1.0 Title Page

Clinical Study Protocol M13-101

An Open-Label Study to Evaluate the Safety, Antiviral Activity and Pharmacokinetics of Direct-Acting Antiviral Agent (DAA) Treatment in Combination with Peginterferon α-2a and Ribavirin (pegIFN/RBV) in Chronic Hepatitis C Virus (HCV) Infected Subjects Who Have Experienced Virologic Failure in a Previous AbbVie or Abbott DAA Combination Study

Incorporating Administrative Changes 1, 2, 3, 4 and 5 and Amendments 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10

AbbVie Investigational Product:	ABT-450, ritonavir, ABT-267
Date:	26 June 2015
Development Phase:	2
Study Design:	This is an open-label rollover study.
EudraCT Number:	2011-005393-32
Investigators:	Multicenter. Investigator Information is on file at AbbVie.
Sponsor:	AbbVie Inc.*

[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.

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

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Update Section 1.2 and Section 5.5.1 to correct the number of subjects

  Rationale for change: A smaller proportion of subjects experienced virologic failure in previous AbbVie or Abbott DAA combination studies than previously anticipated.
- Update Section 1.0, Section 6.5 and Appendix B

  Rationale for change: Reflect the change of the Study Designated Physician.
- Update Section 5.3.1 for study activities

  Rationale for change: To reflect the correct collection time point for HCV RNA level at screening and to change the collection time for Archive Plasma Samples to reflect the updated archive plasma sample analysis strategy.
- Update Section 5.3.1 and Section 5.5.7 concerning Electronic Pill Monitors (MEMS Caps)

  Rationale for change: The collection of MEMS caps data as a daily dosing monitoring tool has been removed as the drug compliance is reviewed and documented by the site, to minimize the workload for the subject and the site. The MEMS caps data collected so far will be analyzed and included in the Clinical Study Report.
- Update Section 5.1.3 and Section 8.0 for Interim analysis

  Rationale for change: Due to the significantly decreased number of subjects expected to enroll in this study, the interim analyses have been removed.
- Update Section 5.3.2.3, Disposition of Samples.

  Rationale for change: To clarify in the protocol how and when samples are to be disposed of.
- Update Section 5.4.2 for Non Efficacy (Futility) Criteria

  Rationale for change: Due to the reduced number of subjects to be enrolled in this study (up to 35), the assessments at subsequent time points will not be relevant.

- Update Section 5.5.6 for treatment compliance

  Rationale for change: To reflect that RBV bottles are no longer re-dispensed to patients according with the last updates to the drug supply strategy and supported by the IRT system.

- Update Section 5.6.4 for Selection of the Doses in the Study

  Rationale for change: To update information about the dose selection and the information from other recent AbbVie studies.

- Update Section 6.1.2 for Serious Adverse Events

  Rationale for change: To specify that elective or spontaneous abortion or stillbirth is considered an important medical event.

- Update Section 6.5 for safety contact or medical emergencies information

  Rationale for change: Offering additional contact information for subject safety concerns or medical emergencies in case it is not possible to contact the Primary Study Designated Physician.

- Update Section 6.6 for Pregnancy

  Rationale for change: To update how to instruct subjects who report a positive pregnancy test during the Treatment Period.

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M13-101
Name of Study Drug: ABT-450, ritonavir, ABT-267, ribavirin, Pegylated interferon α-2a	**Phase of Development:** Phase 2b
Name of Active Ingredient: ABT-267 ABT-450 ritonavir	**Date of Protocol Synopsis:** 26 June 2015
Protocol Title: An Open-Label Study to Evaluate the Safety, Antiviral Activity and Pharmacokinetics of Direct-Acting Antiviral Agent (DAA) Treatment in Combination with Peginterferon α-2a and Ribavirin (pegIFN/RBV) in Chronic Hepatitis C Virus (HCV) Infected Subjects Who Have Experienced Virologic Failure in a Previous AbbVie or Abbott DAA Combination Study	
Objectives: The primary objective of this study is to evaluate the safety and antiviral efficacy, defined as the percentage of subjects with sustained virologic response 12 weeks post-dosing (SVR_{12}; HCV RNA < LLOQ 12 weeks after the last dose of study drug). The secondary objectives of this study are to evaluate the percentage of subjects with sustained virologic response 24 weeks post-dosing (SVR_{24}; HCV RNA < LLOQ 24 weeks after the last dose of study drug) and the percentage of subjects with extended rapid virologic response (eRVR) (HCV RNA < LLOQ at TI Weeks 4 through 12).	
Investigators: Multicenter	
Study Sites: Up to 150 sites who participated in a previous AbbVie/Abbott DAA combination study.	
Study Population: Subjects who have experienced virologic failure in a previous AbbVie/Abbott DAA combination study.	
Number of Subjects to be Enrolled: Up to 35. The enrollment number of this study depends on the treatment failure rate of subjects in previous AbbVie/Abbott DAA combination studies, therefore there will be no lower or upper limit of enrollment.	

Methodology:

This is an open-label, multiple-dose, rollover study exploring the safety, antiviral activity and pharmacokinetics of ABT-450 with ritonavir (ABT-450/r) + ABT-267 in combination with pegIFN and RBV in HCV genotype 1-infected subjects (including subjects with compensated cirrhosis) who have experienced virologic failure in a previous AbbVie/Abbott DAA combination study. Among subjects who previously experienced null or partial response to pegIFN/RBV treatment at any time prior to pre-screening for this study or any prior failure with pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study, enrollment will be limited to only those subjects in whom variants relative to appropriate prototypic reference sequence in HCV protease at positions 155, 156, or 168 or in HCV NS5A at positions 28, 29, 30, 31, 32, 58, or 93 are not present at the Pre-screening Visit. All other subjects will be allowed to enroll in Study M13-101 at the discretion of the investigator, regardless of whether variants at any of these amino acid positions are detected.

This protocol consists of three substudies. In Substudy 1, subjects who have experienced virologic failure in a previous AbbVie/Abbott DAA combination study may choose to enter this study and receive intensified treatment with ABT-450/r, ABT-267, pegIFN and RBV for 24 weeks. Subjects who complete or discontinue DAA treatment in Substudy 1 will enter Substudy 2. In Substudy 2, subjects receive pegIFN and RBV for an additional 24 weeks for a total treatment of up to 48 weeks across Substudies 1 and 2. In Substudy 3, subjects will be monitored for resistance and viral response for 48 weeks after discontinuation of study drug treatment.

Ongoing review of the data is planned in order to determine if a subject meets the virologic stopping criteria as defined in this protocol. Subjects who meet virologic stopping criteria during DAA treatment will discontinue ABT-450/r and ABT-267, but at the investigator's discretion may continue to receive pegIFN and RBV therapy for a total of 48 weeks across Substudies 1 and 2. Ongoing review of the data is also planned for non-efficacy (futility) assessment. Data will be assessed separately for the population of subjects who were null or partial responders to prior pegIFN/RBV or who had any prior failure to pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study, and for the population of subjects who do not fall in the previous population at the time of enrollment into this study.

In Substudy 3, the study will monitor and evaluate subjects for 48 weeks after the last dose of study drug for HCV RNA and the evolution and persistence of viral resistance to DAAs.

Study Procedures:

Subjects will visit the site on an outpatient basis for testing of HCV RNA, pharmacokinetics sampling, safety and resistance. Safety of the treatments will be evaluated throughout the study using assessments of adverse events (AEs), physical exam findings, electrocardiograms (ECGs), and laboratory parameters which will include chemistry, hematology and urinalysis. Additional procedures will be done for cirrhotic subjects to evaluate hepatic compensation and to rule-out hepatocellular carcinoma.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

To be enrolled in this protocol, subjects must meet all of the following inclusion criteria:

1. Subject must have experienced virologic failure as defined in a previous AbbVie/Abbott DAA combination trial.
2. Female subjects of childbearing potential must be willing to use two effective forms of birth control (not including contraceptives containing ethinyl estradiol) while receiving study drug and for 7 months (or per local ribavirin label) after stopping study drug (Note: Estrogen-containing hormonal contraceptives, including oral, injectable, implantable, patch and ring varieties, may not be used during DAA treatment). Females are considered of childbearing potential unless they are either:
   - Post-menopausal 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 history of bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s), or
   - Practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle), or
   - Sexually active with female partner(s) only.
3. Males must be surgically sterile, or have male partners only, or if sexually active with female partner(s) of childbearing potential must agree to practice two effective forms of birth control throughout the course of the study, starting with Study Day 1 and for 7 months (or per local ribavirin label) after the last dose of study drug, unless abstinent from sexual intercourse.
   (Note: Contraceptives containing ethinyl estradiol may be considered effective if used by the female partners of male subjects.)
4. For cirrhotic subjects, compensated cirrhosis defined as Child-Pugh score of ≤ 6 at Screening.
5. Subject is infected with HCV genotype 1 at Screening Visit.

Main Exclusion:

To be enrolled in this protocol, subjects must not meet any of the following exclusion criteria:

1. In subjects with a prior null or partial response to pegIFN/RBV treatment at any time prior to pre-screening for this study or any prior failure with pegIFN/RBV plus telaprevir, the presence of variants relative to the appropriate prototypic reference sequence (H77 for 1a or Con1 for 1b) at any of the following amino acid positions: NS3 protease 155, 156, or 168; NS5A 28, 29, 30, 31, 32, 58, or 93.
2. 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 RBV.
3. Use of known strong inducers (e.g., phenobarbital, rifampin, carbamazepine, St. John's Wort) of CYP3A within 2 weeks prior to study drug administration.

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

Main Exclusion (Continued):

4. Use of any medications contraindicated for use with ABT-450, ABT-267, pegIFN, RBV or ritonavir within 2 weeks prior to study drug administration.
5. Discontinuation of antiviral therapy due to intolerance or a DAA or RBV associated adverse event in a previous AbbVie/Abbott DAA combination study (excluding intolerance or AEs associated with telaprevir).

Investigational Products:	ABT-267 25 mg tablet ABT-450 50 mg tablet Ritonavir 100 mg capsule/tablet
Doses:	ABT-267 25 mg daily (QD) ABT-450/r 200/100 mg QD
Mode of Administration:	Oral
PegIFN and RBV Therapy:	pegylated interferon α-2a (pegIFN) 180 µg per 0.5 mL syringe + ribavirin (RBV) 200 mg tablets
Doses:	pegIFN 180 µg once weekly + weight-based RBV 1000 to 1200 mg divided twice daily
Mode of Administration:	pegIFN – SC injection; RBV – oral

Duration of Treatment:

Subjects will receive ABT-450/r and ABT-267 in combination with pegIFN and RBV from Study Day 1 through Study Week 24 (Substudy 1). Subjects will then proceed to Substudy 2 where they will receive additional pegIFN and RBV for 24 weeks.

Criteria for Evaluation:

Efficacy:

Virologic response (HCV RNA) in $\log_{10}$ IU/mL will be assessed at various time-points from Study Day 1 through 24 weeks after pegIFN and RBV treatment.

Resistance:

The following resistance analyses will be performed for subjects who do not achieve SVR: the variants at each amino acid position identified by population and/or clonal nucleotide sequencing (1) at baseline will be compared to the appropriate prototypic reference sequence, and (2) at available post-baseline time points will be compared to baseline and the appropriate prototypic reference sequences.

Pharmacokinetic:

Plasma concentrations for ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ritonavir, RBV and serum concentrations for pegIFN will be tabulated and summarized, if measured.

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:

The primary efficacy endpoint is the percentage of subjects with sustained virologic response 12 weeks after the last actual dose of study drug (including DAA, pegIFN, and RBV) ($SVR_{12actual}$). The percentage of subjects with $SVR_{12actual}$ and the corresponding 95% exact binomial confidence interval will be calculated overall and by treatment group in the prior study.

Secondary Efficacy Endpoints

The secondary efficacy endpoints are the percentage of subjects with sustained virologic response 24 weeks after the last actual dose of study drug (including DAA, pegIFN, and RBV) ($SVR_{24actual}$) and the percentage of subjects with eRVR (HCV RNA < LLOQ at Weeks 4 through 12 in Substudy 1).

The percentage of subjects with $SVR_{24actual}$ and eRVR and the corresponding 95% exact binomial confidence intervals will be calculated overall and by treatment group in the prior study.

Pharmacokinetic:

Plasma concentrations for ABT-267, ABT-450, ritonavir, and RBV and serum concentrations of pegIFN will be summarized, if measured. Plasma concentrations of metabolites if measured will also be summarized.

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. Tabulations will also be provided in which the number of subjects reporting an adverse event (MedDRA term) is additionally broken down by severity (mild, moderate, or severe) and relationship to study drug. Change from baseline in laboratory tests and vital sign measurements to each time-point of collection will be summarized, and values that are potentially clinically significant, according to predefined criteria, will be identified.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

A1C	Apolipoprotein A1
ABT-450/r	ABT-450 administered with ritonavir
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-HIV Ab	Anti-HIV antibody
aPTT	Activated partial thromboplastin time
AARDEX	Advanced Analytical Research on Drug Exposure
AST	Aspartate aminotransferase
AUC	Area under the curve
BDI-II	Beck Depression Inventory-II
BID	Twice daily
BMI	Body mass index
BUN	Blood urea nitrogen
C_{max}	Maximum observed plasma concentration
CRF	Case report form
CYP3A	Cytochrome P450 3A
CYP3A4	Cytochrome P450 3A4
DAA	Direct-acting antiviral agent
EC	Ethics Committee
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EOTR	End of Treatment Response (Week 12)
eRVR	Extended rapid virologic response
EVR	Early virological response
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice

HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IL28B	Interleukin 28B
IMP	Investigational medical product
INR	International normalized ratio
IRB	Institutional Review Board
IP-10	Interferon gamma-induced protein 10
IRT	Interactive response technology
IU	International units
IUD	Intrauterine device
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MEMS	Medication Event Monitoring System
MDRD	Modification of diet in renal disease
NS3	Nonstructural protein 3
NS4A	Nonstructural protein 4A
NS5A	Nonstructural protein 5A
NS5B	Nonstructural protein 5B
OATP1B1	Organic anion transporting polypeptide 1B1
PCS	Potentially clinically significant
pegIFN	Peginterferon alfa-2a
PO	Oral
POR	Proof of Receipt
PT	Prothrombin time
QD	Once daily
QTcF	QTc using Fridericia's correction formula
RBC	Red blood cells

RBV	Ribavirin
RNA	Ribonucleic acid
RVR	Rapid virologic response
SAE	Serious adverse event
SAS	Statistical Analysis System
SDP	Study Designated Physician
SDS	Sodium dodecyl sulfate
SC	Subcutaneous
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
SVR	Sustained virologic response
SVR_{12}	Sustained virologic response 12 weeks post-dosing
SVR_{24}	Sustained virologic response 24 weeks post-dosing
TI	Treatment intensification
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cells

Definition of Terms

Post-Treatment Period	48 weeks duration after the last dose of study drug in Substudy 1 or 2
Substudy 1 Study Drug	ABT-450/r, ABT-267, pegIFN, RBV
Substudy 2 Study Drug	pegIFN, RBV
Study Day 1	First day a subject took study drug in Substudy 1
Treatment Intensification Period	Substudy 1
Treatment Period	Day 1 through last treatment visit in Substudy 1 or 2

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 infected worldwide.[1] While therapy for this condition has improved considerably, the currently available treatment regimens are not optimal. Until 2011 with the FDA approval of the protease inhibitors (PI) telaprevir and boceprevir, the standard of care (SOC) for treatment of HCV genotypes 1a and 1b (the most common genotypes in North America and Europe) consisted of weekly injections of pegylated interferon-alpha (pegIFN) and daily oral doses of ribavirin (RBV) for up to 48 weeks.[2] Approximately 50% of patients with genotype 1 HCV infection treated with pegIFN and RBV fail to achieve a sustained virologic response (SVR). While the triple drug regimen of PI/pegIFN/RBV increased SVR rates to 70% – 80%, there were many treatment discontinuations due to drug toxicities like rash and anemia, and virologic failure rates were still unacceptably high. These two, distinct eras of HCV therapy generated a large cohort of patients in need of more potent antiviral regimens.

To meet this need, a number of small molecules with direct antiviral activity (direct-acting antiviral agent [DAA]) against specific stages of the HCV life cycle have been developed.[3] Clinical studies to date with these DAA HCV inhibitors, such as the NS3/4A protease inhibitors telaprevir and boceprevir, used in combination with pegIFN plus RBV, have demonstrated improved SVR rates in treatment-naïve and pegIFN-experienced patients, with shorter treatment durations for a subset of naïve subjects. As a result, these regimens are now considered the standard of care for chronic genotype 1 HCV infection.[4] Combinations of multiple DAAs with pegIFN and RBV have also been studied and may further improve SVR rates or shorten duration of therapy.[5,6]

Data from studies on the retreatment of HCV-infected subjects who failed prior treatment with regimens containing one or more DAAs are limited. In one study, an NS5A inhibitor (BMS 790052) and a PI (BMS 650032) combined with pegIFN and RBV for 24 weeks achieved SVR_{24} in over 90% of prior pegIFN/RBV null responders, suggesting that these patients may be successfully treated with a DAA combination added to pegIFN/RBV. In

several exploratory studies, subjects who experienced viral breakthrough or non-response (with emergence of DAA-related associated resistance mutations) were managed by the addition of pegIFN, or pegIFN and RBV to the failing DAA combination regimen. This treatment strategy resulted in suppression of HCV RNA to undetectable levels in a number of subjects despite the presence of resistant virus, including in prior pegIFN/RBV null responders.[7] This response may be related to the impaired replicative capacity of the resistant viral variants, or to improved interferon responsiveness following a course of DAA therapy. The replicative fitness of resistant variants plays a role not only in the likelihood and timing of the emergence of resistance, but also in the likelihood of a quasispecies population dominated by resistant variants reverting to predominantly wild type virus in the absence of drug selective pressure. Continuation of the DAAs in these cases may therefore contribute to antiviral activity even in the presence of resistant variants, by providing selective pressure to maintain a population of poorly fit variants.

The antiviral response in patients whose HCV is re-exposed to a DAA has not yet been studied, but will be important in understanding future treatment options for patients who fail initial therapy. Unlike HIV infection, in which resistant variants generated during unsuccessful antiretroviral therapy are archived as latently integrated proviruses in resting memory T cells, no such long-lived reservoir has been demonstrated for HCV. Thus, it may be possible for patients who initially failed a DAA-containing regimen to achieve successful retreatment with a new regimen that includes DAAs that were components of the initial regimen.

AbbVie has three DAAs that were recently approved by North American and European regulatory agencies. ABT-450 (paritaprevir) is an NS3/4A protease inhibitor, ABT-267 (ombitasvir) is an NS5A inhibitor, and ABT-333 (dasabuvir) is a non-nucleoside NS5B polymerase inhibitor. These 3 DAAs have been studied both with and without RBV in the absence of pegIFN in phase 3 trials in HCV-infected subjects, as summarized below. The current study will explore the utility of pegIFN and RBV, in combination with ABT-450/r and ABT-267, in HCV-infected subjects who have experienced virologic

failure in a previous AbbVie/Abbott trial of combination DAA therapy. Additional information on ABT-450 and ABT-267 is provided below.

ABT-450

ABT-450, (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate, is an NS3/4A protease inhibitor with nanomolar potency against genotype 1 HCV in vitro. ABT-450 is metabolized primarily by cytochrome P450 3A4 (CYP3A4) and thus is dosed with ritonavir, a potent CYP3A4 inhibitor, in order to enhance exposures (ABT-450/r). ABT-450/r has been well tolerated in single- and multiple-dose studies in healthy volunteers, and when administered to HCV-infected subjects at doses of 50/100 mg QD, 100/100 mg QD and 200/100 mg QD for 12 weeks in combination with pegIFN and RBV in Study M11-602. Repeated dosing of ABT-450/r in both healthy volunteers and HCV-infected subjects has been associated with transient asymptomatic increases in total and indirect bilirubin, occurring with greater frequency at total daily doses of 200/100 mg or greater. These increases in bilirubin appear to be due to ABT-450-mediated inhibition of the bilirubin transporter organic anion transporting polypeptide 1B1 (OATP1B1).

In Study M11-602, ABT-450/r monotherapy for 3 days resulted in a mean maximum 4.01 $\log_{10}$ international units (IU)/mL HCV RNA decline, compared to 0.36 $\log_{10}$ IU/mL with placebo (n = 11), $P < 0.001$. Twenty-two of 24 subjects receiving ABT-450/r plus pegIFN/RBV achieved an HCV RNA below the level of detection at Week 12, compared to 2 of 11 receiving pegIFN/RBV alone ($P < 0.001$). Confirmed virologic failure subsequently occurred in 3 subjects receiving ABT-450/r 50/100 mg QD (2 relapses after discontinuing therapy and one failure to achieve undetectable HCV RNA), suggesting that this dose may have less antiviral activity than the higher doses. In an analysis of clonal sequencing results from the monotherapy portion of ABT-450/r administration, variants associated with resistance were observed less commonly in the NS3 protease gene in

subjects receiving ABT-450/r 200/100 mg compared to the lower doses, likely representing suppression of pre-existing resistant variants at the 200/100 mg dose.

ABT-450/r has a favorable safety, tolerability, and pharmacokinetic profile at doses administered to date and has shown potent antiviral activity at doses of 50/100 mg QD and greater in HCV genotype 1-infected subjects. Additional detailed information about preclinical toxicology, metabolism, pharmacology and clinical data can be found in the Investigator's Brochure for ABT-450.[8]

ABT-267

ABT-267, dimethyl ([(2S,5S)-1-(4-tert-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]}) biscarbamate hydrate, is an NS5A inhibitor, with inhibitory concentrations in the picomolar range against genotype 1 HCV in vitro.

ABT-267 has been well tolerated in single- and multiple-dose studies in healthy volunteers, and when administered to HCV-infected subjects at doses of 5 mg QD to 200 mg QD for 12 weeks in combination with pegIFN and RBV in Study M12-114. Three days of ABT-267 monotherapy resulted in approximately a 2.9 $\log_{10}$ IU/mL mean maximal HCV RNA decrease from baseline across a range of doses from 5 mg QD to 200 mg QD.

ABT-267 has a favorable safety, tolerability, and pharmacokinetic profile at all doses administered to date, and has shown potent antiviral activity at doses of 5 mg QD and greater in HCV genotype 1-infected subjects. Additional detailed information about preclinical toxicology, metabolism, pharmacology and clinical data can be found in the Investigator's Brochure for ABT-267.[9]

Combination Antiviral Effect In Vitro

ABT-450 plus ABT-267 has been studied in combination in the in vitro replicon system. This compound combination displayed additive to synergistic interactions at most

concentrations tested. In longer term cell passage studies, the combination of ABT-450 plus ABT-267 reduced replicon RNA to below detectable levels.

Phase 3 studies with ABT-450, ABT-267 and ABT-333

The IFN-free regimen of ABT-450/r, ABT-267, and ABT-333 has been studied with and without RBV in over 2,300 patients in Phase 3 trials across a variety of patient populations, including patients with compensated cirrhosis. Based on these data, the regimen with or without RBV is safe, well tolerated and efficacious in treatment-naïve and treatment-experienced HCV genotype 1-infected subjects including those with compensated cirrhosis. The overall efficacy results (intent-to-treat) from the Phase 3 studies are listed in Table 1.

Table 1. Pooled SVR_{12} Rates (Intent-to-treat, missing = failure) from Phase 3 Studies 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-cirrhotic			
Naïve	99.0	98.9	--
Null	100	94.4	--
Partial	100	98.1	--
Relapser	100	98.5	--
Genotype 1a non-cirrhotic			
Naïve	90.2	95.7	--
Null	--	95.4	--
Partial	--	100	--
Relapser	--	94.0	--
Genotype 1b cirrhotic			
Naïve	--	100	100
Null	--	100	100
Partial	--	85.7*	100
Relapser	--	100	100
Genotype 1a cirrhotic			
Naïve	--	9.4	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 that assessed the safety and efficacy of 12 weeks of therapy with 3 DAAs + RBV in HCV genotype 1-infected treatment-naïve subjects (Study M11-646) and prior pegIFN/RBV non-responders (Study M13-098) without cirrhosis. Subjects received 3 DAAs + RBV

for 12 weeks of treatment. Subjects randomized to the placebo arm received placebo for 12 weeks, after which they received 3 DAAs + RBV in open-label fashion for 12 weeks.

In Study M11-646, a total of 631 subjects were randomized and received at least one dose of study drug, of which 67.7% had HCV genotype 1a and 32.3% had HCV genotype 1b. The SVR_{12} rate for treatment-naïve subjects receiving 3 DAAs + RBV for 12 weeks was 96.2%. Virologic failure was noted in 7/322 (2.2%) genotype 1a-infected subjects (on-treatment virologic failure: n = 1; relapse: n = 6) and 1/151 (0.7%) genotype 1b-infected subjects (relapse).

In Study M13-098, a total of 394 subjects were randomized and received at least one dose of study drug, of which 58.4% had HCV genotype 1a, 41.4% had HCV genotype 1b, 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%. Virologic failure (all relapse) was noted in 5/173 (2.9%) genotype 1a-infected subjects and 2/123 (1.6%) genotype 1b-infected 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 trials that assessed the safety and efficacy of 12 weeks of treatment with 3 DAAs with or without RBV. Studies M13-961 and 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 genotype 1b-infected subjects who did not achieve SVR with pegIFN/RBV, Study M13-961 enrolled genotype 1b-infected subjects who were treatment-naïve, and Study M14-002 enrolled genotype 1a-infected subjects who were treatment-naïve. All three studies excluded subjects with cirrhosis.

In Study M13-389, a total of 186 subjects were randomized and received at least one dose of study drug, of which 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. The difference in SVR_{12} rates between the 2 regimens met the protocol-specified criteria for noninferiority; hence, the 3-DAA regimen without RBV demonstrated noninferiority compared to 3-DAA + RBV. No subject in either arm experienced on-treatment virologic failure or post-treatment relapse.

In Study M13-961, a total of 419 subjects were randomized and received at least one dose of study drug. The SVR_{12} rates for treatment-naïve subjects with HCV genotype 1b infection who received either 3 DAAs with or without RBV for 12 weeks were 99.5% and 99.0%, respectively. The difference in SVR_{12} rates between the 2 regimens in this study also met the protocol-specified criteria for noninferiority. One of the 419 treated subjects (3-DAA + RBV arm) experienced on-treatment virologic failure.

In Study M14-002, 305 subjects were randomized and received at least one dose of study drug. The SVR_{12} rates for treatment-naïve subjects with HCV genotype 1a infection who received either 3 DAAs with or 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. 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 genotype 1a-infected patients and suggests that 3 DAAs + RBV is the optimal regimen for these patients.

Phase 3 Study in Cirrhosis: 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 genotype 1 infection with compensated (Child-Pugh A, Child-Pugh score 5 or 6) cirrhosis. The 3 DAAs + RBV were administered for either 12 or 24 weeks of treatment.

A total of 380 subjects were randomized and received at least one dose of study drug, of which 68.7% had HCV genotype 1a, 31.3% had HCV genotype 1b, 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 a lower SVR_{12} rate among genotype 1a-infected prior null responders who received 12 weeks of treatment, while other subgroups had comparable response rates when treated for 12 or 24 weeks. Thus, a 12-week treatment regimen with 3-DAA + RBV is recommended for all patients with cirrhosis with the exception of genotype 1a-infected prior null responders, for whom 24 weeks of treatment provides a higher SVR.

Integrated Safety Results

A summary of treatment-emergent adverse events from 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-wk 3-DAA + RBV	**12-wk PBO**	**12-wk 3-DAA + RBV**	**12-wk 3-DAA**	**12-wk 3-DAA + RBV**	**24-wk 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	0

wk = week, PBO = placebo

a. Lung cancer.

The most common adverse events regardless of causality are listed in Table 3. Adverse events that occurred with an incidence at least 5% greater in the 3-DAA + RBV regimen compared to placebo were considered to be adverse drug reactions related to the study treatment. These include fatigue, nausea, pruritus, insomnia, asthenia, and anemia. The frequency of these events was generally lower in the arm treated without RBV. In general, rates of adverse events were similar in patients with cirrhosis versus patients without cirrhosis.

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	
Treatment-Emergent Adverse Events, %	**12-wk 3-DAA + RBV**	**12-wk PBO**	**12-wk 3-DAA + RBV**	**12-wk 3-DAA**	**12-wk 3-DAA + RBV**	**24-wk 3-DAA + RBV**
	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

wk = week, 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 have been observed, due to ABT-450 inhibition of the bilirubin transporters OATP1B1 and OATP1B3 and RBV-induced hemolysis. The elevations generally peaked by Weeks 1 and 2, declined through the end of treatment and returned to within the normal range by 4 weeks

post-treatment. Hyperbilirubinemia occurred less frequently in subjects treated with 3 DAAs without RBV compared to 3 DAAs with RBV. The frequency and degree of hyperbilirubinemia were higher in subjects with cirrhosis, but the temporal pattern of elevation followed by resolution was similar and few episodes were symptomatic. Grade 2 + hemoglobin reductions occurred in 6% of subjects without cirrhosis who received the 3-DAA + RBV regimen for 12 weeks, and 7% and 11% of subjects with cirrhosis who received the 3-DAA + RBV regimen for 12 and 24 weeks, respectively. Grade 3 hemoglobin values were rare. The decline in hemoglobin was largely managed with RBV dose reductions. Anemia observed during the clinical trials was largely attributable to the presence of RBV as it was not observed when the 3-DAA regimen was administered without RBV.

Transient asymptomatic postbaseline 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 systemic 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. Concomitant use of systemic estrogen-containing medications is a risk factor for these postbaseline elevations in serum ALT. No ALT elevations > 5 × ULN were observed in subjects receiving progestins only or in subject receiving topical vaginal estrogen preparations. Among the cases of serum ALT elevation thought to be related to the DAA regimen, none resulted in hepatic dysfunction and they generally resolved or improved with ongoing treatment. All cases had resolved completely in the post-treatment follow-up.

ABT-450/ritonavir and ABT-267 (and its major inactive human metabolites) had no effects on embryo-fetal development in rodent and/or nonrodent species at maximal feasible exposures that provided AUC multiples at least 4-fold higher than exposure at the

recommended clinical doses. Clinical studies in women who are pregnant have not been conducted.

The current study is intended to offer subjects with genotype 1 HCV infection who experience virologic failure in a previous AbbVie/Abbott DAA combination study an optional intensified treatment regimen. This study will assess the safety, antiviral activity and resistance profile of ABT-450/r 200/100 mg QD and ABT-267 25 mg QD combined with pegIFN and RBV in subjects who met a virologic failure criterion in a previous study. Among subjects who previously experienced null or partial response to pegIFN/RBV treatment (with or without approved DAAs) at any time prior to pre-screening for this study, or who experienced virologic failure with pegIFN/RBV plus telaprevir in the prior AbbVie/Abbott study, enrollment will be limited to only those subjects in whom variants in HCV NS3/4A protease and NS5A at amino acid residues known to be associated with resistance are not present at a pre-screening visit. Subjects who never experienced prior null or partial response to pegIFN/RBV treatment, and who never experienced virologic failure with pegIFN/RBV plus telaprevir in the prior AbbVie/Abbott study, will be allowed to enroll in Study M13-101 at the discretion of the investigator, regardless of whether resistant variants are detected.

3.1 Differences Statement

The differences between previous DAA combination studies in HCV-infected subjects and this study are as follows:

The current study, Study M13-101, is a single arm study evaluating ABT-450/r in combination with ABT-267, pegIFN and RBV for 24 weeks followed by pegIFN and RBV alone for an additional 24 weeks in subjects who have experienced virologic failure in a previous AbbVie/Abbott DAA combination study. None of the previous AbbVie/Abbott DAA combination studies included pegIFN with both ABT-450 and ABT-267 in the treatment regimen, or explored efficacy of a DAA, pegIFN and RBV containing regimen in subjects who previously failed a DAA-based therapy.

3.2 Benefits and Risks

Risk of Toxicity

The toxicity profile of pegIFN and RBV has been well described and includes headache, myalgia, fatigue, pyrexia, injection site reactions, and cytopenias. Previous studies of pegIFN and RBV in combination with ABT-450/r (Study M11-602) or ABT-267 (Study M12-114) demonstrated that the safety profiles of the respective regimens were generally comparable to those of pegIFN and RBV alone. In contrast, combination dosing of ABT-450/r with ABT-267 has generally been well tolerated both in healthy volunteers and both with and without RBV for up to 12 weeks in HCV-infected subjects (based on ongoing studies). Preclinical toxicology studies have assessed the toxicity of ABT-267 for up to 6 months, and ABT-450 for up to 9 months. ABT-450 and ABT-267 have been administered in clinical trials for up to 24 weeks. Subjects who enroll in Study M13-101 after having completed > 12 weeks of prior combination therapy may ultimately receive ABT-450/r and ABT-267 cumulatively for more than 24 weeks; thus there is also a risk of toxicity due to administration longer than 24 weeks that has not previously been observed. However, no dose-limiting toxicities have thus far been observed in animal studies, or in humans receiving the doses of ABT-450/r and/or ABT-267 used in this study. ABT-450/r and ABT-267 have not previously been dosed together in combination with pegIFN and RBV.

Risk of Treatment Failure

The likelihood of successfully curing HCV-infected subjects with a regimen containing 2 DAAs + pegIFN + RBV after they have previously failed therapy with DAA combination therapy is not known. A previous study by Bristol Myers-Squibb used the NS5A and protease inhibitors BMS-790052 and BMS-650032[10] in combination with pegIFN and RBV in prior pegIFN/RBV null responders and achieved a high rate of virologic suppression. Subjects who experience virologic failure in this study are at risk of selecting HCV variants with resistance to up to 3 classes of DAA (depending on their prior DAA combination therapy), which may compromise future treatment options if the variants persist off treatment. However, it is assumed that many of these subjects will

already have selected resistance to one or more DAA class in the setting of their prior treatment failure. Therefore, the risk of incurring a greater degree of viral drug resistance (and the resulting loss of additional treatment options) must be weighed against the possible benefit of an efficacious treatment regimen. Since this balance may be different depending on multiple factors (including prior treatment experience, stage of liver disease, other available treatment options, IL28B host genotype and others), this study will be made available on a purely optional basis to all subjects who previously experienced virologic failure in an AbbVie/Abbott DAA combination trial. It is expected that subjects will make a decision regarding participation in consultation with the investigator. However, since prior non-responders (null or partial response) to pegIFN/RBV may have a suboptimal response to a second course of pegIFN and RBV, this population will only be eligible if population sequencing of HCV NS3/4A protease and NS5A from a sample collected at the Pre-screening Visit does not detect variants at positions known to be associated with reduced susceptibility to ABT-450 and ABT-267. Likewise, even subjects who had an initial response to pegIFN/RBV plus telaprevir or boceprevir and then failed (due to relapse or breakthrough) may, in fact, be poor responders to interferon, and the initial virologic response may have reflected suppression due to the protease inhibitor. Hence, subjects who received pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study will only be eligible if population sequencing does not detect ABT-450 or ABT-267 resistance-associated variants.

In summary, the risks associated with the individual study drugs to be administered in Study M13-101 have been well characterized and appear limited and manageable. Subjects will be closely monitored for any potential risks which may occur when the DAAs are dosed in combination, including risks of toxicity and of virologic failure. Given the potential benefit of achieving cure in a population of HCV-infected subjects with limited available treatment options, as well as the manageable risks associated with the planned therapy, the risk-benefit comparison is considered favorable.

4.0 Study Objective

4.1 Primary Objective

The primary objective of this study is to evaluate the safety and antiviral efficacy, defined as the percentage of subjects with sustained virologic response 12 weeks post-dosing (SVR_{12}; HCV RNA < LLOQ 12 weeks after the last dose of study drug).

4.2 Secondary Objectives

The secondary objectives of this study are:

- to evaluate the percentage of subjects with sustained virologic response 24 weeks post-dosing (SVR_{24}; HCV RNA < LLOQ 24 weeks after the last dose of study drug) and
- to evaluate the percentage of subjects with extended rapid virologic response (eRVR) (HCV RNA < LLOQ at Weeks 4 through 12 of therapy with ABT-450/r plus ABT-267 plus pegIFN plus RBV).

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

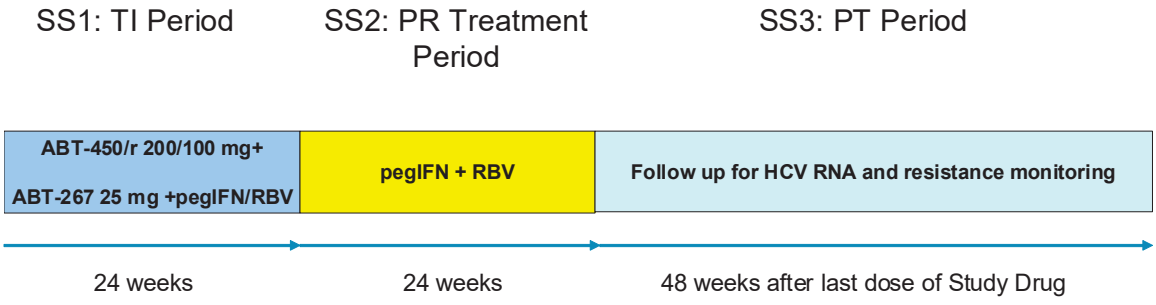
This is a Phase 2, open-label, single arm combination treatment study of ABT-450/r and ABT-267 in combination with pegIFN/RBV in HCV genotype 1-infected subjects (including subjects with compensated cirrhosis) who have experienced virologic failure while participating in a previous AbbVie/Abbott DAA combination study. Among subjects who previously experienced null or partial response to pegIFN/RBV treatment at any time prior to pre-screening for this study, or who experienced any prior failure with pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study, enrollment in this study will be restricted to those in whom population sequencing at the Pre-screening Visit does not detect the presence of variants relative to the appropriate prototypic reference sequence (H77 for 1a or Con1 for 1b) at any of the following amino acid positions: NS3 155, 156, or 168; or NS5A 28, 29, 30, 31, 32, 58, or 93. All other subjects will be

allowed to enroll in Study M13-101 at the discretion of the investigator, regardless of whether variants at any of these amino acid positions are detected.

This study consists of a pre-screening period, a screening period and three substudies:

- Substudy 1 (Treatment Intensification [TI]): 24 weeks of therapy with ABT-450/r plus ABT-267 plus pegIFN plus RBV;
- Substudy 2 (PegIFN/RBV [PR] Treatment): 24 weeks of pegIFN and RBV therapy alone;
- Substudy 3 (Post-treatment [PT] Follow-up Period): 48 weeks after last dose of any study drug for resistance monitoring and HCV RNA viral load testing.

Figure 1. Study Schematic



This study is designed to assess the safety, antiviral activity and pharmacokinetics (PK) of the DAAs ABT-450/r plus ABT-267, dosed for 24 weeks in combination with pegIFN and RBV, followed by an additional 24 weeks of pegIFN and RBV alone. All subjects who receive at least 1 dose of DAA therapy in this protocol, regardless of whether they prematurely discontinue or complete the study drug as planned, will be monitored for viral response and viral resistance on an outpatient basis for an additional 48 weeks following the last dose of any study drug as described in Section 5.1.4.

5.1.1 Pre-screening

Subjects who receive at least 1 dose of DAA and who experience virologic failure either during DAA therapy (rebound, breakthrough or failure to suppress) or after the end of therapy (relapse) in a previous AbbVie/Abbott DAA combination study, will be offered enrollment in this study if the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2, and if study drug therapy is considered medically appropriate based on the opinion of the investigator.

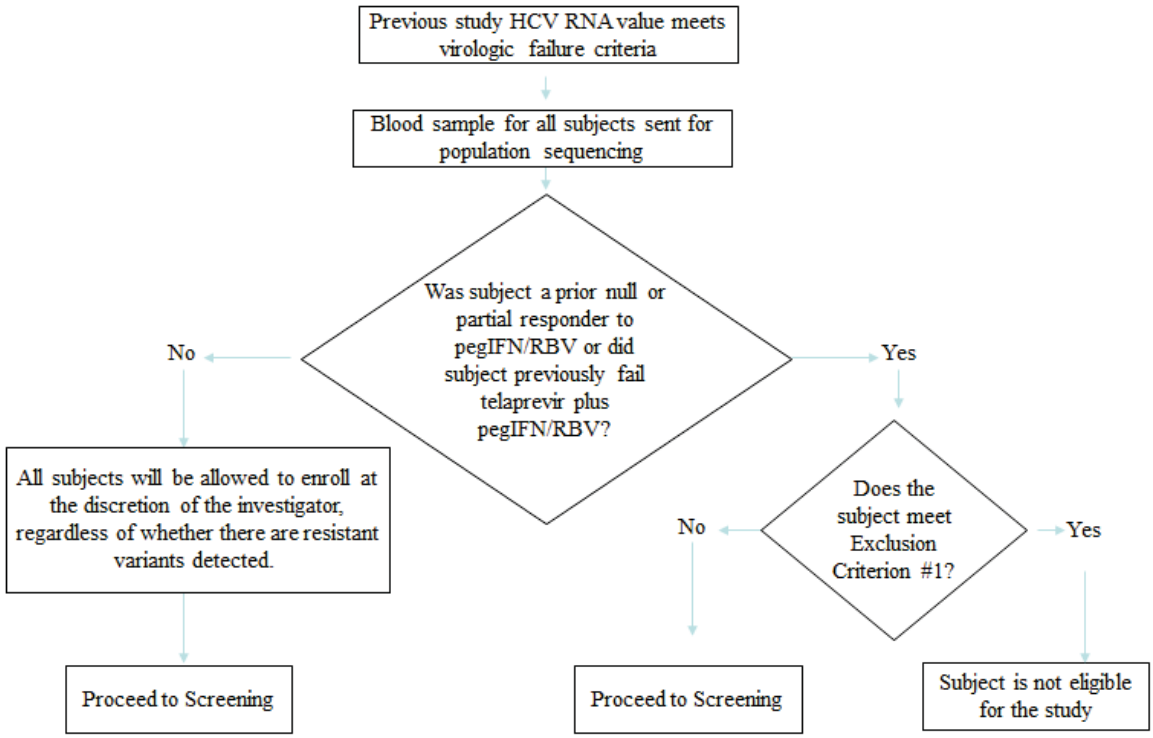
The Pre-screening Visit may be conducted at any time after the subject is confirmed failure from the previous AbbVie/Abbott DAA combination study. Once the subject is confirmed to meet all the eligibility criteria then the subject must discontinue from the previous AbbVie/Abbott DAA combination study. Subjects must provide written (signed and dated) informed consent for Study M13-101 prior to any study-specific procedures, including the population sequencing analysis done at the Pre-screening Visit. The investigator will record the details of the informed consent process in the subject's medical records. A blood sample will be collected for all subjects at the Pre-screening Visit for population sequencing of the HCV NS3/4A protease and NS5A genes. Another sample will be drawn at the same time at this visit to determine the HCV RNA level. The HCV RNA level must be at least 2000 IU/mL in order to perform the population sequencing testing. The Pre-screening Visit may be repeated at a later date per the investigator's discretion if the HCV RNA level is < 2000 IU/mL. Subjects will retain their subject number from the previous DAA combination study. This information will be entered into the Interactive Response Technology (IRT) system under the Pre-screening Visit flow. This number will be written on the Pre-screening Visit blood collection tubes and on the lab requisition form prior to shipping the samples to the central laboratory. The results of the population sequencing will take approximately 3 weeks to complete.

Among subjects who previously experienced null or partial response to pegIFN/RBV treatment at any time prior to pre-screening for this study, or who had any prior failure with pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study, enrollment will be limited to only those subjects in whom variants in HCV NS3/4A protease and NS5A at

amino acid residues known to be associated with resistance are not present at the Pre-screening Visit. All other subjects will be allowed to enroll in Study M13-101 at the discretion of the investigator, regardless of whether resistant variants are detected. If the results of population sequencing do not exclude the subject from participation, the subject should undergo a Screening Visit for this study as soon as possible. However, subjects will have up to 12 weeks after the Pre-screening Visit to perform the Screening Visit. If it is longer than 12 weeks, the site must get approval from the Study Designated Physician prior to conducting the Screening Visit. Refer to Figure 2 for the Pre-screening Visit flow chart.

Subjects who do not meet inclusion criteria for HCV RNA level or who meet the exclusion criteria for resistance at the Pre-screening Visit must be entered into the IRT system as a Pre-screen failure under the Discontinuation Visit flow. Subjects with exclusionary resistance-associated variants detected at the Pre-screening Visit will not be allowed to repeat the Pre-Screening Visit.

Figure 2. Pre-screening Visit Flow Chart



5.1.2 Screening

Once the Investigator has established that the subject does not meet exclusion criteria No. 1 (by review of results of the Pre-screening resistance testing, if applicable), the Screening Visit can be performed. The subject will be entered into the Interactive Response Technology (IRT) system under the Screening Visit flow. The subjects will undergo the study procedures identified in Table 5 and Table 6 (for cirrhotic subjects).

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 TI Day 1 prior to dosing, capture the concomitant medication and record the results of all assessments in the subject's medical records. Eligible subjects have up to

42 days following the Screening Visit to enroll into the study. Prior to enrollment, subjects should agree to practice two effective methods of birth control while receiving study drugs starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. Subjects using systemic estrogen-containing contraceptive therapy (including estrogen-containing oral contraceptives) have a higher risk for elevated ALT levels. Subjects using these medications must discontinue them at least 2 weeks prior to study drug administration or 10 half-lives (if known), whichever is longer. Subjects may replace the systemic estrogen-containing contraceptive with a progestin-only hormonal contraceptive method.

Once the subject is confirmed to meet all the eligibility criteria then the subject must discontinue from the Post-Treatment Period of the previous AbbVie/Abbott DAA combination study.

Subjects who otherwise meet all eligibility criteria, but have a positive urine alcohol screen, may have only the urine drug screen repeated. If the repeat urine drug screen is qualifying (does not meet Exclusion Criterion No. 4), the subject may be considered eligible.

Subjects who meet all inclusion criteria and none of the exclusion criteria with the exception of one exclusionary lab parameter may rescreen once without prior AbbVie approval. AbbVie Study Designated Physician approval is required to rescreen a subject who has multiple exclusionary laboratory results. Subjects undergoing rescreening must repeat all laboratory tests that were initially out-of-range. Subjects who fail to enroll within 42 days of the Screening Visit may be allowed to rescreen only once without approval of the AbbVie Study Designated Physician and must be rescreened for all laboratory and eligibility criteria (with the exception of HCV genotype, Anti-HCV Ab, FSH, BDI-II Scale and fundoscopic exam). Liver ultrasound and alpha-fetoprotein testing for subjects with cirrhosis do not need to be repeated unless 6 months or more have elapsed since the initial screening.

Subjects with an exclusionary HCV genotype, exclusionary drug screen (other than a positive urine alcohol), positive anti-HIV antibodies or hepatitis B surface antigen, a Becks Depression Inventory II (BDI–II) score > 21 or positive pregnancy test will be excluded and may not rescreen.

Subjects who are not eligible to enroll per the inclusion/exclusion criteria after the Screening Visit must be entered into the IRT system as a screen failure under the Discontinuation flow.

5.1.3 Treatment Period (Substudy 1 and Substudy 2)

Substudy 1 – Treatment Intensification (TI) Period

There is one treatment group for this study. After meeting entry criteria, subjects will receive ABT-450/r 200/100 mg, ABT-267 25 mg, pegIFN and RBV. ABT-450/r and ABT-267 will be administered once daily; pegIFN will be dosed once weekly and RBV will be dosed twice daily. See Section 5.5.1 for details.

At the TI Day 1 Visit, subjects will undergo the study procedures identified in Table 5 (and Table 6 for cirrhotic subjects).

Subjects will be administered study drugs at the site on TI Day 1. Plasma and serum samples for pharmacokinetic analysis will be collected at TI Week 1 through TI Week 24 (Substudy 1). All subjects will continue to return to the site on an outpatient basis through TI Week 24 for the study procedures identified in Table 5 (and Table 6 for cirrhotic subjects). Sites should ensure that subjects adhere to the study visits listed in Table 5 (and Table 6 for cirrhotic subjects). Subjects who cannot complete their study visit per the visit schedule through TI Week 24 should ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure. Some of the Treatment Period study visits and visit activities (including but not limited to vital signs, clinical laboratory tests and concomitant medication assessment) may be conducted in the home or non-hospital/clinic environment by qualified individuals at the request of the investigator and with the agreement of the subject.

Subjects who prematurely discontinue from the DAA study drug treatment in Substudy 1 should return for a TI Week 24/TI Discontinuation Visit and undergo study procedures as defined in Table 5 (and Table 6 for cirrhotic subjects) and as described in Section 5.4.1. The subject should either proceed to Substudy 2 if the investigator feels it is appropriate or proceed to Substudy 3 if it is not appropriate to continue on Substudy 2. Refer to Figure 3, Subject Flow Chart.

Substudy 2 – PegIFN/RBV (PR) Treatment Period

Subjects who complete TI treatment will continue on to Substudy 2, the PR Treatment Period, for continued dosing of pegIFN and RBV. Subjects who prematurely discontinue TI treatment may also continue on to Substudy 2, unless the investigator feels it is not appropriate to continue pegIFN and RBV either due to toxicity or to lack of virologic response. Substudy 2 will begin the day after the last dose of DAA. Substudy 2 is designed to allow completion of pegIFN + RBV treatment for a total duration of 48 weeks across Substudies 1 and 2 and to monitor HCV RNA levels and emergence of any ABT-450 and ABT-267 resistance-associated variants.

For subjects who complete Substudy 1, an additional 24 weeks of pegIFN and RBV will be administered in Substudy 2. Subjects who complete 24 weeks of treatment in Substudy 2 should undergo the procedures listed in the PR Final/PR Discontinuation Visit in Table 5 (and Table 6 for cirrhotic subjects), not the PR Week 24 visit and then continue on to Substudy 3.

Subjects who receive less than 24 weeks of TI treatment in Substudy 1 may receive pegIFN and RBV in Substudy 2 at the discretion of the investigator, up to a total of 48 weeks across Substudies 1 and 2. All subjects will continue to return to the site on an outpatient basis for the PR Treatment study procedures identified in Table 5 (and Table 6 for cirrhotic subjects). For those subjects who do not complete 24 weeks of TI treatment in Substudy 1, additional study visits as indicated in Table 5 (and Table 6 for cirrhotic subjects) should be performed if required to complete a total of 48 weeks across Substudies 1 and 2. These additional visits are PR Week 24, PR Week 36 and PR

Final/PR Discontinuation Visit (which may be out to 48 weeks or earlier). All subjects should complete the PR Final/PR Discontinuation Visit procedures at that subject's final visit in Substudy 2. In some cases this final visit may fall in between study visits listed in Table 5. Sites should ensure that subjects adhere to the study visits listed in Table 5 (and Table 6 for cirrhotic subjects). 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.

Subjects who prematurely discontinue Substudy 2 should return to the site for a PR Final/PR Discontinuation Visit as outlined in Table 5 (and Table 6 for cirrhotic subjects).

Safety and tolerability of the treatments will be assessed throughout the study. Laboratory testing will include chemistry, hematology, and urinalysis (refer to Table 9). Ongoing review of the data is planned in order to determine if subjects meet the virologic stopping criteria.

Ongoing review of the data is also planned for non-efficacy (futility) assessment. Data will be assessed separately for the population of subjects who were null or partial responders to prior pegIFN/RBV treatment or experienced any prior failure with pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study, and for the population of subjects who do not fall in the previous population at the time of enrollment into this study. Refer to Section 5.4.2 for further details regarding these ongoing reviews.

5.1.4 Post-Treatment Follow-Up Period (Substudy 3)

In Substudy 3, the Post-treatment (PT) Period, subjects will be followed for 48 weeks after the last dose of study drugs for evaluation of the emergence, evolution and persistence of viral resistance to ABT-450/r and ABT-267 and for viral response.

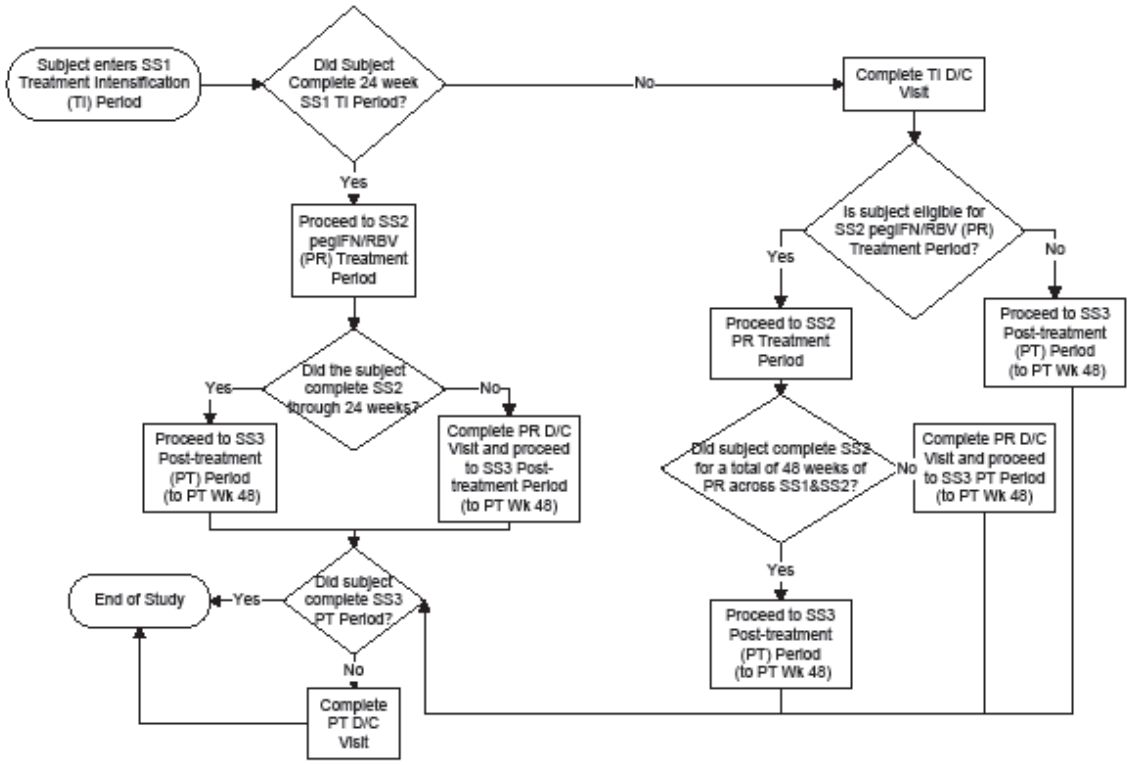
All subjects who receive at least 1 dose of DAA will be monitored for viral resistance on an outpatient basis for an additional 48 weeks following the last dose of study drugs, regardless of whether they prematurely discontinue study drug treatment or complete treatment as planned in Substudies 1 and 2. Refer to Figure 3, Subject Flow Chart.

Subjects will return to the study site as outlined in Table 7 (and Table 8 for cirrhotic subjects) for post-treatment visit procedures including resistance monitoring, HCV RNA testing, and assessment of adverse events (for 30 days post-treatment only) and serious adverse events. Substudy 3 will begin the day after the last dose of study drug treatment. Subjects who prematurely discontinue Substudy 3 should return to the site for a PT Week 48/PT Discontinuation Visit as outlined in Table 7 (and Table 8 for cirrhotic subjects).

Some of the Post-Treatment Period study visits and visit activities (including but not limited to vital signs, clinical laboratory tests and concomitant medication assessment) may be conducted in the home or non-hospital/clinic environment at the request of the Investigator and with the agreement of the subject.

All subjects who receive at least one dose of DAA may be offered participation in a separate AbbVie-sponsored observational study to evaluate the durability of virologic response for subjects who achieve SVR or to study the emergence and persistence of resistant variants in subjects who fail treatment.

Figure 3. Subject Flow Chart



5.2 Selection of Study Population

Subjects who have experienced virologic failure in a previous AbbVie/Abbott DAA combination study and who meet the inclusion criteria, and who do not meet any of the exclusion criteria, will be eligible for enrollment into the study. In addition, no more than ten (10) subjects who received pegIFN/RBV plus telaprevir in a previous AbbVie/Abbott study will be enrolled.

5.2.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1. Must voluntarily sign and date an informed consent, approved by an Institutional Review Board/Ethics Committee (IRB/EC), prior to the initiation of any study specific procedure.
2. Subject must be able to understand and adhere to the study visit schedule and all other protocol requirements.
3. Subject must have experienced virologic failure as defined in a previous AbbVie/Abbott DAA combination study.
4. Female who is:
   - not of childbearing potential, defined as:
     - 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), or
     - practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle), or
     - sexually active with female partners only
   - 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 practice 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 (Estrogen-containing hormonal contraceptives, including oral, injectable, implantable, patch and ring varieties, may not be used during DAA treatment).

5. Females must have negative results for pregnancy tests performed:
   - at Screening by urine specimen within 42 days prior to initial study drug administration, and
   - at Baseline (prior to dosing) by urine specimen.

   Female subjects with a borderline hCG result at 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.
6. Sexually active males must be surgically sterile or have male partners only or if sexually active with female partner(s) of childbearing potential must agree to practice two effective forms of birth control (as outlined in the subject information and consent form or other subject information documents) throughout the course of the study, starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. (Note: Contraceptives containing ethinyl estradiol are considered effective if used by the female partners of male subjects.)
7. Subject must be considered an appropriate candidate for pegIFN, RBV, ABT-450/r and ABT-267 therapy in the opinion of the investigator.
8. Subject is infected with HCV genotype 1 at the Screening Visit.
9. Subject has a plasma HCV RNA level ≥ 2,000 International Units (IU)/mL at the Pre-screening Visit.

In addition to Inclusion Criteria 1 through 9, subjects diagnosed with cirrhosis must also meet the following criteria:

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

11. Absence of hepatocellular carcinoma (HCC) based on a negative ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) performed within 3 months prior to Screening or during the Screening period.

Rationale for Inclusion Criteria

(1, 2) In accordance with harmonized Good Clinical Practice (GCP).

(3 – 7) For safety of the subjects.

(8 – 11) To select the appropriate subject population.

5.2.2 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

1. In subjects with a prior null or partial response to pegIFN/RBV treatment at any time prior to pre-screening for this study or any prior failure with pegIFN/RBV plus telaprevir, the presence of variants relative to the appropriate prototypic reference sequence (H77 for 1a or Con1 for 1b) at any of the following positions: NS3 155, 156, or 168; or NS5A 28, 29, 30, 31, 32, 58, or 93.
2. Prior use of an investigational HCV therapy or approved DAA not included in this protocol or the previous AbbVie/Abbott DAA combination study.
3. 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 as per local RBV label) after their last dose of RBV.
4. Positive result of a urine drug screen at the Screening Visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, and propoxyphene with the exception of a positive result (including methadone), associated with documented short-term use or chronic stable use of a prescribed medication in that class.

5. Positive test for hepatitis B surface antigen (HBsAg) or anti-HIV antibodies (anti-HIV Ab).
6. Use of known strong inducers (e.g., phenobarbital, rifampin, carbamazepine, St. John's Wort) of CYP3A within 2 weeks prior to study drug administration.
7. Use of any medications listed in Table 4 within 2 weeks or 10 half-lives, of the medication, whichever is longer, prior to study drug administration, including but not limited to:

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

Alfuzosin Astemizole Carbamazepine Cisapride Efavirenz	Ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergometrine) Fusidic Acid Lovastatin Midazolam (oral) Phenobarbital Phenytoin Pimozide	Rifampin Salmeterol Sildenafil* Simvastatin St. John's Wort Terfenadine Triazolam Estrogen-containing medications for systemic use

* When used for the treatment of pulmonary arterial hypertension.

Not all medications contraindicated with ritonavir, ribavirin and pegIFN are listed in Table 4. Refer to the most current product labeling for each drug for a complete list.

8. Discontinuation of antiviral therapy due to intolerance or a DAA- or RBV-associated adverse event in the previous AbbVie/Abbott DAA combination study (excluding intolerance or AEs associated with telaprevir).
9. Beck's Depression Inventory-II (BDI-II) score of > 21 at Screening. Subjects with BDI-II score > 21 will not be allowed to rescreen.
10. Clinically significant abnormal ECG, ECG with QT interval corrected for heart rate using Fridericia's correction formula (QTcF) > 470 msec at Screening or TI Day 1 visits.

11. Screening laboratory analyses show any of the following abnormal laboratory results:
    - Alanine aminotransferase (ALT) > 7 × upper limit of normal (ULN);
    - Aspartate aminotransferase (AST) > 7 × ULN;
    - Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min;
    - Albumin < LLN;
    - International normalized ratio (INR) > 1.7; (Subjects with a known inherited blood disorder and INR > 1.7 may be enrolled with permission of the AbbVie Study Designated Physician.)
    - Hemoglobin < LLN;
    - Platelets < 90,000 cells per mm^3;
    - Absolute neutrophil count < 1,500 cells/µL (< 1200 cells/µL for subjects of black/African descent);
    - Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN;
    - Thyroid stimulating hormone (TSH) values outside the normal range.
12. The use of colony stimulating factors, such as granulocyte colony stimulating factor (GCSF) or erythropoietin within 2 months of the Screening Period.
13. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that, in the opinion of the investigator, could preclude adherence to the protocol.
14. Clinically significant abnormalities, other than HCV infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile and a 12-lead electrocardiogram (ECG) that make the subject an unsuitable candidate for this study in the opinion of the investigator.
15. Evidence of infection with other HCV genotypes other than genotype 1 at the Screening Visit.

16. Current enrollment in another clinical study or previous enrollment in this study. Concurrent participation in a non-interventional, epidemiologic or registry trials may be permitted with approval by the AbbVie Study Designated Physician.
17. History of solid organ transplantation.

In addition to Exclusion criteria 1 through 18, subjects with compensated cirrhosis must not meet the following criteria:

18. Any current or past clinical evidence of Child-Pugh B or C Classification or clinical history of liver decompensation such as ascites (noted on physical exam), variceal bleeding or hepatic encephalopathy.
19. Serum Alpha-Fetoprotein (sAFP) > 100 ng/mL at Screening.
20. A screening ultrasound suspicious for hepatocellular carcinoma (HCC) and confirmed with a subsequent CT scan or MRI during the screening period.

Rationale for Exclusion Criteria

(1) To exclude subjects with a high likelihood of virologic failure.

(2 – 5, 10 – 12, 14, 15) To ensure safety of the subjects throughout the study.

(6 – 9, 13) To avoid medication interactions which could complicate evaluation of efficacy and safety.

(16 – 21) To select the appropriate subject population.

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment, or receives during the time periods defined below, must be recorded 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. The investigator should confirm that concomitant medication can be safely administered with DAAs as well as ritonavir, pegIFN and RBV. Some medications may require dose adjustments due to potential for drug-drug interactions. Subjects should be on a stable dose of concomitant medications for at least 2 weeks prior to initiation of study drug.

Use of all medications at the time of enrollment and through 30 days after the last dose of DAAs in Substudy 1 will be recorded in the electronic case report form (eCRF). During Substudy 2 and Substudy 3, only antiviral therapies related to the treatment of HCV and medications prescribed in association with a serious adverse event (SAE) will be recorded in the eCRF.

During Substudy 3, investigators should reassess concomitant medications and subjects may resume previously prohibited medications, or revert to pre-study doses, 2 weeks following discontinuation of DAAs, if applicable.

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

Any HCV therapy the subject received after terminating from the previous AbbVie/Abbott DAA combination study and prior to enrollment in this study must be recorded. Use of any investigational anti-HCV agents or approved DAAs during this period excludes a subject from this study. Subjects who received pegIFN and RBV during this period may be enrolled in the study. These subjects should have complete documentation of pegIFN and RBV treatment history, including start and stop dates, type of response (if known), and reason for discontinuation. Categories on the eCRF will include the following:

- **Null responder:** Subject has documentation that they previously received PegIFN/RBV for at least 10 weeks and failed to achieve a 2 $\log_{10}$ IU/mL HCV RNA decrease at Week 12 (Week 10 to Week 16)
- **Partial responder:** Received at least 20 weeks of PegIFN/RBV for the treatment of HCV and achieved ≥2 $\log_{10}$ reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment
- **Relapser:** Received at least 36 weeks of PegIFN/RBV for the treatment of HCV and was undetectable at the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up
- **Not documented/Other**

5.2.3.2 Prohibited Therapy

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

Use of any medications contraindicated with pegIFN or RBV is prohibited within 2 weeks prior to the initial dose of study drug through the first 2 weeks after the subject has completed Substudy 2.

Prior to enrollment, subjects should agree to practice two effective methods of birth control while receiving study drugs starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. Subjects using systemic estrogen-containing contraceptive therapy (including estrogen-containing oral contraceptives) have a higher risk for elevated ALT levels. Subjects using these medications must discontinue them at least 2 weeks prior to study drug administration or 10 half-lives (if known), whichever is longer. Subjects may replace the systemic estrogen-containing contraceptive with a progestin-only hormonal contraceptive method. Estrogen-containing contraceptives may be resumed 2 weeks after the last dose of DAAs.

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

Use of hematopoietic growth factors is not permitted during this study without the approval of the AbbVie Study Designated Physician. Management of hematologic growth factor therapy is the responsibility of the investigator; growth factors will not be provided by the Sponsor, and the Sponsor 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.

5.2.3.3 Post-Treatment Therapy

No further treatment is planned after subjects have ended their participation in the study. This study is intended to offer intensified therapy with two investigational drugs plus pegIFN and RBV for subjects who have failed treatment for HCV infection in a previous AbbVie/Abbott study. Some safety assessments, measurements of HCV RNA (HCV viral levels) and monitoring for viral resistance are performed for 48 weeks following the last dose of study treatment.

If a subject meets virologic failure criteria in this study or relapses in the post-treatment follow-up period (Substudy 3), the investigator should treat the subject according to his/her best clinical judgment.

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

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures are summarized in Table 5 and Table 6 (for cirrhotic subjects).

Table 5. Study Activities

Activity	Pre-SCR	SCR	Substudy 1 Treatment Intensification (TI) Period									Substudy 2-PegIFN/RBV Alone (PR) Treatment Period						
			TI Day 1[b]	TI Wk 1	TI Wk 2	TI Wk 4	TI Wk 8	TI Wk 12	TI Wk 16	TI Wk 20	TI Wk 24/ TI D/C[c]	PR Wk 2	PR Wk 4	PR Wk 8	PR Wk 12	PR Wk 24[d]	PR Wk 36[d]	PR Final/ PR D/C[d,e]
Informed Consent[a]	X																	
Population Sequencing Assessment	X																	
Provide pegIFN/RBV Information and Medication Guides[f]		X																
Medical History[g]		X	X															
Adverse Event Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Assessment		X	X	X	X	X	X	X	X	X	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Physical Examination		X[i]	X			X					X							X
Vital Signs and Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG		X	X					X			X				X			X
Pregnancy Test[j] (Females) Serum (s) Urine (u)		X(u)	X(u) (s)			X(u)	X(u)	X(u)	X(u)	X(u)	X(u)		X(u)	X(u)	X(u)	X(u)	X(u)	X(u)
FSH (all females)		X																

Table 5. Study Activities (Continued)

Activity	Pre-SCR	SCR	Substudy 1 Treatment Intensification (TI) Period									Substudy 2-PegIFN/RBV Alone (PR) Treatment Period						
			TI Day 1[b]	TI Wk 1	TI Wk 2	TI Wk 4	TI Wk 8	TI Wk 12	TI Wk 16	TI Wk 20	TI Wk 24/ TI D/C[c]	PR Wk 2	PR Wk 4	PR Wk 8	PR Wk 12	PR Wk 24[d]	PR Wk 36[d]	PR Final/ PR D/C[d,e]
HBsAg, Anti HIV Ab		X																
Drug/Alcohol Screen		X																
HCV Genotype		X																
Clinical Laboratory Tests		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total Insulin			X															
TSH		X	X					X			X				X	X	X	X
BDI-II Depression Scale		X																
Study Drugs Dispensed/ Drug Accountability[k]			X			X	X	X	X	X	X		X	X	X	X	X	X
Dispense MEMS Cap[l]			(X)															
Download MEMS[l]				(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)							
Collect MEMS Cap[l,m]											(X)							

Table 5. Study Activities (Continued)

Activity	Pre-SCR	SCR	Substudy 1 Treatment Intensification (TI) Period									Substudy 2-PegIFN/RBV Alone (PR) Treatment Period						
			TI Day 1[b]	TI Wk 1	TI Wk 2	TI Wk 4	TI Wk 8	TI Wk 12	TI Wk 16	TI Wk 20	TI Wk 24/ TI D/C[c]	PR Wk 2	PR Wk 4	PR Wk 8	PR Wk 12	PR Wk 24[d]	PR Wk 36[d]	PR Final/ PR D/C[d,e]
HCV RNA Sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV Resistance Testing Sample			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DAA/ritonavir, PegIFN/RBV Assay (PK) Sample[n]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP-10 Testing			X			X					X							X

SCR = Screening; D/C = Premature discontinuation; Wk = Week

a. Prior to performing any study-specific procedures.

b. Activities to be performed prior to first dose of any study drug.

c. Subjects who prematurely discontinue from the DAA study drug treatment in Substudy 1 should return for a TI Week 24/TI Discontinuation Visit. These subjects will continue on to Substudy 2 if the investigator feels it is appropriate or proceed to Substudy 3 if it is not appropriate to continue on Substudy 2.

d. These visits are only needed for subjects who did not complete 24 weeks of pegIFN/RBV in Substudy 1 such that the subject completes a total of 48 weeks of pegIFN/RBV across Substudy 1 and Substudy 2.

e. Subjects who prematurely discontinue from the pegIFN/RBV study drug treatment in Substudy 2 should return for a PR Final/PR Discontinuation Visit. These subjects will continue on to Substudy 3.

Table 5. Study Activities (Continued)

f. Where applicable/locally available.

g. The subject's medical history will be updated at the Screening Visit with any relevant information that was not collected in the previous AbbVie/Abbott DAA combination study and any new medical history that occurred between the end of the previous AbbVie/Abbott DAA combination study and this study. The subject's medical history will also be updated if needed for the period between the Screening Visit and the TI Day 1 Visit.

h. Only concomitant medications related to HCV treatment and/or medications prescribed in association with a serious adverse event will be collected during Substudy 2.

i. Height will be measured at Screening only. Will include a thorough eye exam to confirm that the subject is an appropriate candidate for pegIFN therapy.

j. Urine pregnancy testing is not required after the TI Day 1 Visit for female subjects with a documented prior hysterectomy or bilateral oophorectomy or bilateral tubal ligation or those confirmed to be postmenopausal. Urine pregnancy tests must be conducted monthly during treatment in Substudy 1 and Substudy 2 (per local RBV label) for women of childbearing potential. Subjects may come to the clinic for an unscheduled visit for pregnancy testing at PR Study Weeks 16 and 20 and PR Weeks 28, 32, 40 and 44 if needed or perform the tests at home with test kits provided by the site. Sites may substitute serum pregnancy testing for urine pregnancy testing only if required per local regulations.

k. Refer to Section 5.5.1 for additional information on treatments administered and Section 5.5.8 for additional information on drug accountability. Drug Accountability is not assessed at TI Day 1.

l. Collected from subjects participating in study under original protocol and Amendments 1 – 9.

m. MEMS cap is collected at any point upon completion of Substudy 1.

n. A total of two pharmacokinetic samples will be drawn at each time-point, one plasma and one serum. The site will contact the subject approximately 2 days prior to the scheduled PK blood collection date to review the importance of proper study drug administration.

Table 6. Additional Study Activities for Cirrhotic Subjects Only

Activity	Pre-SCR	SCR	Substudy 1 Treatment Intensification (TI) Period									Substudy 2-PegIFN/RBV Alone (PR) Treatment Period						
			TI Day 1	TI Wk 1	TI Wk 2	TI Wk 4	TI Wk 8	TI Wk 12	TI Wk 16	TI Wk 20	TI Wk 24/ TI D/C	PR Wk 2	PR Wk 4	PR Wk 8	PR Wk 12	PR Wk 24[d]	PR Wk 36[d]	PR Final/ PR D/C[d,e]
Child-Pugh Score		X						X			X				X			X
Clinical Assessment of Hepatic Decompensation			X[a]															
HCC Screening: Liver Ultrasound and Alpha Fetoprotein[c]		X[b]									X					X		X

a. Clinical assessment of hepatic decompensation based on physical exam on TI Day 1 prior to dosing.

b. 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.

c. 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.

d. These visits are only needed for subjects who did not complete 24 weeks of pegIFN/RBV in Substudy 1 such that the subject completes a total of 48 weeks of pegIFN/RBV across Substudy 1 and Substudy 2.

e. Subjects who prematurely discontinue from the pegIFN/RBV study drug treatment in Substudy 2 should return for a PR Final/PR Discontinuation Visit. These subjects will continue on to Substudy 3.

Table 7. Study Activities – Substudy 3 Post-Treatment

Activity	Substudy 3 Post-Treatment (PT) Period						
	PT Wk 2	PT Wk 4	PT Wk 8	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48/ PT D/C
Adverse Event Assessment[a]	X	X	X	X	X	X	X
Concomitant Medication Assessment[b]	X	X	X	X	X	X	X
Vital Signs and Weight	X	X	X	X	X	X	X
Pregnancy Test (Females) Urine (u)[c]		X	X	X	X		
Clinical Laboratory Tests	X	X					X[d]
IP-10					X		X[d]
HCV RNA Sample	X	X	X	X	X	X	X
HCV Resistance Testing	X	X	X	X	X	X	X
Archive Plasma Sample	X	X					X

PT = Post-treatment; Wk = week; D/C = discontinuation

a. AEs will be collected for only 30 days following last dose of study drugs. SAE's will be collected during the entire Substudy 3 period.

b. Only concomitant medications related to HCV treatment and/or medications prescribed in association with a serious adverse event will be collected during Substudy 3.

c. Post-treatment pregnancy testing is to be completed at the visits outlined in Table 7. Additional pregnancy testing (urine and/or serum) during the Post-treatment Period, e.g., at PT Week 16, PT Week 20, PT Week 28 or at other time points should be completed according to the local RBV label and/or local treatment guidelines for RBV or local legal requirements. Additional pregnancy testing (urine and/or serum) done outside of the visits specified in Table 7 should be completed using the unscheduled test kit or the subject can perform the tests at home with test kits provided by the site.

d. Sample to be drawn only if conducting a Discontinuation Visit.

Table 8. Additional Study Activities for Cirrhotic Subjects Only – Substudy 3 Post-Treatment

Activity	Substudy 3 Post-Treatment (PT) Period						
	PT Wk 2	**PT Wk 4**	**PT Wk 8**	**PT Wk 12**	**PT Wk 24**	**PT Wk 36**	**PT Wk 48/ PT D/C**
Clinical Laboratory Tests	X	X			X		X
Child-Pugh Score				X			
HCC Screening: Liver Ultrasound and Alpha Fetoprotein[a]					X		X

a. If additional liver ultrasound testing is required it should be completed as an unscheduled visit. An ultrasound result suspicious for HCC will be confirmed with CT scan or MRI

5.3.1.1 Study Procedures

Informed Consent

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Population Sequencing Assessment

Population Sequencing will be performed for all subjects on blood samples drawn at the Pre-screening Visit (after signing the informed consent). This testing will only be performed on samples with an HCV RNA level ≥ 2000 IU/mL, so another sample will also be drawn to measure the HCV RNA level. If the HCV RNA level is < 2000 IU/mL, the Pre-Screening Visit may be repeated at a later date per the investigator's discretion.

A certified laboratory will be utilized to perform the testing and provide results for the population sequencing. The sample will be sent to Covance central laboratory which will then ship them to the following address for testing:

[redacted]

Approximately 3 weeks should be allowed for the testing of the population sequencing to be completed. For subjects who were null or partial responders to prior pegIFN/RBV treatment, or who experienced any prior failure with pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study, results from this sequencing will be assessed for exclusionary variants in NS3 or NS5A at any of the following positions: NS3 155, 156, or 168; or NS5A 28, 29, 30, 31, 32, 58, or 93.

For all other subjects the results should be taken into account in the investigator's determination of the subject's appropriateness for enrollment in this study. After this assessment, the subject may proceed with the Screening Visit procedures if appropriate.

PegIFN and Ribavirin Information

Subjects will be given copies of the Medication Guides for Peginterferon α-2a (PEGASYS®) and Ribavirin (RIBASPHERE® or Copegus®) where applicable and locally available prior to dosing. Sexually active subjects must use two effective forms of birth control during the study and for 7 months (or as per local RBV labeling) after stopping study drugs unless surgically sterile. Male subjects will be given the RBV Partner Risk Fact Sheet to share with their female partner(s).

Medical History

The subject's medical history will automatically be transferred from the previous AbbVie/Abbott DAA combination study to the Study M13-101 EDC system. The subject's medical history will then be updated at the Screening Visit with any relevant information that was not collected in the previous AbbVie/Abbott DAA combination study and any new medical history that occurred between the end of the previous AbbVie/Abbott DAA combination study and this study. The subject's medical history will also be updated, if needed, for the period between the Screening Visit and the TI Day 1 Visit. The updated medical history as of TI Day 1 will serve as the baseline for clinical assessment.

Concomitant Medication Assessment

Use of medications (prescription or over-the-counter, including vitamins and herbal supplements) at the time of enrollment through 30 days after last dose of DAAs in Substudy 1 will be recorded in the electronic case report form (eCRF).

During Substudy 2 and Substudy 3, only antiviral therapies related to the treatment of HCV and medications prescribed in association with an SAE will be recorded in the electronic case report form (eCRF).

Physical Examination

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

The physical examination at the Screening Visit will include a thorough eye exam to confirm that the subject is an appropriate candidate for pegIFN therapy. The physical examination performed on TI Day 1 will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after the first dose will be recorded as adverse events.

Height will be measured only at Screening; the subject will not wear shoes.

Vital Signs and Weight

Body temperature (oral), blood pressure, pulse and body weight will be measured at each study visit as specified in Table 5 and Table 7 and upon subject discontinuation. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes. The subject should wear light weight clothing and no shoes during weighing.

12-Lead ECG

A 12-lead resting ECG will be obtained at the visits specified in Table 5 and upon subject discontinuation (or as clinically needed).

When an ECG is scheduled on the same day as a blood collection, the ECG will be obtained prior to the blood collection.

ECGs will be recorded after the subject has been supine for at least 5 minutes. Subjects should be instructed to remain completely stationary during the ECG recording (approximately 10 seconds), with no talking, laughing, deep breathing, sleeping, or swallowing.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will interpret, 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

The local reader will capture the assessment of the ECG tracing in the subject's source notes. Only the local reader's assessment of the ECG tracing will be collected on case report forms, entered into the database and summarized.

Pregnancy Test

A serum pregnancy test will be performed at TI Day 1 for all female subjects and analyzed by the central laboratory. In addition, a urine pregnancy test will be performed for female subjects at the visits specified in Table 5 and Table 7. All urine pregnancy tests will be performed on-site during the study visit, if there is a scheduled visit. Urine pregnancy tests are not required after TI Day 1 for female subjects with a documented prior hysterectomy or bilateral tubal ligation or bilateral oophorectomy or who are confirmed to be postmenopausal. Confirmation of postmenopausal status will be determined based on the subject's history and the FSH level obtained at the Screening Visit. Sites may substitute serum pregnancy testing for urine pregnancy testing only if required per local regulations.

Women of childbearing potential should have urine pregnancy testing completed monthly during treatment with RBV and monthly for 7 months after the discontinuation of RBV or according to the local RBV label and/or local treatment guidelines for RBV. During the PR Treatment Period and the PT Period where there is not a scheduled study visit (i.e., PR Weeks 16 and 20, 28, 32, 40 and 44, and PT Week 16, 20 and 28), 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 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 testing is elected. Serum pregnancy testing will be completed by the central laboratory.

If urine pregnancy result is positive a confirmatory hCG serum test should be collected and sent to the central lab.

Hepatitis and HIV Screen

HBsAg and anti-HIV Ab, will be performed at Screening (Table 5). 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, and the HBsAg results will be reported by the central laboratory to the clinical database. The anti-HIV Ab results will not 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 9. 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.

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

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 9 at the visits specified in Table 5 and Table 7 for all subjects. Additional clinical laboratory tests for cirrhotic subjects are outlined in Table 6 and Table 8.

Blood samples for serum chemistry tests, whenever possible, 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. 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.

In addition to the standard chemistry, hematology and urinalysis, coagulation panel and total insulin results will be reported.

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

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study. The certified laboratory chosen for this study is shown below.

For sites in North America and South America:

Covance
8211 SciCor Drive
Indianapolis, IN 46214
USA

For sites in Europe:

Covance
7 rue Marcinhes
1217 Geneva
Meyrin Switzerland

For sites in Asia, Australia and New Zealand:

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

Table 9. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Platelet count Neutrophils Bands (if detected) Lymphocytes Monocytes Basophils (if detected) Eosinophils (if detected) Absolute neutrophil count (ANC) Prothrombin time (PT)/ International Normalized Ratio (INR) Activated partial thromboplastin time (aPTT)	Blood urea nitrogen (BUN) Creatinine Total bilirubin Direct and indirect bilirubin Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Cholesterol Total protein Glucose Triglycerides Albumin Chloride Bicarbonate Magnesium Serum glutamic oxaloacetic transaminase/Aspartate aminotransferase (SGOT/AST) Serum glutamic pyruvic transaminase/Alanine aminotransferase (SGPT/ALT) Gamma-glutamyl transferase (GGT) Creatinine clearance TSH Free T4 (performed for any abnormal TSH after screening) Uric acid Alpha fetoprotein[d]	Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocyte esterase Microscopic (reflex) **Additional Tests** HBsAg[a] Anti-HIV-1 Ab[a] Anti-HIV-2 Ab[a] Opiates[a] Barbiturates[a] Amphetamines[a] Cocaine[a] Benzodiazepines[a] Alcohol[a] Phencyclidine[a] Propoxyphene[a] Methadone[a] Human chorionic gonadotropin (hCG) (females)[b] Total insulin[c] HCV RNA IP-10 FSH (all females)[a] HCV genotype and subgenotype[a]

a. Performed only at Screening.

b. Urine pregnancy testing is not required after TI Day 1 Visit for female subjects with a documented prior hysterectomy or bilateral oophorectomy or bilateral tubal ligation or confirmed postmenopausal. Pregnancy testing post-treatment is to be completed per local label and/or local treatment guidelines and at a minimum at the visits detailed in Table 7.

c. Performed at TI Day 1 only.

d. Tested for cirrhotic subjects only as indicated on Table 6 and Table 8.

For any laboratory test value after the subject has enrolled that is outside the reference range and 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 discontinue study drug or to be discontinued from the study, or that requires 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.

BDI-II Depression Inventory

The Beck Depression Inventory will be completed by all subjects at Screening. Subjects with a score > 21 at the Screening Visit will not be enrolled. Subjects will not be allowed to retake the BDI-II unless rescreening is required due to more than 42 days elapsing since the initial screening procedures (due to reasons beyond the investigator's control).

Assignment of Subject Numbers

Subjects will retain their subject number from the previous AbbVie/Abbott DAA combination study and will enter the previous study number and subject number into the IRT system at the Pre-Screening Visit.

Subjects who meet the inclusion criteria and do not meet any of the exclusion criteria will proceed to enrollment via the IRT system on TI Day 1.

Study Drug Dosing Card

On TI Day 1, subjects will be provided with self-administration instructions for each study drug of the intensified treatment regimen.

MEMS Cap

Subjects participating in the study prior to approval of Amendment 10:

Subjects will be assigned a MEMS cap for the following ABT-450 and ABT-267 bottles. Subjects whose treatment includes ritonavir capsules will also receive a MEMS cap for that bottle. Subjects who receive ritonavir tablets will not receive a MEMS cap for the ritonavir bottle. To ensure that a dosing event is recorded for the first dose of study drug at the site on T1 Day 1, the site should place the MEMS cap on each bottle before dispensing the first dose. Additionally, at each visit, site personnel should download the MEMS dosing history data from the MEMS caps. The MEMS cap will be collected from the subject at the completion of study drug treatment during Substudy 1. Additional information regarding treatment compliance and MEMS can be found in Section 5.5.6 and Section 5.5.8.

Following approval of Amendment 10, all MEMS caps assigned to subjects participating in Substudy 1 will be collected at the subject's next study visit. Site personnel should download the MEMS dosing history data from the MEMS caps. MEMs caps will not be used for the remaining Substudy 1 visits.

HCV Genotype and HCV RNA Levels

Plasma samples for HCV genotype and subtype will be collected at Screening. Genotype and subtype will be assessed using the Versant® HCV Genotype Inno-LiPA Assay, version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY). Genotype will be tested again to rule out any additional infection by another HCV genotype which may not have been present or detected when the subject screened for the previous study. Subjects with evidence of non-genotype 1 infection will be excluded.

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 v2.0. The lower limit of detection (LLOD) is 15 IU/mL and lower limit of quantitation (LLOQ) for this assay is 25 IU/mL.

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 7.

Specific instructions for preparation and storage of IP-10 samples will be provided by the central laboratory, AbbVie, or its designee. Results for IP-10 will not be released to the sites. This testing is done for research purposes only, and has no role in subject management. In the event the data are needed per local requirements, the data can be provided upon request.

HCV Resistance Testing Sample

A plasma sample for resistance testing will be collected at the study visits, indicated in Table 5 and Table 7.

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

Archive Plasma Sample

An archive plasma sample will be collected at the study visits indicated in Table 7. 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, and/or HCV resistance testing, and other possible predictors of response, such as IP10, as determined by AbbVie.

5.3.1.1.1 Additional Procedures for Cirrhotic Subjects Only

Child-Pugh Score and Category

The Child-Pugh score uses five clinical measures of liver disease 3 laboratory parameters (bilirubin, serum albumin, prothrombin time INR) and 2 clinical assessments (ascites and encephalopathy). Child-Pugh score will be determined at the visits indicated in Table 6 and 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

As a result of the physical exam findings, hepatic encephalopathy and ascites will be assessed at TI 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 6 for the Screening and Treatment Period and in Table 8 during the Post-Treatment Period. 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.

Ultrasound findings suspicious for HCC at screening must be confirmed with CT scan or MRI during the screening period. Suspicious ultrasound lesions confirmed by CT or MRI are exclusionary.

Ultrasound findings 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.

5.3.1.2 Meals and Dietary Requirements

ABT-450, ritonavir and ABT-267 should be dosed together and administered with food (for example, ABT-450, ritonavir, ABT-267 and RBV may be taken together in the morning with food and RBV taken in the evening with food).

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples will be collected by venipuncture for assay of ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ritonavir, RBV and pegIFN in Substudy 1 starting at TI Week 1 and at each specified study visit (irrespective of study drug dosing time) or upon subject discontinuation as indicated in Table 5. Blood samples for assay of pegIFN and RBV will be collected in Substudy 2 at each specified study visit (irrespective of study drug dosing time) or upon subject discontinuation as indicated in Table 5.

The time that each blood sample is collected will be recorded to the nearest minute in the subject's records and eCRF. Site personnel will record the last dose of PegIFN and RBV prior to each pharmacokinetic blood sample in the subject's records and eCRF based on subject interview.

A total of approximately 30 samples are planned for pharmacokinetic analysis per subject in the study. The exact number of samples to be collected in this study is unknown and depends on the number of subjects who enroll.

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, ritonavir and RBV and for serum samples for pegIFN will be provided by the central laboratory, AbbVie, or its designee.

5.3.2.3 Disposition of Samples

The frozen plasma samples for the pharmacokinetic assays of ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ritonavir and RBV, frozen serum sample for pegIFN will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory. An inventory of the samples included will accompany the package.

The central laboratory will then ship the samples according to a predetermined schedule to the appropriate location.

ABT-450, ABT-267, ritonavir and RBV samples will be sent to AbbVie:

[redacted]

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

The central laboratory will ship pegIFN samples to:

An inventory of the included pegIFN samples will accompany the package and an electronic copy of the manifests (including subject number, study day, the time of sample

PK samples will be maintained by AbbVie at least until the analytical reports have been finalized but no longer than 6 months from completion of the Clinical Study Report.

5.3.2.4 Measurement Methods

Plasma concentrations of ABT-450, ritonavir, ABT-267 and RBV will be determined using validated assay methods under the supervision of the Drug Analysis Department at AbbVie. Plasma concentrations of metabolites of ABT-267 and ABT-450 may also be determined using non-validated methods. Serum concentrations of pegIFN will be determined using a validated assay method under the supervision of the Sponsor's Drug Analysis Department.

5.3.3 Efficacy Variables

Virologic response will be assessed by HCV RNA in $\log_{10}$ IU/mL at various time-points from Study Day 1 through 48 weeks after completion of pegIFN and RBV treatment.

5.3.3.1 Primary Variable

The primary efficacy endpoint is the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last dose of study drug), both overall and according to treatment in the previous study.

5.3.3.2 Secondary Variable

The secondary efficacy endpoints are the percentage of subjects with SVR_{24} (HCV RNA < LLOQ 24 weeks after the last dose of study drug) and the percentage of subjects with eRVR (HCV RNA < LLOQ at TI Weeks 4 through 12). The endpoints will be examined for the overall treated group and according to the previous treatment as appropriate.

5.3.3.3 Resistance Variables

The following resistance analyses will be performed for subjects who do not achieve SVR: the variants at each amino acid position identified by population and/or clonal nucleotide sequencing (1) at baseline will be compared to the appropriate prototypic reference sequence, and (2) at available post-baseline time points will be compared to baseline and the appropriate prototypic reference sequences.

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

Plasma concentrations for ribavirin, ritonavir, ABT-450, ABT-267 and possible metabolites of ABT-450 or ABT-267, and serum concentrations for pegIFN will be summarized.

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 Substudy 1 Treatment Intensification Period, the procedures outlined for the Treatment Intensification Discontinuation (TI D/C) Visit should be completed as defined in Table 5. Ideally, this should occur 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. The dosing end dates for each DAA and ritonavir and reason for discontinuation from Substudy 1 will be recorded in the eCRF.

The subject should continue to Substudy 2, the pegIFN/RBV Treatment Period, unless the investigator considers continued pegIFN and RBV inappropriate due to either intolerance or inadequate virologic response. If the subject prematurely discontinues during Substudy 2, the subject should return for PR D/C visit procedures as defined in Table 5 and proceed to Substudy 3. If the investigator does not consider the subject appropriate to participate in Substudy 2, the subject should start Substudy 3, the Post-treatment Period for monitoring of HCV resistance and viral response. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment. The dosing end dates for RBV and pegIFN and reason for discontinuation from Substudy 2 will be recorded in the eCRF.

If a subject discontinues from the Post-treatment Period, the subject should return for post-treatment discontinuation procedures (PT D/C) as defined in Table 7. The reason for discontinuation from Substudy 3 will be recorded in the Study Completion eCRF.

If a subject is discontinued prematurely 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 of the study, 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 continue to be monitored for antiviral drug resistance in the Post-Treatment Period as described in Section 5.1.4. The investigator is also encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry.

5.4.1.1 Virologic Failure Criteria

During the Treatment Period and Follow-up Period of the study, the virologic data will be reviewed by the investigator to evaluate if subjects have met virologic failure criteria.

The following criteria will be considered evidence of virologic failure:

- Failure to achieve HCV RNA level < 1,000 IU/mL at TI Week 4. Subject will stop all DAAs and continue pegIFN and RBV at the investigator's discretion.
- Failure to achieve at least a 2 $\log_{10}$ IU/mL HCV RNA reduction from baseline at TI Week 12. Subject will stop all study drugs.
- HCV RNA ≥ 25 IU/mL at TI Week 24. Subject will stop all study drugs.
- Confirmed HCV RNA increase of > 1 $\log_{10}$ from nadir (defined as 2 consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir) in HCV RNA at any time-point. Subject will stop all study drugs.
- Confirmed breakthrough or relapse: HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point after HCV RNA < LLOQ. Subject will stop all study drugs (if applicable).

For the latter 2 criteria, confirmatory testing should be completed as soon as possible. If the investigator feels that a subject who meets one of these criteria should still remain on DAA + pegIFN + RBV or pegIFN + RBV treatment, the subject would only be allowed to remain on DAA + pegIFN + RBV or pegIFN + RBV treatment with approval of the AbbVie Study Designated Physician.

5.4.2 Non Efficacy (Futility) Criteria

In order to categorize subjects according to type of response to prior HCV therapy, for subjects who receive pegIFN and RBV during the period between the previous AbbVie/Abbott DAA combination study and enrollment in this study, the type of response to the PegIFN and RBV treatment will be recorded on the eCRF, if known. Categories on the eCRF will include the following:

- **Null responder:** Subject has documentation that they previously received PegIFN/RBV for at least 10 weeks and failed to achieve a 2 $\log_{10}$ IU/mL HCV RNA decrease at Week 12 (Week 10 to Week 16)
- **Partial responder:** Received at least 20 weeks of PegIFN/RBV for the treatment of HCV and achieved ≥2 $\log_{10}$ reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment
- **Relapser:** Received at least 36 weeks of PegIFN/RBV for the treatment of HCV and was undetectable at the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up
- **Not documented/Other**

Data will be assessed separately for the population of subjects who were null or partial responders to prior pegIFN/RBV treatment or who experienced any prior failure with pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study and for the population of subjects who do not fall in the previous population at the time of enrollment into this study.

- After the first 20 subjects who were not null or partial responders to prior pegIFN/RBV treatment (and who never received pegIFN/RBV plus telaprevir in the previous AbbVie study) have completed 24 weeks of ABT-450/r + ABT-267 + pegIFN/RBV treatment or prematurely discontinued, the percentage of these subjects meeting the protocol defined virologic stopping criteria will be calculated.

  If greater than or equal to 50% of subjects have met virologic stopping criteria, enrollment in Study M13-101 will be stopped for all subjects. All investigators will be notified that enrollment in the study has been suspended due to virologic stopping criteria having been met.
- Similarly, after the first 20 subjects who were null or partial responders to prior pegIFN/RBV treatment or who experienced any prior failure with pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study have completed 24 weeks of ABT-450/r + ABT-267 + pegIFN/RBV treatment or prematurely discontinued, the percentage of these subjects meeting the protocol defined virologic stopping criteria will be calculated.

  If greater than or equal to 50% of subjects have met virologic stopping criteria, enrollment in Study M13-101 will be stopped for all prior null or partial responder subjects, as well as for those who failed treatment with pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study. Subjects who were not null or partial responders to prior pegIFN/RBV treatment and who never received pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study may continue to enroll. All investigators will be notified that enrollment in this population has been suspended due to virologic stopping criteria having been met.

If enrollment is stopped in a population, subjects who are already on study may remain on treatment if, in the opinion of their investigator, the potential benefits of continued treatment outweigh the risks.

5.4.3 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 notify the investigator and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Each dose of study drug will be dispensed in the form of tablets (ABT-450, ABT-267, ritonavir and RBV), capsules (ritonavir) or pre-filled syringes (pegIFN) at the visits listed in Table 5. Subjects will receive either ritonavir as capsules or tablets, but not both during Substudy 1.

At TI Day 1, subjects will be administered study medications by the study site personnel and receive instructions for self-administration of assigned study medications from TI Day 2 through 24 weeks in PR (Substudy 2) or later. ABT-450, ritonavir, and ABT-267 will be administered from TI Day 1 through TI Week 24 in Substudy 1. PegIFN and RBV will be administered from TI Day 1 through TI Week 24 in Substudy 1 and PR Treatment Period Day 1 through 24 weeks or later in Substudy 2.

Following the screening period, the site will contact the IRT to obtain the study drug kit numbers to dispense at the study visits specified in Table 5. Study drug must not be dispensed without contacting the IRT. Study drug may only be dispensed to subjects enrolled in the study through the IRT. After study drug accountability and compliance have been assessed at the study drug dispensation visits specified in Table 5, the site will contact the IRT to provide visit date information and study drug return information for each kit.

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

Table 10. Dosing Schematic

N	Treatment	Duration
Approximately 35	ABT-450/r 200/100 mg QD + ABT-267 25 mg QD + pegIFN + RBV[a]	24 weeks
	pegIFN + RBV[a]	24 weeks[b]

a. pegIFN 180 µg once weekly, RBV weight-based dosing 1,000 to 1,200 mg divided twice daily.

b. Duration could be longer if the subject did not complete 24 weeks of treatment during Substudy 1.

5.5.2 Identity of Investigational Products

Information about the study medications to be used in this study is presented in Table 11.

Table 11. Identity of Investigational Products

Investigational Product	ABT-450	Ritonavir	ABT-267	RBV	PegIFN
Manufacturer	AbbVie/Abbott	AbbVie/Abbott	AbbVie/Abbott	Roche or Generic Manufacturer	Roche
Mode of Administration	Oral	Oral	Oral	Oral	SC Injection
Dosage Form	Tablet	Soft Gelatin Capsule or Tablet	Tablet	Tablet	Syringe
Strength	50 mg	100 mg	25 mg	200 mg	180 mcg/ 0.5 mL

5.5.2.1 Packaging and Labeling

ABT-450 will be packaged in bottles containing 36 tablets. Ritonavir will be packaged in bottles containing 30 or 84 capsules, or in bottles containing 30 tablets. ABT-267 will be packaged in bottles containing 30 tablets. RBV tablets will be supplied to the site in bottles containing 168 tablets each. PegIFN will be supplied in a carton containing 4 or 1 pre-filled syringe(s). Canadian sites will receive PegIFN co-packaged with Ribavirin in a carton containing 4 pre-filled syringes and 1 × 168-count bottle of Ribavirin, plus an

additional 28-ct bottle of Ribavirin supplied with each carton. Each bottle or carton will be labeled as required per country requirements.

Labels must remain affixed to the bottle or carton.

5.5.2.2 Storage and Disposition of Study Drugs

ABT-450, ABT-267, RBV, and ritonavir tablets must be stored at 15° to 25°C (59° to 77°F). Ritonavir capsules must be stored at 2° to 8°C (36° to 46°F) and protected from light. Do not freeze and avoid exposure to excessive heat PegIFN α-2a must be stored at 2° to 8°C (36° to 46°F), protected from light, not frozen and not shaken.

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

5.5.3 Method of Assigning Subjects to Treatment Groups

Contact information and user guidelines for the IRT system will be provided to each site. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

The site will enter the previous study number that the subject participated in and the previous subject number into the IRT system at the Pre-screening visit. If the subject is a failure at the Pre-screening Visit due to inclusion criterion No. 9 or exclusion criterion No. 1 they will be entered as a Pre-screen failure in the IRT system under the Discontinuation flow (refer to Section 5.1.1). For subjects who are eligible after the Pre-screening Visit, the site will enter the Screening Visit into the IRT. After the Screening Visit, for those subjects who do not meet the study selection criteria, the site personnel must identify the subject as a screen failure via IRT under the Discontinuation flow (refer to Section 5.1.2). For enrollment of eligible subjects, at the TI Day 1 Visit, site personnel must receive unique study drug kit numbers via IRT. All subjects will be assigned the same treatment regimen.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.6.4. Study drug dosing will be initiated on the TI Day 1 Visit. ABT-450, ritonavir and ABT-267 will be dosed QD and RBV will be dosed BID. PegIFN will be dosed weekly. Thus with normal dosing, 4 ABT-450 tablets, 1 ritonavir capsule/tablet and 1 ABT-267 tablet should be taken in the morning. RBV should be dosed BID, e.g., 2 to 3 tablets taken in the morning, and 3 RBV tablets should be taken in the evening. All study drugs should be dosed together and administered with food. All medications should be taken at the same time (for example, ABT-450, ritonavir, ABT-267 and RBV should be taken together in the morning with food and RBV should be taken in the evening with food). PegIFN should be taken once every 7 days.

5.5.5 Blinding

There will be no blinding since this is a single arm, open-label study.

5.5.6 Treatment Compliance

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

All study drugs will be dispensed to subjects by study-site personnel under the direction of the investigator. At the start of the study, each subject 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 TI Day 1 Visit. The start and stop dates of all study drugs will be recorded in the source documents and eCRFs.

At each study drug dispensation visit specified in Table 5, study site personnel will inspect the contents of the bottles (full, partial or empty) subjects have brought back and record the status of each one as well as the exact number of remaining tablets of

ABT-450, ABT-267 and RBV or capsules/tablets of ritonavir and the date of reconciliation in the IRT system. If poor compliance is noted, the subject should be counseled and this should be documented in the subject's source.

ABT-450, ritonavir, ABT-267 and RBV should be returned for destruction and reconciliation performed at the study drug dispensation visits and discontinuation visits indicated in Table 5. ABT-450, ritonavir and ABT-267 and RBV should not be re-dispensed to the subject. The date of reconciliation will be recorded in the IRT system.

Subjects will be given a safe disposal needle container for the pegIFN syringes. Once the container is full, subjects will be required to bring the container back to the site for proper disposal. The number of used syringes returned in the disposal container will not be counted and should remain in the safe disposal container for destruction.

The subject will write on the pegIFN kit the date (s) and approximate time the injection (s) was/were taken. The subject will return the empty pegIFN kit(s) at each study dispensation visit and discontinuation visit as indicated in Table 5. Study site personnel will inspect the pegIFN kit(s) returned and transcribe the date each injection was taken in the subject's source as well as record the number of syringes used and the date of reconciliation in the IRT system. (For Canadian sites, pegIFN and RBV are co-packaged into one kit so only the RBV drug return will be captured in the IRT and pegIFN accountability will be documented using paper accountability forms.) In all cases, if poor compliance is noted, the subject should be counseled and this should be documented in the subject's source.

Dose modifications, interruptions or discontinuations of pegIFN or RBV should be undertaken in accordance with local prescribing information.

5.5.7 Electronic Pill Monitors (MEMS Caps)

All subjects participating under Protocol Amendment 10 will not utilize MEMS caps to obtain dosing histories.

Subjects enrolled in the protocol prior to the implementation of the Protocol Amendment 10 will utilize a MEMS monitor (cap), manufactured by Advanced Analytical Research on Drug (AARDEX Group Ltd., Switzerland) on the bottles of ABT-450, ABT-267 during Substudy 1. Subjects receiving ritonavir capsules will also receive a MEMS cap for use on the ritonavir bottle. Subjects receiving ritonavir tablets will not receive a MEMS cap for that bottle. The MEMS caps will be used to obtain daily dosing histories for ABT-450, ritonavir capsules and ABT-267 for all subjects. In addition, MEMS data may be used to assess PK time relative to dose. In the event MEMS data are not available, site personnel will perform subject interviews to obtain the date and approximate dosing time, which will be entered into the eCRF prior to a scheduled pharmacokinetic sample collection. MEMS data will not be provided to the investigator or included as part of source documentation as it will not be used to guide treatment compliance.

The MEMS cap is a threaded cap containing an internal electronic clock, with an integrated electronically erasable programmable read-only memory, a special micro-switch and battery. Once fastened onto the medication bottle, the MEMS cap silently records the date and time of all dosing events (event = opening + closing). This electronic monitor provides a means of objectively measuring a subject's adherence with the study medication.

At the TI Day 1 Visit, subjects will be assigned the appropriate number of MEMS caps that will be placed on the ABT-450, ritonavir capsules and ABT-267 bottles in place of the original caps. Subjects who receive ritonavir tablets will not receive a MEMS cap for the bottle. For the study drugs that will use the MEMS cap, the original cap should be saved so it can be placed back on the bottle by the investigator or designee in order to store returned study drug. Each drug will be assigned a specific color, identified by a color coded marking on the drug bottle. The colored marking which corresponds to a particular drug will also be placed on the MEMS cap so that the same MEMS cap is used for only one drug throughout the study.

The MEMS caps must only be used by the subject to whom it was assigned. Each MEMS cap has a unique serial number that must be recorded in the MedAmigo system. It is suggested that the subject's subject number be written on his or her MEMS caps in permanent ink.

The subjects will be instructed to open the bottle when it is time to take the medicine, to remove the proper amount of medication and promptly close the bottle, then ingest the prescribed dose. The subject should be instructed to transfer the MEMS cap to the next full bottle of study drug at the same time that they take their last dose from the current in-use bottle.

At each study visit specified in Table 5, subjects should return to the clinic with all bottles of study medication (full, partial or empty) with the MEMS cap attached to the bottles. The site staff will download the data collected on the MEMS cap at each visit designated in Table 5 via the MEMS reader. Instructions on how to transfer the MEMS data will be provided to the site by AbbVie.

The MEMS cap will be collected from the subject at the completion of study drug treatment during Substudy 1 or at the subject's first study visit following approval of Amendment 10 at the site. The collected MEMS caps should be sent to AbbVie or its designee. Additional instructions for the subject on how to use the MEMS caps will be provided by the Sponsor.

5.5.8 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/capsules/syringes dispensed, subject number and the date on which study drug is dispensed to the subject. An overall accountability of the study drug will be performed and verified by the AbbVie monitor

throughout the study. Final accountability will be performed 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 kit, the misplaced or damaged study drug kit must be registered in the IRT system. If study drug kit is misplaced or damaged, the subject will be requested to return the remaining study drug to the site. A new study drug kit may only be dispensed to the subject by contacting the IRT system. Study drug replacement and an explanation of the reason for misplaced or damaged study drug kit will be documented in the subject's source documents. Study drug start/end dates will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each bottle/kit of syringes, number of tablets/capsules/syringes returned and the date of reconciliation will be recorded in the IRT system (Note: co-packaged kits of RBV/pegIFN dispensed in Canada will only track RBV in the IRT system.). The drug accountability recorded in the IRT may be considered source documents if the site is not using their own accountability forms. In this case, copies of reports from the IRT must be placed in the subject's source documents.

Upon completion of study drug or discontinuation from Substudies 1 or 2, all original containers with unused study drug will be returned to AbbVie (or designee) according to instructions from AbbVie and according to local regulations following completion of drug accountability procedures. The number of capsules, tablets and syringes of each type of study drug returned will be noted in the IRT (if not previously recorded) and appropriate drug return forms. Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This study is specifically intended to provide an optional intensified treatment regimen for subjects who experienced virologic failure in a previous AbbVie/Abbott DAA combination study. No control group is included in this study. Safety and efficacy of the study regimen will be compared with historical data for pegIFN and RBV therapy.

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. Population sequencing done by Monogram Biosciences at the Pre-screening Visit is validated for both NS3/4A and NS5A sequence. Clonal sequencing, population sequencing methods and phenotype assays during the study after pre-screening are experimental.

5.6.3 Suitability of Subject Population

Because this study is specifically intended to provide an optional intensified treatment regimen for subjects who experienced virologic failure in a previous AbbVie/Abbott DAA combination study, the population consisting of subjects who experienced virologic failure in a previous study is appropriate. The decision to enroll in this study will be made by the subject in consultation with the investigator, and will be based on review of multiple factors, such as the subject's HCV disease status, the previous study treatment regimen, HCV RNA responses and virologic failure category during the previous study, HCV genotype, IL28B genotype, treatment adherence history, any available resistance data and availability of alternative treatment options. Discussion of the use of a DAA combination with pegIFN and RBV in subjects who have failed previous therapy with a DAA-based regimen is contained in Section 3.0.

Subjects who have previously experienced null or partial response to pegIFN/RBV treatment at any time prior to pre-screening for this study or who experienced any prior failure with pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study will not be enrolled in this study if population sequencing identifies the presence of variants relative to the prototypic reference sequence (H77 for 1a or Con1 for 1b) at any of the following positions: NS3 155, 156, or 168; or NS5A 28, 29, 30, 31, 32, 58, or 93. Because in vitro and in vivo studies have shown that exposure to ABT-450 or ABT-267 leads to the selection of variants at one or more of these positions, any variant at one or more of these positions may have the potential to decrease viral susceptibility to the corresponding DAA. Until prospective data are available on the response to treatment of patients with

virus harboring these variants, variants at any one or more of these positions are therefore considered as potentially decreasing susceptibility to the study drug regimen. Subjects with prior non-response to pegIFN/RBV are more likely to have a suboptimal response to a second course of pegIFN/RBV, and the presence of variants associated with decreased susceptibility to ABT-450 and/or ABT-267 could therefore lead to an unacceptable risk of treatment failure (with possible worsening of genotypic resistance). Until further data are available on response to ABT-450/r and ABT-267 in subjects who previously failed pegIFN/RBV telaprevir in the previous AbbVie study, these subjects will conservatively be treated as pegIFN nonresponders.

5.6.4 Selection of Doses in the Study

Doses of the DAAs to be used in this study have shown significant antiviral activity both as monotherapy and in combination with pegIFN and RBV. 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 HCV-infected subjects as monotherapy or in combination with pegIFN and RBV and found to have a good safety profile and well tolerated. Of note, co-administration of ABT-450/r and ABT-267 at the doses planned for use in this study does not clinically significantly impact plasma exposures compared to administration as single agents. Therefore doses selected based on data from monotherapy studies are considered appropriate for use when these agents are combined.

ABT-450/r

The dose of ABT-450/r is 200/100 mg QD. This is higher than the 150 mg dose used in Phase 3 studies and the approved dose of ABT-450 for HCV GT1 infection with the interferon free 3-DAA regimen. The 200 mg dose has been evaluated in Phase 2a study (Study M11-602) with peg-IFN and ribavirin for 12 weeks; in the Phase 2a and 2b Studies M12-998 and M11-652, the 200 mg dose was administered for 12 to 24 weeks with 25 mg ABT-267 with and without ribavirin. Doses higher than 200 mg have been evaluated in Phase 2 Study M12-746 with ABT-333 and ribavirin for 12 weeks as well as

in Phase 1 Study M12-187 and Study M12-221 for up to 14 days with ABT-267. Studies in both healthy volunteers (Study M12-187) and HCV-infected subjects (Study M12-746) suggest that a higher dose of ABT-450/r (250/100 mg QD) may be associated with a risk of elevated ALT levels when co-administered with other DAAs (ABT-333 or ABT-267 + ABT-333). Therefore, the maximum ABT-450 dose administered in this study will not exceed 200 mg daily for 24 weeks.

ABT-267

The 25 mg dose of ABT-267 is the dose evaluated in Phase 3 studies and the approved dose of ABT-267 for HCV GT1 infection with the interferon free 3-DAA regimen. This was the same dose that has been evaluated in multiple Phase 2 studies (Studies M11-652, M12-998, M13-393). The dose of ABT-267 in this study is 25 mg QD. Following 3 days of ABT-267 monotherapy at doses of 1.5 mg, 5 mg QD, 25 mg QD, 50 mg QD and 200 mg QD, in Study M12 116 and Study M13-386, mean viral load decreases were 2 to 3 $\log_{10}$ IU/mL and comparable across doses. In addition, data from Phase 2a study of ABT-267 with pegIFN and RBV (Study M12-114) suggest that the 3 doses used in that study (5 mg QD, 50 mg QD and 200 mg QD) are all well tolerated and show comparable short term antiviral activity. Resistance analysis from a short-term monotherapy trial (Study M12-116) suggests that ABT-267 doses greater than 25 mg QD do not appear to confer an advantage in suppression of commonly selected resistant variants. The maximum ABT-267 dose administered in this study will not exceed 25 mg daily for 24 weeks.

RBV

The daily dose of RBV in this study is 1,000 mg to 1,200 mg, divided twice daily. This dose is approved for treatment of adult patients with chronic hepatitis C in combination with pegIFN. This dose is selected for this study because the 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.

pegIFN

PegIFN will be dosed per the package insert in this study.[11] PegIFN will be dosed at 180 µg/0.5 mL SC once a week for the duration of 48 weeks. This dose is approved for treatment of adult patients with chronic hepatitis C in combination with RBV. The same dose is selected for this study because the safety profile has been well characterized when administered with RBV, and there are well-defined dose reduction criteria in the event of hematologic adverse effects.

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, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to 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. 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 DAA (ABT-450/r or ABT-267), RBV and pegIFN:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an Other cause of event is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to the study drug and an Other cause of event is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely Other cause of event exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely Other cause of event).

For causality assessments, events meeting the categories of probably or possibly will be considered "associated." Events that are probably not or not related 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.

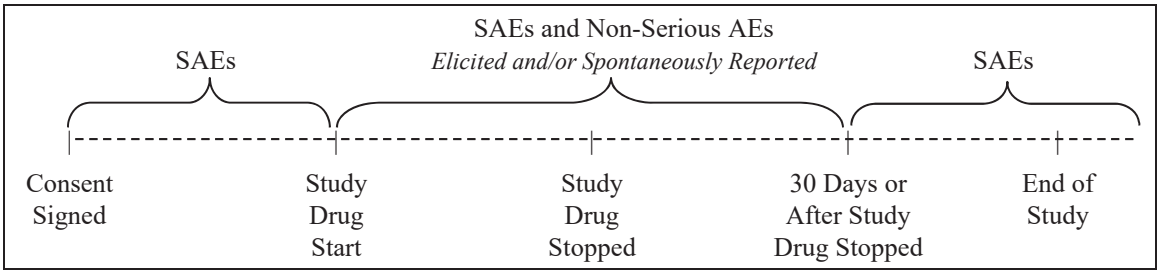
If an investigator's opinion of possibly, probably not, or not related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration (including pegIFN and RBV) have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signed the study-specific informed consent through the end of Substudy 3 (End of Study).

Adverse event information will be collected as shown in Figure 4.

Figure 4. 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 EDC system. Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable 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.

[redacted]

For safety concerns, contact the Antiviral Safety Team at:

[redacted]

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

[redacted]

In emergency situations involving study subjects when the primary Study Designated Physician (SDP) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated AbbVie SDP.

[redacted]

AbbVie 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 Study Day 1 and for 7 months (or per local RBV label) after the last dose of 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. Administration of DAA's, including ritonavir, and Peginterferon may be continued at the investigator's discretion if the benefit of continuing therapy is felt to outweigh the risk (Section 5.4.1). Subjects will continue to be monitored for antiviral drug resistance in the Post-Treatment Period as described in Section 5.1.4.

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. The investigator is encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry as applicable.

Male subjects who are not surgically sterile must either abstain from sexual intercourse or agree to use a double barrier method of birth control (condom), including informing their partner(s) to use an effective method of birth control (e.g., contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams) for 7 months (or per local RBV label) after the last dose of RBV. In the event of pregnancy occurring in the partner of an enrolled subject, the investigator should contact the AbbVie Study Designated Physician to discuss the potential benefit of the male subject remaining on study drug treatment. If considered appropriate, the subject may remain in the study and the investigator should counsel the subject on the pregnancy risks associated with RBV, and instruct him to use 2 effective forms of contraception (including at least one barrier method) for the remainder of the partner's pregnancy. The investigator is encouraged to report the partner's pregnancy information to the voluntary RBV Pregnancy Registry.

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

6.7 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 through Section 6.7.5.

A drug-related toxicity is an adverse event or laboratory value outside of the reference range reported as an adverse event that is judged by the investigator or AbbVie to be either "possibly related" or "probably related" to the study drug (Section 6.3). A toxicity is deemed "clinically significant" based on the medical judgment of the investigator. During the study, timeliness of EDC data entry to reflect study drug dose interruptions and/or dose modifications and consequent required adverse events insures that the AbbVie Safety Team (Study Designated Physician, safety monitor) have the data necessary for signal detection at safety data review meetings. The investigator should ensure that any interruptions or modifications and consequent required adverse events are entered into the appropriate eCRFs within 5 business days.

Lowering of the pegIFN and RBV dose for reasons not provided in the protocol is permitted. The following guidelines should be used for study drug-related toxicity management.

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

Subjects who develop a study drug-related mild or moderate adverse event or Grade 1 or 2 laboratory abnormality, other than those discussed separately in Section 6.7.3, 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

If a subject experiences a Grade 3 or greater laboratory abnormality during the study (other than those discussed in Section 6.7.3 and Section 6.7.4 below), the abnormal laboratory test should be repeated. If the Grade 3 or greater abnormality is confirmed, then all study drugs should be interrupted and the subject monitored until the laboratory parameter has returned to its baseline level or stabilized. Study drugs may be resumed only with approval of the AbbVie Study Designated Physician. If the investigator believes that a Grade 3 or greater laboratory parameter is not clinically significant or is not related to study drug and that study drug discontinuation is not warranted, the study drug may be continued with approval of the AbbVie Study Designated Physician.

Study drug-related Grade 3 or higher elevations in uric acid, total cholesterol or triglycerides do not require study drug discontinuation, but study drug may be interrupted if deemed necessary by the investigator.

If a subject experiences a severe adverse event or a serious adverse event and that event is considered possibly or probably related to study drug by the investigator, the AbbVie Study Designated Physician should be notified and all study drugs should be interrupted. The investigator should ensure that the serious adverse event is report to AbbVie Safety within 24 hours of awareness of it; a severe event should be entered into EDC within 5 business days. Dose interruptions (or discontinuations) should be entered into the appropriate eCRFs within 5 business days.

6.7.3 Management of Decreases in Hemoglobin

Reductions in hemoglobin are a well characterized side effect of ribavirin exposure. Hematologic abnormalities which the investigator believes are due to RBV therapy may be managed according to Table 12. Management will be different for subjects without a history of known cardiac disease and subjects with known cardiac disease.

If a subject experiences a hemoglobin decrease (as outlined in Table 12), a confirmatory test should be performed. If the hemoglobin decrease is confirmed, the management guidelines in Table 12 should be followed.

Use of hematologic growth factors (e.g., epoetin, filgrastim) is permitted at the discretion of the investigator, only with approval of the AbbVie Study Designated Physician (see Section 5.2.3.2 for further details). 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 requires approval of the AbbVie Study Designated Physician.

Alternative management of the RBV dose in the setting of reduced renal function will also require approval of the AbbVie Study Designated Physician.

Table 12. Hematologic Toxicities

Hemoglobin in Patients with No History of Cardiac Disease	
Hemoglobin < 10.0 g/dL, but ≥ 8.5 g/dL	Study drugs may be continued
	Reduce RBV dose to 600 mg/day and continue to monitor hemoglobin per protocol
	If hemoglobin increases to ≥ 10 g/dL, may increase RBV; with gradual dose increases in 200 mg increments towards original dose
	If Hb decreases to < 8.5 g/dL see appropriate row below
Hemoglobin < 8.5 g/dL	Permanently discontinue all study drugs
	Manage the subject as medically appropriate
	Enter discontinuation into appropriate eCRFs and create corresponding adverse event
Hemoglobin in Patients with History of Stable Cardiac Disease	
Hemoglobin decrease of ≥ 2 g/dL during a 4-week treatment period	Study drugs may be continued
	Reduce RBV dose to 600 mg/day and continue to monitor hemoglobin levels per protocol; manage subject as medically appropriate; AbbVie Study Designated Physician may be contacted
	If a subsequent hemoglobin result is greater than the level that triggered the dose reduction, the investigator may gradually increase RBV in 200 mg increments towards original dose
Hemoglobin <12 g/dL despite 4 weeks at reduced dose	Permanently discontinue all study drugs; manage subject as medically appropriate
	Enter discontinuation into appropriate eCRFs and create corresponding adverse event (AE)

6.7.4 Management of ALT Elevations

Transient asymptomatic Grade 3-4 ALT elevations have been observed in approximately 1% of subjects receiving ABT-450/r-containing regimens. If a subject experiences a post-baseline increase in ALT to > 5 × ULN that is increased from the previous measurement, the subject should have a confirmatory ALT measurement performed.

If the ALT increase is confirmed to be > 5 × ULN, the recommendations below should be followed:

- 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.
- Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and INR within 1 week. Repeat liver chemistries as indicated until resolution.
- Discontinue study drugs if any of the following is observed at any time:
  - ALT level is > 20 × ULN
  - Increasing direct bilirubin, increasing INR, or onset of symptoms/signs of hepatitis.

Alternate management of ALT increases is permitted with approval of the AbbVie Study Designated Physician.

6.7.5 Management of Creatinine Clearance Decreases

If calculated creatinine clearance (by Cockcroft-Gault formula) is confirmed to have decreased to < 50 mL/minute, (in a subject with a baseline creatinine clearance ≥ 50 mL/min), or to below 30 mL/minute (in a subject with a baseline creatinine clearance < 50 mL/min), 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 13. 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 creatinine clearance, and whether discontinuation or substitution of the possible interacting drug might be needed. For example, drug interactions between DAAs and some antihypertensive medications could potentially increase exposures of the antihypertensive, which may lead to reduction in renal function. If anti-hypertensive medications are adjusted, vital signs should be

monitored to ensure appropriate blood pressure control. Refer to Section 5.2.3 for additional information regarding drug-drug interactions.

Table 13. Dosing of RBV in Subjects with Renal Impairment

CrCl Value	RBV Dose
30 – 50 mL/min	Alternating doses, 200 mg and 400 mg every other day
< 30 mL/min	200 mg daily
Hemodialysis	200 mg daily

If creatinine clearance improves, the site should perform all necessary readjustment of any dose modifications that have been made. If creatinine clearance improves to above the level that triggered the RBV dose reduction, RBV dose may be increased accordingly.

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

6.7.6 Management of Neuropsychiatric Complications

Refer to the pegIFN label for management of depression.[11]

History of past or current severe psychiatric conditions should be taken into account when determining if enrollment in this study is warranted. Such subjects should only be enrolled after appropriate individualized diagnostic and therapeutic management of the psychiatric condition has been undertaken.

All patients receiving pegIFN should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear while a subject is receiving study drug treatment, the severity of those symptoms and potential risk to the subject should be assessed, and the need for adequate therapeutic management should be determined. If psychiatric symptoms persist or worsen, discontinuation of study drug treatment and/or psychiatric intervention should be considered, based on the risk of additional psychiatric adverse events compared to the potential benefit of continuing study drug treatment. If

suicidal ideation is identified, study drug treatment must be discontinued and the subject should be referred for psychiatric intervention as appropriate.

6.7.7 Management During Peginterferon Therapy

An eye examination should be scheduled for any subject complaining of decrease or loss of vision.

Good dental hygiene and regular dental examinations should be encouraged while subjects are receiving pegIFN.

6.7.8 Management of Neutropenia and Thrombocytopenia

Refer to the pegIFN prescribing information for management of neutropenia and thrombocytopenia.

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 study 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

There will be no interim analysis. The final analysis will occur after all enrolled subjects have completed the Post-Treatment Period or prematurely discontinued from the study. Data will be locked after performing appropriate data cleaning.

In addition, ongoing review of the data is also planned for non-efficacy (futility) assessment. Data will be assessed separately for the population of subjects who were null or partial responders to prior pegIFN/RBV treatment or who experienced any prior failure with pegIFN/RBV plus telaprevir in the previous AbbVie/Abbott study, and for the population of subjects who do not fall in the previous population at the time of enrollment into this study. Refer to Section 5.4.2 for further details regarding these ongoing reviews.

SAS for the UNIX operating system will be used for all analyses. All confidence intervals will be two-sided with an α level of 0.05.

Efficacy, safety and demographic analyses will be performed on all subjects who receive at least one dose of study drug.

No data will be imputed for any efficacy or safety analysis except for analyses of the HCV RNA endpoints or RVR, eRVR, EOTR, and all SVR endpoints. For the endpoints of RVR, eRVR, and EOTR, if an HCV RNA value is missing within the window, the closest values before and after the window, regardless of the value chosen for the subsequent and preceding window, will be used for flanking imputation. 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 the succeeding value, the HCV RNA

level will be imputed as undetectable or unquantifiable, respectively, at this visit for this subject. For SVR analyses, if there is no value in the appropriate window a backward imputation approach will be used such that if the nearest HCV RNA value after the SVR window is unquantifiable, then it will be used to impute the response in the SVR window. Subsequent to these imputations, if a subject is missing a value for the analysis time-point, the subject will be imputed as a failure.

8.1 Statistical and Analytical Plans

8.1.1 Demographics

Demographics and baseline characteristics will be summarized overall, and based on treatment in the previous study. Demographics include age, weight, and body mass index (BMI), and the frequency of gender, race, ethnicity, age category (< 50 years and ≥ 50 years; < 65 years and ≥ 65 years), birth year (< 1945, 1945 to 1965, > 1965), BMI category (< 30 kg/m^2 and ≥ 30 kg/m^2), and geographic region (North America, Europe, Australia/New Zealand, Latin America). Baseline characteristics will include HCV genotype/subtype (1a, 1b, other 1 subtype), IL 28B genotype (CC, CT, and TT; CC and non-CC), RBV dose modifications (yes, no), history of diabetes, history of bleeding disorders, baseline fibrosis score (equivalent to Metavir F0–F1, F2, F3–F4), prior response to pegIFN/RBV, type of response to combination DAA treatment in prior study, treatment during the gap between the prior study and Study M13-101 (none, pegIFN/RBV), baseline $\log_{10}$ HCV RNA levels, baseline IP-10, baseline HOMA-IR, and tobacco and alcohol use status. Summary statistics (N, mean, median, 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 Pharmacokinetics

Plasma concentrations for ABT-267, ABT-450, ritonavir (where applicable) and possible metabolites of ABT-450 and ABT-267 will be determined at each study visit up to 24 weeks. Plasma concentrations for RBV and serum concentrations for pegIFN may be determined at each study visit up to 48 weeks.

8.1.2.1 Pharmacokinetics Endpoints

Plasma concentrations for ABT-267, ABT-450, ritonavir and possible metabolites of ABT-450 and ABT-267 will be determined at each study visit up to 24 weeks. Plasma concentrations for RBV and serum concentrations for pegIFN may be determined at each study visit up to 48 weeks.

8.1.3 Efficacy

Analyses of primary and secondary endpoints will be performed by the overall treatment cohort, and by previous treatment group. No statistical comparisons will be made between groups according to previous treatment.

8.1.3.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the percentage of subjects with sustained virologic response 12 weeks after the last actual dose of study drug (including DAA, pegIFN, and RBV) ($SVR_{12actual}$; HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). The percentage of subjects with $SVR_{12actual}$ and the corresponding 95% exact binomial confidence interval will be calculated overall and by treatment group in the prior study.

8.1.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are the percentage of subjects with sustained virologic response 24 weeks after the last actual dose of study drug (including DAA, pegIFN, and RBV) ($SVR_{24actual}$; HCV RNA < LLOQ 24 weeks after the last actual dose of study drug) and the percentage of subjects with eRVR (HCV RNA < LLOQ at TI Weeks 4 through 12).

The percentage of subjects with $SVR_{24actual}$ and eRVR and the corresponding 95% exact binomial confidence intervals will be calculated overall and by treatment group in the prior study.

8.1.3.3 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized for the overall treatment group as specified:

- the percentage of subjects with rapid virologic response (RVR) (HCV RNA < LLOQ at TI Week 4),
- the percentage of subjects with complete early virologic response (EVR) (HCV RNA < LLOQ at TI Week 12),
- the percentage of subjects with end of treatment response (EOTR: HCV RNA < LLOQ at the end of treatment [DAAs, pegIFN, and RBV]),
- the percentage of subjects with unquantifiable HCV RNA at each post-baseline visit during treatment,
- the percentage of subjects with $SVR_{12planned}$ (12 weeks after the last planned dose of pegIFN and RBV, i.e., 60 weeks after the first dose of study drug) and $SVR_{24planned}$ (24 weeks after the last planned dose pegIFN and RBV, i.e., 72 weeks after the first dose of study drug),
- The percentage of subjects with sustained virologic response (HCV RNA < LLOQ) 4 weeks after the last dose of study drug (SVR_4),
- the percentage of subjects who fail to suppress (never achieving HCV RNA < LLOQ) during treatment and received at least 6 weeks of treatment (i.e., study drug duration ≥ 36 days),
- the number of subjects with virologic rebound (two consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir during treatment or two consecutive HCV RNA measurements ≥ LLOQ during treatment after HCV RNA < LLOQ) at each protocol-specified visit during treatment,
- the percentage of subjects with on-treatment virologic failure during the Treatment Period (defined as rebound or failure to suppress during treatment, i.e., all on-treatment values of HCV RNA ≥ LLOQ, with at least 6 weeks of treatment),
- the percentage of subjects with relapse through Post-Treatment Week 12 and any time post-treatment, among subjects completing treatment and with HCV RNA < LLOQ at the Final Treatment Visit,

- the percentage of subjects who achieved SVR_{24} and subsequently relapsed,
- time to suppression in HCV RNA(defined as the study day of the first occurrence of HCV RNA < LLOQ),
- time to relapse at any time post-treatment, among subjects completing treatment and with HCV RNA < LLOQ at the Final Treatment Visit

The percentages of subjects with RVR, ETR, SVR_4, $SVR_{12planned}$, and $SVR_{24planned}$, and the corresponding 95% exact binomial confidence intervals will be calculated overall. Similarly, the percentage of subjects with on-treatment virologic failure and the percentage of subjects who relapse through Post-Treatment Week 12 and any time post-treatment, among subjects completing treatment and with HCV RNA < LLOQ at the Final Treatment Visit, will be calculated overall along with the corresponding 95% exact binomial confidence intervals.

From HCV RNA levels, the time to suppress, and the time to relapse, will be calculated for each subject, will be displayed graphically using a Kaplan-Meier curve.

8.1.4 Exploratory Analyses

Logistic regression will be used with $SVR_{12actual}$ as the dependent variable to explore potential predictors of response. The following variables will be considered as possible independent variables: baseline log_{10} HCV RNA level, HCV subgenotype (1a, 1b), geographic region, IL-28B genotype (CC, non-CC), IP10, GGT, sex, race, age, and baseline BMI.

8.1.5 Resistance Analyses

The genes of interest for population sequencing in this study are those encoding full length NS3/4A and NS5A, while for clonal sequencing they are those encoding NS3 amino acids 1 to 181 and NS5A amino acids 1 to 215. 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 are: 155, 156, and 168 in NS3 for ABT-450; 28, 30, 31, 58, and

93 in NS5A for ABT-267. This list may be expanded if treatment-emerged resistance-conferring variants are identified at additional amino acid positions in DAA-treated patients. The prototypic reference sequences used for analysis will be H77 for genotype 1a or Con1 for genotype 1b.

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore, if the HCV RNA level at the time of virologic failure is < 1000 IU/mL, the sample closest in time after the failure with an HCV RNA level ≥ 1000 IU/mL will be used. Clonal sequencing of a given target will be performed only if no variants are detected at signature resistance-associated amino acid positions by population sequencing in that sample. In addition, clonal sequencing may be performed if there is a complex mixture of amino acids at one or more signature resistance-associated position that cannot be resolved by population sequencing.

Included time points for analyses on samples from subjects who experience virologic failure (as defined in Section 5.4.1.1) are (1) time of virologic failure or sample closest in time after failure with an HCV RNA level of ≥ 1000 IU/mL, (2) 24 weeks post-DAA treatment, provided that resistance-associated variants were detected by either population or clonal sequencing at the time of failure, and (3) 48 weeks post-DAA treatment, provided that resistance-associated variants were detected by either population or clonal sequencing at post-DAA treatment Week 24.

The following definitions will be used in the resistance analyses:

- 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 or NS5A).
- Post-baseline variant by population sequencing: an amino acid variant in a post-baseline time point sample that was not detected at baseline and is detectable by population sequencing.

- Post-baseline variant by clonal sequencing: a variant at a signature resistance-associated amino acid position that was not present by population sequencing at baseline that is detected in a post-baseline sample by clonal sequencing in at least 2 clones from that sample (among the subset of subjects for whom clonal sequencing is performed).
- Emerged variant by population sequencing: a post-baseline variant that is observed in 2 or more subjects of the same HCV subgenotype by population sequencing.
- Linked variant by population sequencing: 2 or more signature resistance-associated or emerged amino acid variants identified within a target 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.
- Linked variant by clonal sequencing: at least 2 clones from a given sample containing the same 2 or more signature resistance-associated amino acid variants by clonal sequencing.

For those subjects whose baseline sample has an HCV RNA level ≥ 1000 IU/mL, a listing by subject of all baseline variants relative to prototypic reference sequence at signature resistance-associated amino acid positions will be provided for each DAA target (NS3 and NS5A).

The following analyses will be performed on the samples from subjects who experienced virologic failure and have post-baseline resistance data available.

The HCV amino acid sequence as determined by population sequencing will be compared with the baseline and appropriate prototypic reference amino acid sequences. Listings by subject of all post-baseline variants detected by population sequencing relative to the baseline amino acid sequences will be provided for each DAA target (NS3 and NS5A). In addition, listings by subject of variants detected by population sequencing at signature resistance-associated amino acid positions relative to baseline and the appropriate prototypic reference amino acid sequences will be provided.

For the subset of samples for which clonal sequencing is performed, the amino acid variants determined by clonal sequencing will be summarized by counting the number of clones whose amino acid sequence does not match that of the population baseline sequence by subject at each time point and amino acid position, out of the total number of clones analyzed. Listings by subject of post-baseline variants at signature resistance-associated positions detected by clonal sequencing will be provided for each DAA target.

Linkage between emerged or signature variants by population sequencing will also be evaluated. A listing by subject and time point of the linked variants by population sequencing for each target will be provided. Furthermore, where clonal sequencing is performed and the sample has at least 2 clones with the same 2 or more signature resistance-associated amino acid variants within a DAA target, then a listing by subject and time point of the linked variants by clonal sequencing will be provided.

8.1.6 Safety

All subjects who receive at least 1 dose of study drug will be included in the safety analyses. Safety data will be summarized for the overall treatment cohort but not by prior treatment.

8.1.6.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).[12] The number and percentage of subjects having DAA treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-DAA) will be tabulated by primary MedDRA System Organ Class and preferred term. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided with further breakdown by severity rating and relationship to DAA (ABT-450/r or ABT-267), pegIFN, and RBV. Subjects reporting more than 1 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

1 type of event within a System Organ Class will be counted only once for that System Organ Class.

The number and percentage of subjects experiencing adverse events with an onset date greater than 30 days post-DAA dosing through 30 days after the last dose of pegIFN/RBV will also be tabulated by primary MedDRA System Organ Class and preferred term.

Additional analyses will be performed if useful and appropriate.

8.1.6.2 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 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 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 (PCS) laboratory values will be summarized. For hemoglobin and the liver function tests of ALT, AST, alkaline phosphatase, and total bilirubin, the frequency and percentage of subjects with a maximum CTCAE Grade of 1, 2, 3, or 4 will be summarized.

8.1.6.3 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 descriptively. Frequencies and percentages of subjects with post-baseline values meeting pre-defined criteria for PCS Vital Signs values will be summarized.

8.2 Determination of Sample Size

There is no predetermined sample size for this study. Subjects who experience virologic failure in a previous AbbVie/Abbott DAA combination study and who meet the eligibility criteria will be treated in this study.

9.0 Ethics

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

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

Any amendments to the protocol will require IEC/IRB approval 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.

A copy of the informed consent form medication guides for pegIFN and RBV will be given to the subject.

Male subjects will also be given instructions and copies of the RBV medication guide and RBV Partner Risk Fact Sheet to share with their female partner(s).

The original informed consent 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 of the consent and copies of the RBV medication guide and RBV Partner Risk Fact Sheet (for male subjects). Refer to Section 6.6 for partner pregnancy information.

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, MEMS data, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

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

10.2 Case Report Forms

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

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

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person

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

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

11.0 Data Quality Assurance

Computer logic checks will be run to identify items such as inconsistent study dates. Any necessary corrections will be made by the site to the eCRF.

12.0 Use of Information

All information concerning ABT-450/r, and ABT-267, and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of ABT-450/r and ABT-267. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to

provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie and shall not be used except in the performance of this study.

The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study, including each subject's name, subject number, address, phone number and emergency contact information. This list will be maintained at the study site with other study records under adequate security and restricted access and will not be retrieved by AbbVie.

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, and ABT-267 and the product labeling for ritonavir, pegIFN 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.

Protocol Title:	An Open-Label Study to Evaluate the Safety, Antiviral Activity and Pharmacokinetics of Direct-Acting Antiviral Agent (DAA) Treatment in Combination with Peginterferon α-2a and Ribavirin (pegIFN/RBV) in Chronic Hepatitis C Virus (HCV) Infected Subjects Who Have Experienced Virologic Failure in a Previous AbbVie/Abbott DAA Combination Study
Protocol Date:	26 June 2015

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

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11. Pegasys® [package insert]. Nutley, New Jersey; Hoffmann-La Roche Inc., 2010.
12. Medical Dictionary for Regulatory Activities (MedDRA), Version 12.1.

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's Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

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

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

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

Appendix B. List of Protocol Signatories

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

Clinical Toxicity Grades for HCV Studies
v1.1; 08 June 2009

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

Clinical Toxicity Grades for HCV Studies
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Appendix D. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

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

[redacted]

Has been changed to read:

[redacted]

Section 1.2 Synopsis
Subsection Number of Subjects to be Enrolled:
First sentence previously read:

Up to 150.

Has been changed to read:

Up to 35.

Section 3.0 Introduction
First paragraph, third sentence previously read:

Until recently, the standard of care (SOC) for treatment of HCV genotypes 1a and 1 b (the most common genotypes in North America and Europe) consisted of weekly injections of

pegylated interferon-alpha (pegIFN) and daily oral doses of ribavirin (RBV) for up to 48 weeks.[2]

Has been changed to read:

Until 2011 with the FDA approval of the protease inhibitors (PI) telaprevir and boceprevir, the standard of care (SOC) for treatment of HCV genotypes 1a and 1b (the most common genotypes in North America and Europe) consisted of weekly injections of pegylated interferon-alpha (pegIFN) and daily oral doses of ribavirin (RBV) for up to 48 weeks.[2]

Section 3.0 Introduction
First paragraph, last sentence previously read:

Thus, there is a clear unmet need for effective anti-HCV compounds which can increase the likelihood of successful treatment for this population.

Has been changed to read:

While the triple drug regimen of PI/pegIFN/RBV increased SVR rates to 70% – 80%, there were many treatment discontinuations due to drug toxicities like rash and anemia, and virologic failure rates were still unacceptably high. These two, distinct eras of HCV therapy generated a large cohort of patients in need of more potent antiviral regimens.

Section 3.0 Introduction
Delete: third paragraph

Limited data suggest regimens containing pegIFN, RBV and DAAs may also represent a potential treatment option for subjects who previously failed HCV therapy. In one study, an NS5A inhibitor (BMS-790052) and a protease inhibitor (BMS-650032) combined with pegIFN and RBV for 24 weeks achieved 24-week SVR (SVR_{24}) in over 90% of prior pegIFN/RBV null responders. While the study is still ongoing, these preliminary findings suggest that prior pegIFN/RBV null responders may be successfully treated with a DAA combination added to pegIFN/RBV.

Section 3.0 Introduction
Fourth paragraph, first and second sentence previously read:

Data from studies on the retreatment of HCV-infected subjects who have failed prior treatment with regimens containing one or more DAAs are currently very limited. In several of the exploratory studies, subjects who experienced viral breakthrough or non-response (with emergence of DAA-related associated resistance mutations) were managed by the addition of pegIFN, or pegIFN and RBV to the failing DAA combination regimen.

Has been changed to read:

Data from studies on the retreatment of HCV-infected subjects who failed prior treatment with regimens containing one or more DAAs are limited. In one study, an NS5A inhibitor (BMS 790052) and a PI (BMS 650032) combined with pegIFN and RBV for 24 weeks achieved SVR_{24} in over 90% of prior pegIFN/RBV null responders, suggesting that these patients may be successfully treated with a DAA combination added to pegIFN/RBV. In several exploratory studies, subjects who experienced viral breakthrough or non-response (with emergence of DAA-related associated resistance mutations) were managed by the addition of pegIFN, or pegIFN and RBV to the failing DAA combination regimen.

Section 3.0 Introduction
Sixth paragraph, first sentence previously read:

AbbVie currently has a number of DAA compounds in clinical development: ABT-450 is an NS3/4A protease inhibitor, ABT-267 (ombitasvir) is an NS5A inhibitor, and ABT-333 (dasabuvir) is a non-nucleoside NS5B polymerase inhibitor.

Has been changed to read:

AbbVie has three DAAs that were recently approved by North American and European regulatory agencies. ABT-450 (paritaprevir) is an NS3/4A protease inhibitor, ABT-267 (ombitasvir) is an NS5A inhibitor, and ABT-333 (dasabuvir) is a non-nucleoside NS5B polymerase inhibitor.

Section 5.1.3 Treatment Period (Substudy 1 and Substudy 2)
Subsection Substudy 2 – PegIFN/RBV (PR) Treatment Period
Last paragraph, first, second and third sentence previously read:

There will be interim analyses of available data at time-points determined based on the rate of enrollment into this study. Appropriate data base clean up procedures will be performed for each interim analysis. In addition, ongoing review of the data is also planned for non-efficacy (futility) assessment.

Has been changed to read:

Ongoing review of the data is also planned for non-efficacy (futility) assessment.

Table 5. Study Activities
Twentieth through twenty-fifth row previously read:

			Substudy 1 Treatment Intensification (TI) Period									Substudy 2-PegIFN/RBV Alone (PR) Treatment Period						
Activity	**Pre-SCR**	**SCR**	**TI Day 1[b]**	**TI Wk 1**	**TI Wk 2**	**TI Wk 4**	**TI Wk 8**	**TI Wk 12**	**TI Wk 16**	**TI Wk 20**	**TI Wk 24/ TI D/C[c]**	**PR Wk 2**	**PR Wk 4**	**PR Wk 8**	**PR Wk 12**	**PR Wk 24[d]**	**PR Wk 36[d]**	**PR Final/ PR D/C[d,e]**
Dispense MEMS Cap			X															
Download MEMS				X	X	X	X	X	X	X	X							
Collect MEMS Cap[l]											X							
HCV RNA Sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV Resistance Testing Sample			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DAA/ritonavir, PegIFN/RBV Assay (PK) Sample[m]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Has been changed to read:

Activity	Pre-SCR	SCR	Substudy 1 Treatment Intensification (TI) Period									Substudy 2-PegIFN/RBV Alone (PR) Treatment Period						
			TI Day 1[b]	TI Wk 1	TI Wk 2	TI Wk 4	TI Wk 8	TI Wk 12	TI Wk 16	TI Wk 20	TI Wk 24/ TI D/C[c]	PR Wk 2	PR Wk 4	PR Wk 8	PR Wk 12	PR Wk 24[d]	PR Wk 36[d]	PR Final/ PR D/C[d,e]
Dispense MEMS Cap[l]			(X)															
Download MEMS[l]				(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)							
Collect MEMS Cap[l,m]											(X)							
HCV RNA Sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV Resistance Testing Sample			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DAA/ritonavir, PegIFN/RBV Assay (PK) Sample[n]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5. Study Activities
Delete: last row

Activity	Pre-SCR	SCR	Substudy 1 Treatment Intensification (TI) Period									Substudy 2-PegIFN/RBV Alone (PR) Treatment Period						
			TI Day 1[b]	TI Wk 1	TI Wk 2	TI Wk 4	TI Wk 8	TI Wk 12	TI Wk 16	TI Wk 20	TI Wk 24/ TI D/C[c]	PR Wk 2	PR Wk 4	PR Wk 8	PR Wk 12	PR Wk 24[d]	PR Wk 36[d]	PR Final/ PR D/C[d,e]
Archive Plasma Sample			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5. Study Activities
Table note "l." and "m." previously read:

l. MEMS cap is collected at any point upon completion of Substudy 1.

m. A total of two pharmacokinetic samples will be drawn at each time-point, one plasma and one serum. The site will contact the subject approximately 2 days prior to the scheduled PK blood collection date to review the importance of proper study drug administration.

Has been changed to read:

l. Collected from subjects participating in study under original protocol and Amendments 1 – 9.

m. MEMS cap is collected at any point upon completion of Substudy 1.

n. A total of two pharmacokinetic samples will be drawn at each time-point, one plasma and one serum. The site will contact the subject approximately 2 days prior to the scheduled PK blood collection date to review the importance of proper study drug administration.

Table 7. Study Activities – Substudy 3 Post-Treatment
Last row previously read:

	Substudy 3 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/ PT D/C**
Archive Plasma Sample	X	X	X	X	X	X	X

Has been changed to read:

	Substudy 3 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/ PT D/C**
Archive Plasma Sample	X	X					X

Section 5.3.1.1 Study Procedures
Subsection MEMS Cap
Add: new first paragraph

Subjects participating in the study prior to approval of Amendment 10:

Section 5.3.1.1 Study Procedures
Subsection MEMS Cap
Add: second paragraph

Following approval of Amendment 10, all MEMS caps assigned to subjects participating in Substudy 1 will be collected at the subject's next study visit. Site personnel should download the MEMS dosing history data from the MEMS caps. MEMs caps will not be used for the remaining Substudy 1 visits.

Section 5.3.1.1 Study Procedures
Subsection Archive Plasma Sample
First sentence previously read:

An archive plasma sample will be collected at the study visits indicated in Table 5 and Table 7.

Has been changed to read:

An archive plasma sample will be collected at the study visits indicated in Table 7.

Section 5.3.2.3 Disposition of Samples
Add: new last paragraph

PK samples will be maintained by AbbVie at least until the analytical reports have been finalized but no longer than 6 months from completion of the Clinical Study Report.

Section 5.4.2 Non Efficacy (Futility) Criteria
Delete: third and fourth bullet following second paragraph

- Subsequently, for each population, after the next 20 subjects have completed 24 weeks of ABT-450/r + ABT-267 + pegIFN/RBV treatment or prematurely discontinued, the percentage of subjects meeting virologic stopping criteria will be assessed relative to the same thresholds. Again, study drug treatment will be stopped for all subjects or subjects within a population if the threshold is reached.
- Similar assessments will then continue to occur after each additional 40 subjects within a population have completed 24 weeks of ABT-450/r + ABT-267 + pegIFN/RBV treatment or prematurely discontinued.

Table 10. Dosing Schematic
Previously read:

N	Treatment	Duration
Approximately 150	ABT-450/r 200/100 mg QD + ABT-267 25 mg QD + pegIFN + RBV[a]	24 weeks
	pegIFN + RBV[a]	24 weeks[b]

Has been changed to read:

N	Treatment	Duration
Approximately 35	ABT-450/r 200/100 mg QD + ABT-267 25 mg QD + pegIFN + RBV[a]	24 weeks
	pegIFN + RBV[a]	24 weeks[b]

Section 5.5.6 Treatment Compliance
Fourth paragraph, second and third sentence previously read:

ABT 450, ritonavir and ABT-267 should not be re-dispensed to the subject. RBV bottles may be re-dispensed to the subject.

Has been changed to read:

ABT-450, ritonavir and ABT-267 and RBV should not be re-dispensed to the subject.

Section 5.5.7 Electronic Pill Monitors (MEMS Caps)
Add: new first paragraph

All subjects participating under Protocol Amendment 10 will not utilize MEMS caps to obtain dosing histories.

Section 5.5.7 Electronic Pill Monitors (MEMS Caps)
First paragraph, first sentence previously read:

All subjects will utilize a MEMS monitor (cap), manufactured by Advanced Analytical Research on Drug (AARDEX Group Ltd., Switzerland) on the bottles of ABT-450, ABT-267 throughout Substudy 1.

Has been changed to read:

Subjects enrolled in the protocol prior to the implementation of the Protocol Amendment 10 will utilize a MEMS monitor (cap), manufactured by Advanced Analytical Research on Drug (AARDEX Group Ltd., Switzerland) on the bottles of ABT-450, ABT-267 during Substudy 1.

Section 5.5.7 Electronic Pill Monitors (MEMS Caps)
First paragraph, fifth sentence previously read:

In addition, MEMS data will be the primary data used to assess PK time relative to dose.

Has been changed to read:

In addition, MEMS data may be used to assess PK time relative to dose.

Section 5.5.7 Electronic Pill Monitors (MEMS Caps)
Last paragraph, first sentence previously read:

The MEMS cap will be collected from the subject at the completion of study drug treatment during Substudy 1.

Has been changed to read:

The MEMS cap will be collected from the subject at the completion of study drug treatment during Substudy 1 or at the subject's first study visit following approval of Amendment 10 at the site.

Section 5.6.4 Selection of Doses in the Study
Subsection ABT-450/r
Second sentence previously read:

This dose is greater than or equal to the dose subjects will have received in a previous AbbVie/Abbott DAA combination study.

Has been changed to read:

This is higher than the 150 mg dose used in Phase 3 studies and the approved dose of ABT-450 for HCV GT1 infection with the interferon free 3-DAA regimen. The 200 mg dose has been evaluated in Phase 2a study (Study M11-602) with peg-IFN and ribavirin for 12 weeks; in the Phase 2a and 2b Studies M12-998 and M11-652, the 200 mg dose was administered for 12 to 24 weeks with 25 mg ABT-267 with and without ribavirin. Doses higher than 200 mg have been evaluated in Phase 2 Study M12-746 with ABT-333 and ribavirin for 12 weeks as well as in Phase 1 Study M12-187 and Study M12-221 for up to 14 days with ABT-267.

Section 5.6.4 Selection of Doses in the Study
Subsection ABT-267
Previously read:

The dose of ABT-267 in this study is 25 mg QD. Following 3 days of ABT-267 monotherapy at doses of 5 mg QD, 25 mg QD, 50 mg QD and 200 mg QD, in

Study M12-116, mean viral load decreases were 2 to 3 $\log_{10}$ IU/mL and comparable across doses. In addition, preliminary data from subjects in an ongoing Phase 2a study of ABT-267 with pegIFN and RBV (Study M12-114) suggest that the 3 doses used in that study (5 mg QD, 50 mg QD and 200 mg QD) are all well tolerated and show comparable short term antiviral activity. Preliminary resistance analysis from a short-term monotherapy trial (Study M12-116) suggests that ABT-267 doses greater than 25 mg QD do not appear to confer an advantage in suppression of commonly selected resistant variants. Modeling and simulation to predict SVR rates suggest that ABT-267 25 mg is optimal when combined with ABT-450/r. The maximum ABT-267 dose administered in this study will not exceed 25 mg daily for 24 weeks.

Has been changed to read:

The 25 mg dose of ABT-267 is the dose evaluated in Phase 3 studies and the approved dose of ABT-267 for HCV GT1 infection with the interferon free 3-DAA regimen. This was the same dose that has been evaluated in multiple Phase 2 studies (Studies M11-652, M12-998, M13-393). The dose of ABT-267 in this study is 25 mg QD. Following 3 days of ABT-267 monotherapy at doses of 1.5 mg, 5 mg QD, 25 mg QD, 50 mg QD and 200 mg QD, in Study M12 116 and Study M13-386, mean viral load decreases were 2 to 3 $\log_{10}$ IU/mL and comparable across doses. In addition, data from Phase 2a study of ABT-267 with pegIFN and RBV (Study M12-114) suggest that the 3 doses used in that study (5 mg QD, 50 mg QD and 200 mg QD) are all well tolerated and show comparable short term antiviral activity. Resistance analysis from a short-term monotherapy trial (Study M12-116) suggests that ABT-267 doses greater than 25 mg QD do not appear to confer an advantage in suppression of commonly selected resistant variants. The maximum ABT-267 dose administered in this study will not exceed 25 mg daily for 24 weeks.

Section 6.1.2 Serious Adverse Events
In-text table
Row "Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome"
Add: new second sentence

Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event.

Section 6.1.2 Serious Adverse Events
In-text table
Delete: row "Spontaneous Abortion" and "Elective Abortion"

Spontaneous Abortion	Miscarriage experienced by study subject.
Elective Abortion	Elective abortion performed on study subject.

Section 6.5 Adverse Event Reporting
Address following third paragraph previously read:

Has been changed to read:

[redacted]

Section 6.5 Adverse Event Reporting
Last paragraph previously read:

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

Has been changed to read:

In emergency situations involving study subjects when the primary Study Designated Physician (SDP) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated AbbVie SDP.

[redacted]

AbbVie 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.

Section 6.6 Pregnancy
Second paragraph, second sentence previously read:

Subjects who report a positive pregnancy test during the treatment period must be notified to stop all study medication (Section 5.4.1).

Has been changed to read:

Subjects who report a positive pregnancy test during the Treatment Period must be notified to stop RBV immediately. Administration of DAA's, including ritonavir, and Peginterferon may be continued at the investigator's discretion if the benefit of continuing therapy is felt to outweigh the risk (Section 5.4.1).

Section 6.7 Toxicity Management
First paragraph, last sentence previously read:

This table should be used in determination of the appropriate toxicity management as discussed in Section 6.7.1 and Section 6.7.2.

Has been changed to read:

This table should be used in determination of the appropriate toxicity management as discussed in Section 6.7.1 through Section 6.7.5.

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

Alternate Contact:

Has been changed to read:

Alternate Contact:

Section 8.0 Statistical Methods and Determination of Sample Size
First paragraph previously read:

There will be interim analyses of cumulative data at appropriate intervals based on enrollment in this study. For each interim analysis, appropriate data base clean up procedures will be performed. There will be no statistical adjustment employed due to these analyses as this is a single-arm, open-label trial and no trial design changes will be made as a result of these analyses.

Has been changed to read:

There will be no interim analysis. The final analysis will occur after all enrolled subjects have completed the Post-Treatment Period or prematurely discontinued from the study. Data will be locked after performing appropriate data cleaning.

Appendix B. List of Protocol Signatories
First row previously read:

Name	Title	Functional Area
[redacted]		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical

Document Approval

Study M13101 - An OL Study to Evaluate the Safety, Antiviral Activity and Pharmacokinetics of DAA Treatment in Combination with Peginterferon α-2a and Ribavirin (pegIFN/RBV) in Chronic HCV Infected Subjects Who Have Experienced Virologic Failure in a Previous AbbVie or Abbott DAA Combination Study - Amendment 10 - EudraCT 2011-005393-32 - 26Jun2015

Version: 1.0 **Date:** 30-Jun-2015 07:01:56 PM **Company ID:** 06302015-00F9F680D1E67E-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	26-Jun-2015 02:06:32 PM	Author
	26-Jun-2015 02:16:11 PM	Approver
	26-Jun-2015 03:51:08 PM	Approver
	26-Jun-2015 04:30:07 PM	Approver
	26-Jun-2015 04:41:12 PM	Approver
	30-Jun-2015 07:01:51 PM	Approver