies. J Hepatol. 2011;54:S4-4.

48. Gane EJ, Roberts SK, Stedman CA, et al. Oral Presentation at: 60th AASLD, Boston 2009. Oral Presentation No. 193.

49. Zeuzem S, Asselah T, Angus PW, et al. Strong antiviral activity and safety of IFN sparing treatment with the protease inhibitor BI 201335, the HCV polymerase inhibitor BI 207127 and ribavirin in patients with chronic hepatitis C. Hepatology. 2010;52 (Suppl):876A.

50. Lok AS, Gardiner DF, Lawitz E, et al. Combination therapy with BMS-790052 and BMS-650032 alone or with PegIFN and RBV results in undetectable HCV RNA through 12 weeks of therapy in HCV genotype 1 null responders [Abstract]. Hepatology. 2010;52 (Suppl):877A.

51. Zeuzem S, Andreone P, Pol S, et al. Realize Trial final results: Telaprevir based regimen for genotype 1 hepatitis C virus infection in patients with prior null response, partial response or relapse to pegInterferon/Ribavirin. J Hepatol. 2011;54(1):S3.

52. Chayama K, Takahashi S, Kawakami Y, et al. Dual Oral Combination Therapy with the NS5A Inhibitor BMS-790052 and the NS3 Protease Inhibitor BMS 650032 Achieved 90% Sustained Virologic Response (SVR12) in HCV Genotype 1b-Infected Null Responders. Paper Presented at: 62nd Annual Meeting of the American Association for the Study of Liver Disease (AASLD 2011). November 4 – 8, 2011; San Francisco, CA. Abstract LB-4.

53. Soriano V, Gane E, Angus P, et al. The efficacy and safety of the interferon-free combination of BI 201335 and BI 207127 in genotype 1 HCV patients with cirrhosis: interim analysis from SOUND-C2. Poster Presented at: International Liver Congress™, the 47th Annual Meeting of the European Association of the Study of the Liver (EASL 2012). 2012 Apr 18 – 22; Barcelona, Spain].

54. Gane E, et al, Paper Presented at: 64th Annual Meeting of the American Association for the Study of Liver Disease; November 1-5, 2013; Washington, DC, Abstract 73, 2013.

55. Everson et al, Abstract LBI, 2013 AASLD.

56. INCIVEKTM (telaprevir) [package insert]. Cambridge, MA; Vertex Pharmaceuticals Inc., 2012.

57. EU Summary of Product Characteristics for INCIVO® (telaprevir). Available from: the European Public Assessment Report:http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002313/WC500115507.pdf.

58. Sherman K, Flamm S, Afdhal N, et al; ILLUMINATE Study Team. Response guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011;365(11):1014-24.

59. Xie R, Fan X, Yang S, et al. Expert consensus for antiviral treatment of chronic hepatitis C. Chinese J Exp Clinic Infect Dis (Electronic Edition). 2009;3(3):343-52.

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 materia1 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
		Clinical
		Clinical
		Pharmacokinetics
		Statistics
		Global Drug Supply Management

Appendix C. Clinical Toxicity Grades

Clinical Toxicity Grades for HCV Studies[1,2]				
	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
HEMATOLOGY				
ABSOLUTE NEUTROPHIL COUNT DECREASED	<LLN – 1500/mm3 <LLN – 1.5 × 10e9/L	<1500 – 1000/mm3 <1.5 – 1.0 × 10e9/L	<1000 – 500/mm3 <1.0 – 0.5 × 10e9/L	<500/mm3 <0.5 × 10e9/L
EOSINOPHIL COUNT INCREASED	650-1500 cells/mm3	1501-5000 cells/mm3	>5000 cells/mm3	Hypereosinophilic
HEMOGLOBIN DECREASED	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L
INTERNATIONAL NORMALIZED RATIO (INR), INCREASED	>1 – 1.5 × ULN	>1.5 – 2 × ULN	>2 × ULN	
LYMPHOCYTE COUNT DECREASED	<LLN – 800/mm3 <LLN × 0.8 – 10e9/L	<800 – 500/mm3 <0.8 – 0.5 × 10e9/L	<500 – 200 mm3 <0.5 – 0.2 × 10e9/L	<200/mm3 <0.2 × 10e9/L
PLATELETS DECREASED	<LLN – 75,000/mm3 <LLN – 75.0 x 109 /L	<75,000-50,000/mm3 <75.0 – 50.0 x 109 /L	<50,000-25,000/mm3 <50.0 – 25.0 x 109 /L	<25,000/mm3 <25.0 x 109 /L
PTT	>1 – 1.5 × ULN	>1.5 – 2 × ULN	>2 × ULN	
WHITE BLOOD CELL COUNT DECREASED	<LLN – 3000/mm3 <LLN – 3.0 × 10e9/L	<3000 – 2000/mm3 <3.0 – 2.0 × 10e9/L	<2000 – 1000/mm3 <2.0 – 1.0 × 10e9/	<1000/mm3 <1.0 × 10e9/L
WHITE BLOOD CELL COUNT INCREASED	10,800 – 15,000 cells/mm3	>15,000 – 20,000 cells/mm3	>20,000 – 25,000 cells/mm3	>25,000 cells/mm3
CHEMISTRIES				
ALBUMIN, SERUM, LOW	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	
BILIRUBIN, HIGH	>ULN – 1.5 × ULN	>1.5 – 3.0 × ULN	>3.0 – 10.0 × ULN	>10.0 × ULN
BUN	1.25-2.5 × ULN	>2.5 -5.0 × ULN	>5 -10.0 × ULN	>10 × ULN
CALCIUM, SERUM LOW	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
CALCIUM, SERUM HIGH	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
CALCIUM, IONIZED, LOW	<LLN – 1.0 mmol/L	<1.0 – 0.9 mmol/L	<0.9 – 0.8 mmol/L	<0.8 mmol/L
CALCIUM, IONIZED, HIGH	>ULN – 1.5 mmol/L	>1.5 – 1.6 mmol/L	>1.6 – 1.8 mmol/L	>1.8 mmol/L

Clinical Toxicity Grades for HCV Studies
v1.1; 08June2009

Clinical Toxicity Grades for HCV Studies (Continued)				
	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
CHOLESTEROL HIGH	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
CREATININE	1.5 – 1.7 mg/dL	1.8 – 2.0 mg/dL	2.1 – 2.5 mg/dL	>2.5 mg/dL or requires dialysis
GLUCOSE, SERUM, LOW	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L
GLUCOSE, SERUM, HIGH (Fasting)	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis
MAGNESIUM, SERUM, LOW	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L
MAGNESIUM, SERUM, HIGH	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L		>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L
PHOSPHATE, SERUM, LOW	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L
POTASSIUM, SERUM, LOW	<LLN – 3.0 mmol/L		<3.0 – 2.5 mmol/L	<2.5 mmol/L
POTASSIUM, SERUM, HIGH	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L
PROTEIN, SERUM, LOW	5.5 – 6.0 g/dL	<5.5 – 5.0 g/dL	<5.0 g/dL	
SODIUM, SERUM, LOW	<LLN – 130 mmol/L		<130 – 120 mmol/L	<120 mmol/L
SODIUM, SERUM, HIGH	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L Hospitalization may be indicated	>160 mmol/L
TRIGLYCERIDES HIGH (fasting)	150-300 mg/dL; 1.71 – 3.42 mmol/L	>300-500 mg/dL; >3.42-5.7 mmol/L	>500-1000 mg/dL; >5.7 – 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L
URIC ACID, SERUM, HIGH	7.5 – 10.0 mg/dL	10.1-12.0 mg/dL	12.1-15.0 mg/dL	>15.0 mg/dL

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Clinical Toxicity Grades for HCV Studies (Continued)				
	GRADE 1 TOXICITY	**GRADE 2 TOXICITY**	**GRADE 3 TOXICITY**	**GRADE 4 TOXICITY**
ENZYMES				
ALT/SGPT	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN;	>5.0 – 20.0 x ULN	>20.0 x ULN
AST/SGOT	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN;	>5.0 – 20.0 x ULN	>20.0 x ULN
ALKALINE PHOSPHATASE	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AMYLASE	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN
LIPASE	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN

1 Adapted from the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0 (CTCAE)
2 Used for all HCV development compounds

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Document Approval

Study M14491 - An Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Treatment-Naïve and Treatment-Experienced Asian Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Compensated Cirrhosis - 11Feb2015

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