1.0 Title Page

Clinical Study Protocol M13-576

A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy (ABT-493 and/or ABT-530) in Subjects Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection

Incorporating Administrative Change 1 and Amendments 1, 2, 2.01 (UK only), and 3

AbbVie Investigational Product:	There is no AbbVie Investigational Product administered
Date:	09 October 2017
Development Phase:	2/3
Study Design:	This is a rollover study to assess resistance and durability of response to ABT-493 and/or ABT-530 in subjects who have participated in Phase 2 or 3 clinical studies with these agents for the treatment of chronic HCV.
EudraCT Number:	2015-000452-24
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Sponsor:	AbbVie
Sponsor/Emergency Contact:	[redacted], MD Antiviral Clinical Project Team 1500 Seaport Boulevard Redwood City, CA 94063 Phone: [redacted] eFax: Fax: Mobile: 24 hour back-up number:

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	22 December 2014
Amendment 1	03 April 2015
Amendment 2	19 July 2016
Amendment 2.01 (UK Only)	19 January 2017

The purpose of this amendment is to:

- Section 1.2, Synopsis, update the phase of the study from Phase 2 to Phase 2/3 to be consistent with the rest of the document.

  Rationale: *To make the update to this page that was not made in previous version of the document.*

- Section 1.2, Synopsis – Objectives, Section 4.0 – Study Objectives, Section 5.3.1 – Clinical Laboratory Tests, Clinical Laboratory Tests Table 1, Section 5.3.3.1 – Clinical Variables: Remove collection of alpha fetoprotein.

  Rationale: *Alpha fetoprotein is an unreliable test for screening for liver disease including hepatocellular carcinoma (HCC) and is no longer recommended in the AASLD HCV guidelines (2017)[29] for this purpose.*

- Section 1.2, Synopsis, Main Inclusion: Incorporate language from Administrative Change 1 for Inclusion Criterion 3 to clarify the criterion by adding a sentence to note that subjects who have been retreated with a commercially available anti-HCV treatment are able to enroll in the study greater than 2 years after the last dose of the AbbVie DAA therapy from the previous AbbVie clinical study.

  Rationale: *The 2 year timeframe should not apply to subjects who have been retreated, for whom we will not be collecting blood samples to evaluate the persistence of resistance substitutions. The additional text clarifies the intent of Protocol Amendment 2, which allowed the enrollment of these retreated subjects. The inclusion criteria should have been amended at that time but*

was not, therefore this administrative change is necessary. The change will not have impact on the safety or well-being of subjects enrolled in the study.

- Section 5.2.1, Inclusion Criteria: Incorporate clarification language from Administrative Change 1 for Inclusion Criterion 3 – Clarify the criterion by adding a sentence to note that subjects who have been retreated with a commercially available anti-HCV treatment are able to enroll in the study greater than 2 years after the last dose of the AbbVie DAA therapy from the previous AbbVie clinical study.

  Rationale: *The 2 year timeframe should not apply to subjects who have been retreated, for whom we will not be collecting blood samples to evaluate the persistence of resistance substitutions. The additional text clarifies the intent of Protocol Amendment 2, which allowed the enrollment of these retreated subjects. The inclusion criteria should have been amended at that time but was not, therefore this administrative change is necessary. The change will not have impact on the safety or well-being of subjects enrolled in the study.*

- Section 5.3.1.1, Collection of Liver Diagnostic Results: Screening for Hepatocellular Carcinoma (HCC) by liver ultrasound has been added to the final study visit for cirrhotic subjects, in order to screen them for development of HCC as part of long-term follow-up.

  Rationale: Subjects with cirrhosis may be at-risk for developing HCC, and therefore will be screened for HCC by liver ultrasound testing at the final visit.

- Section 5.3.4, Safety Variables, Incorporate language from Amendment 2.01 (UK only): Revise wording to clarify that the investigator is responsible for collecting Serious Adverse Event data.

  Rationale: *To clarify the language to say that the investigator collects Serious Adverse Event data. The previous language was redundant.*

- Section 6.0, Adverse Events, Incorporate language from Amendment 2.01 (UK only): Revise wording to clarify that the investigator is responsible for collecting Serious Adverse Event data.

  Rationale: *To clarify the language to say that the investigator collects Serious Adverse Event data. The previous language was redundant.*

- Section 6.5, Adverse Event Reporting, Incorporate language from Amendment 2.01 (UK only): Add language regarding reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR).

  Rationale: *To clarify that AbbVie is responsible for the reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR).*

- Section 7.0, Protocol Deviations, Incorporate language from Amendment 2.01 (UK only): Clarify language to state that the investigator is responsible for reporting protocol deviations to the Independent Ethics Committee (IEC)/Independent Review Board (IRB) and to AbbVie.

  Rationale: *To clarify to whom investigators should report protocol deviations.*

- Section 9.0, Ethics, Incorporate language from Amendment 2.01 (UK only): Clarify that all protocol amendments must be approved by the Independent Ethics Committee (IEC)/Independent Review Board (IRB as well as Regulatory Authority(ies), if required by local regulations, and to clarify that the Sponsor is responsible for reporting Suspected Unexpected Serious Adverse Reactions.

  Rationale: *To clarify requirements for approval of protocol amendments and reporting of Suspected Unexpected Serious Adverse Reactions.*

- Section 13.0, Completion of the Study, Incorporate language from Amendment 2.01 (UK only): Clarify that the Clinical Study report will be provided by AbbVie to the Regulatory Authority(ies), if required by local regulations.

  Rationale: *To clarify the responsibility of providing the Clinical Study Report to Regulatory Authority(ies), if required by local regulations.*

- Appendix C, Study Activities A and B, Incorporate language from Amendment 2.01 (UK only): Clarify the need for collection of total bilirubin at Month 12 and Month 18 for calculating Child-Pugh in cirrhotic subjects.

  Rationale: *To clarify that total bilirubin is required at Month 12 and Month 18 for calculation of the Child-Pugh for cirrhotic subjects.*

- Appendix C, Study Activities A and B: Screening for Hepatocellular Carcinoma (HCC) by liver ultrasound has been added to the final study visit

for cirrhotic subjects only in order to screen them for development of HCC as part of long-term follow-up.

Rationale: *Subjects with cirrhosis may be at-risk for developing HCC, and therefore will be screened for HCC by liver ultrasound testing at the final visit.*

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M13-576
Name of Study Drug: Not applicable. There is no AbbVie Investigational Product administered.	**Phase of Development:** 2/3
Name of Active Ingredient: There is no AbbVie Investigational Product administered.	**Date of Protocol Synopsis:** 09 October 2017
Protocol Title: A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy (ABT-493 and/or ABT-530) in Subjects Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection	
Objectives: The primary objectives of this study are as follows: • Assess the durability of response for subjects who achieved SVR_{12} with a regimen including ABT-493 and/or ABT-530. • Assess the emergence and persistence of specific HCV amino acid variants associated with drug resistance in subjects who experience virologic failure. The secondary objectives of the study are as follows: • Summarize medical events related to progression of liver disease including: o Events of hepatic decompensation (per Section 5.3.1.1), o Change in Child-Pugh classification, o Liver transplantation, o Hepatocellular carcinoma, o Death. • Summarize results of the following laboratory tests and scores: FibroTest, APRI, IP-10, alpha fetoprotein (if collected under a previous protocol version), FibroScan, and liver biopsy.	
Investigators: Multicenter	
Study Sites: Approximately 35 sites	
Study Population: This Phase 2/3, multicenter study will be conducted in subjects who received at least one dose of an ABT-493- and/or ABT-530-containing regimen at any dose level in a prior AbbVie Phase 2 or 3 study for the treatment of chronic HCV and elect to enroll in this study.	
Number of Subjects to be Enrolled: Approximately 400. An attempt will be made to enroll all virologic failures who will not receive immediate treatment with a regimen containing ABT-493/ABT-530.	

Methodology:

At the Day 1 Visit, subjects will provide written (signed and dated) informed consent prior to any study specific procedures being performed. The investigator will evaluate whether the subject meets all of the eligibility criteria prior to enrollment in this rollover study.

Subjects will have completed the post-treatment period of the prior AbbVie HCV clinical study. All subjects will be followed for approximately 3 years following their last dose of DAA in the previous AbbVie HCV clinical study, with the exception of re-treated subjects who will be followed through post-treatment Week 12. The 3 years will be inclusive of any post-treatment period in the prior study, as well as any gap between the end of the prior study and enrollment into this study.

Subjects who are not re-treated will return to the study site for their scheduled visits on an outpatient basis at Month 3, Month 6 and every 6 months thereafter for approximately 3 years after the last dose of DAA in the previous clinical study. Subjects with virologic failure who receive re-treatment will only have one additional outpatient visit subsequent to beginning re-treatment, at post-treatment Week 12 to assess the SVR_{12} result, and then they will discontinue from the study.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. The subject has received at least one dose of an ABT-493- and/or ABT-530-containing regimen in a prior AbbVie HCV Phase 2 or 3 study which has been conducted under a US IND (see Appendix D for list of eligible prior studies).
2. The interval between the last dose of the AbbVie DAA therapy from the previous clinical study and enrollment in Study M13-576 must be no longer than 2 years for subjects who have not been retreated. Subjects who have been treated with a commercially-available anti-HCV treatment may be enrolled greater than 2 years after the last dose of the AbbVie DAA therapy from the previous clinical study.
3. The subject must voluntarily sign and date the informed consent form approved by an Independent Review Board or Ethics Committee prior to the initiation of any study-specific procedures.
4. Subject completed the post-treatment period of an eligible prior study.

Main Exclusion:

1. The investigator considers the subject unsuitable for the study for any reasons (e.g., failure to comply with study procedures in the prior AbbVie clinical study).
2. Receipt of any investigational HCV antiviral treatment after receiving ABT-493 and/or ABT-530 in the prior study.
3. Subjects who experienced non-virologic treatment failures due to premature discontinuation of study drug in the prior study of ABT-493/ABT-530.
4. Participation in AbbVie's Study M15-942 protocol for re-treatment for virologic failures in the prior Phase 2 or 3 study.

Investigational Products: There is no AbbVie Investigational Product administered.

Criteria for Evaluation:

Efficacy:

Virologic response will be assessed by HCV RNA in $\log_{10}$ IU/mL at various time points.

Criteria for Evaluation (Continued):

Resistance:

The persistence of amino acid variants associated with drug resistance will be assessed by population, and/or deep sequencing at the Day 1 Visit, and at various subsequent time points, as appropriate, for a period of up to 3 years after the subject's last dose of DAA therapy in the prior AbbVie clinical study.

Liver Disease Progression:

Liver Disease progression will be assessed by laboratory test results (FibroTest and APRI) and the recording of medical events related to progression of liver disease including, events of hepatic decompensation (per Section 5.3.1.1), change in Child-Pugh classification, liver transplantation, hepatocellular carcinoma, death.

Safety:

Only serious adverse events related to study procedures or those considered by the investigator to be reasonably related to exposure to ABT-530 and/or ABT-493 in a prior study will be assessed.

Statistical Methods:

Efficacy:

The primary efficacy endpoints are the percentage of subjects who maintain a sustained virologic response and the percentage of subjects who relapse or have new HCV infection at any time up to the last follow-up in this study out of subjects who achieved SVR_{12} in the previous study and enroll in this study. The summary will be separate for subjects who have probable relapse as distinguished from subjects who have probable new HCV infection based on DNA sequence phylogenetic analysis of HCV drug target genes. In addition, the time to relapse or new infection from the end of DAA treatment for subjects who achieved HCV RNA < LLOQ at the end of treatment in the previous study and from SVR_{12} time point for the subset of subjects who achieved SVR_{12} in the previous study will be displayed graphically using Kaplan-Meier curves.

Resistance:

The variants at each amino acid position by population and/or deep sequencing at available post-baseline time points compared to baseline and prototypic reference standard sequences will be summarized by DAA target genes and accompanying listings will be provided.

Safety:

Serious adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class (SOC) and preferred term (PT). A summary of medical events related to the progression of liver disease and shifts in laboratory measurements will be provided.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse event
DAA	Direct-acting antiviral agent
DNA	Deoxyribonucleic acid
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HCV	Hepatitis C virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP-10	Interferon gamma-induced protein 10
IRB	Institutional Review Board
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PegIFN	Pegylated-interferon
RBV	Ribavirin
RNA	Ribonucleic acid
SAE	Serious adverse event
SVR	Sustained virologic response

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] There are 6 major HCV genotypes, with genotype 1 (GT1) being most prevalent worldwide, including in the United States. HCV genotypes 2 (GT2) and 3 (GT3) infections are more common in Latin America (5% to 30%), Europe (20% to 40%) and Asia (30% to 45%).[2,3] Recent data suggest that HCV GT3 causes 12% of HCV infections in the United States.[4] HCV GT4 is commonly found in parts of Africa and the Middle East, particularly in Egypt, GT5 is primarily found in South Africa, and GT6 is primarily found in south-east Asia.[5] Depending on various risk factors, between 10% and 40% of patients with chronic HCV infection will develop cirrhosis.[6] Death related to the complications of cirrhosis may occur at an incidence of approximately 4% per year; hepatocellular carcinoma occurs in this population at an estimated incidence of 1% to 5% per year.[6] Patients diagnosed with hepatocellular carcinoma have a 33% probability of death during the first year.[6] Successful treatment of HCV has been shown to significantly reduce the risk of disease progression and related mortality as well as the development of hepatocellular carcinoma.[7,8]

Since the identification of HCV in the early 1990's, the mainstay of treatment, until the recent development of direct acting antivirals (DAAs), had been interferon alpha (IFN). Despite multiple advances in treatment with IFN, including co-administration with ribavirin (RBV), development of pegylated interferon (pegIFN), suboptimal efficacy in many populations and poor safety and tolerability limit widespread use of these therapies for HCV-infected patients.

Further advances in treatment for HCV GT1 infection have been the addition of DAAs, such as an HCV nonstructural (NS) 3/4A protease inhibitor (PI) (telaprevir, boceprevir, or simeprevir), the HCV NS5A inhibitor daclatasvir, or the HCV nucleotide NS 5B RNA polymerase inhibitor (sofosbuvir) to pegIFN/RBV (PR). This latter regimen demonstrated increased sustained virologic response (SVR) rates in PR treatment-naïve (TN) HCV GT1-infected patients from 55% to 90%; however, response rates are lower in

a number of subpopulations including blacks, Hispanics, PR-experienced patients, and cirrhotics.[9-14] Many of the current approved treatments for HCV GT1 include use of PR, which is associated with considerable, often treatment limiting toxicities (fever, chills, rigor, fatigue, depression, and anemia). The addition of first generation PIs to a PR regimen has resulted in additional toxicities (anorectal discomfort) and augmented others (anemia, rash).[15,16]

As of October 2014, an IFN- and RBV-free combination of SOF plus NS5A inhibitor ledipasvir has been approved in the US for the treatment of chronic HCV GT1 infection, including an option of 8-week therapy in non-cirrhotic patients with HCV viral load < 6 million at baseline.[17] As of late December 2014, an IFN-free combination of ombitasvir (NS5A inhibitor), paritaprevir (protease inhibitor), dasabuvir (non-nucleoside NS5b polymerase inhibitor) and ritonavir, given with or without RBV, has been approved for the treatment of chronic HCV GT1 infection.[18] These newest pegIFN free treatments provide a significant advance over all prior HCV treatment options.

Additionally, subjects that have failed DAAs with or without PR are likely to have mutant HCV variants and therefore have limited future treatment options. Current data on DAA resistance are generally limited to clinical trials of telaprevir, boceprevir, simeprevir, and the NS5A inhibitor daclatasvir. In the telaprevir Phase 3 clinical trials, treatment-emergent NS3 resistance substitutions emerged in the majority of isolates from subjects who did not achieve SVR_{12}. Further, these resistance-associated substitutions persisted following treatment failure.[19] HCV replicon variants with patient-derived telapravir-associated resistance showed a wide variation of in-vitro resistance to telapravir, depending on the amino-acid substitutions involved. Generally, the in vitro replication capacity of telapravir-resistant variants was lower than that of wild-type virus[20] suggesting reduced viral fitness. For subjects treated with daclatasvir-containing regimens, daclatasvir resistance-associated NS5A substitutions emerged in almost all subjects who failed these treatments while some of these substitutions were detected in a small number of baseline samples.[21-23] Replicons with these substitutions demonstrated various level of resistance to daclatasvir in vitro. Many of the NS5A resistance-associated

substitutions also persisted after treatment.[22,23] Emergence of resistance to DAAs may be even more common in the clinical setting where adherence may be lower than what has been observed in the clinical trials.

The aim of treatment of chronic HCV infection is to achieve a sustained virologic response (SVR). HCV infection is cured in more than 99% of patients who achieve an undetectable HCV RNA 24 weeks after treatment completion.[6] The validity of using undetectable HCV RNA at 12 weeks after completion of therapy (SVR_{12}) has been accepted by regulatory authorities in the U.S. and Europe given that the concordance with SVR_{24} approaches 99%.[6] The long-term durability of SVR has been demonstrated among subjects with HCV infection with multiple different genotypes treated with IFN-based regimens (i.e., IFN alone or IFN plus RBV). For example, among the first 103 patients treated at the U.S. National Institutes of Health, 100 patients, or 97%, maintained SVR at a median follow-up of 7.5 years.[24]

Although achievement of an SVR has been associated with laboratory and histological improvements in chronic HCV,[25] the SVR endpoint is a surrogate for the ultimate aim of therapy, which is prevention of progression to cirrhosis, end-stage liver disease, hepatocellular carcinoma, and death from liver disease.[24] These "hard" clinical endpoints, however, generally take years to decades to occur, making them impractical and unethical primary endpoints for clinical trials of HCV therapies. Thus the relationship between SVR to clinical outcomes must be evaluated through long-term follow-up studies.

In contrast to what is known from studies from IFN-based regimens, little data is available to date for SVR and long-term clinical outcomes for subjects who have been treated with DAA plus IFN and RBV, or IFN and RBV-free all DAA regimens. Such studies are needed in order to demonstrate the long-term benefits of DAAs, whether given with IFN and/or RBV, or given as all-DAA regimens.

AbbVie is currently developing 2 "next generation" DAA drugs for use together or in combination with a third DAA or Ribavirin. AbbVie's next generation DAAs, including ABT-493, an NS3/4A protease inhibitor and ABT-530, an NS5A inhibitor are denoted

"next generation" compounds because each demonstrated potent antiviral activity against all major HCV GTs in vitro with no or little loss of potency against known common single resistance mutants.

ABT-493

ABT-493, (3aR,7S,10S,12R,21E,24aR)-7-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl] carbamoyl}cyclopropyl]-20,20-difluoro-5,8-dioxo-2,3,3a,5,6,7,8,11,12,20,23,24a-dodecahydro-1H,10H-9,12-methanocyclopenta[18,19][1,10,17,3,6]trioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide, is an NS3/4A PI with potent, pangenotypic activity and a high barrier to resistance with activity against common variants that emerge following exposure to first generation PIs. In the HCV subgenomic replicon assay, ABT-493 is active against replicons with NS3 from GT1, 2, 3, 4, and 6. ABT-493 activity against GT5 NS3 is unknown because a replicon with GT5 NS3 is not available. Based on findings that each of 5 well characterized HCV PIs, including 2 linear and 3 macrocyclic PIs, demonstrated similar activity against GT2a, 5a, and 6a NS3 protease,[26] it is predicted ABT-493 would inhibit NS3 protease of GT5a with activity similar to that of GT2a and 6a. In resistant colony selection experiments with chimeric replicons containing GT1-4 or GT6 NS3, ABT-493 selected fewer resistant colonies than ABT-450 in most replicons, indicating overall it has a higher genetic barrier to resistance than ABT-450 in vitro. Furthermore, in GT1-4 replicons, the overall resistance profile of ABT-493, which selects mostly A156 variants, is different from that of ABT-450, which selects predominantly R155 and D/Q168 variants. ABT-493 maintains most of its activity in vitro against common HCV GT1-4 R155 or D/Q168 variants that are resistant to ABT-450. AbbVie is developing ABT-493 to be used in combination with other AbbVie DAAs for the treatment of chronic HCV infection.

In Phase 2a Study M13-595, preliminary results showed the ABT-493 exposures in subjects with HCV-infection were 2-fold of healthy subjects following 100, 200 or 700 mg QD dosing and 4.9-fold of healthy subjects following 400 mg QD dosing. ABT-493 exposures following 200 mg QD dosing in cirrhotic patients were approximately 5- to 6-fold of the exposure in non-cirrhotic HCV-infected patients.

Antiviral activity of ABT-493 monotherapy for 3 days was evaluated in treatment-naïve HCV genotype 1-infected patients over a range of doses up to 700 mg QD of ABT-493. Preliminary data show that the 200 mg dose of ABT-493 provides strong anti-viral activity (e.g., greater than 3 $\log_{10}$ decline of HCV plasma RNA in all available patients) and was selected as ABT-493 dose to be further evaluated in this study.

In general ABT-493 has been well-tolerated when administered to over 320 healthy volunteers and 49 HCV GT1-infected subjects.

Preliminary data are suggestive of possible dose/responsive transaminase and bilirubin elevations. ABT-493 doses of 700 mg and 1200 mg have been associated with few incidences of asymptomatic Grade 2 (n = 1) and Grade 3 (n = 2) ALT elevations in healthy volunteers. One subject experienced a Grade 3 ALT elevation at the 1200 mg dose level (Study M13-586) which resulted in treatment discontinuation, and another subject experienced a Grade 3 ALT elevation at the 700 mg dose level in Study M14-066 which resolved after dosing was concluded without intervention. Based on the integrated pharmacokinetic exposures of ABT-493 and safety data in Phase 1 studies, a shallow trend was observed for ALT elevation when ABT-493 AUC was higher than 60000 ng•h/mL, which is approximately 64× higher than projected mean AUC exposures at ABT-493 200 mg in non-cirrhotics and 12× higher – for cirrhotics.

Bilirubin elevations (primarily indirect hyperbilirubinemia) initiated independently and did not mirror the course of ALT elevations. Observed few total bilirubin elevations were asymptomatic and likely contributed by the known ABT-493 inhibition of organic anion transporter polypeptides, including OATP1B1, which is the transporter responsible for clearing indirect bilirubin from blood. Based on integrated pharmacokinetic exposures of ABT-493 and safety data in Phase 1 studies, a shallow trend was observed for bilirubin elevations when ABT-493 AUC was higher than 25,000 ng•h/mL, which is approximately 27× higher than projected mean AUC exposures at ABT-493 200 mg for non-cirrhotics and 5× higher – for cirrhotics. All ALT, AST and bilirubin elevations improved/normalized following completion or discontinuation (n = 1) of ABT-493 dosing.

In summary, ABT-493 is a potent, pangenotypic NS3/4A PI with potential for treatment of chronic HCV infection. A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[27]

ABT-530

ABT-530, Methyl {(2S,3R)-1-[(2S)-2-{6-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(5-fluoro-2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl] pyrrolidin-2-yl}-1H-benzimidazol-6-yl) pyrrolidin-2-yl]-5-fluoro-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate, is an NS5A inhibitor with pangenotypic activity and a high barrier to resistance. ABT-530 is highly active against HCV replicons containing wild-type HCV NS5A from GT1, 2, 3, 4, 5, and 6. ABT-530 retains activity against all common single nucleotide change resistance associated variants in NS5A in all GTs. ABT-530 is > 100-fold more active than the first generation NS5A inhibitors (ombitasvir, daclatasvir, and ledipasvir) against key resistance-associated variants selected by these inhibitors in the clinic at NS5A amino acid positions 28, 30, 31, and 93. ABT-530 selected very few or no resistant colonies in HCV replicons with NS5A from GTs 1 – 6 at 10-fold or 100-fold over its EC_{50} value indicating it has a high genetic barrier to resistance in vitro. Measured in this way, the genetic barrier to resistance for ABT-530 is higher than ombitasvir across all GTs. AbbVie is developing ABT-530 to be used in combination with other AbbVie DAAs for the treatment of chronic HCV infection.

Pharmacokinetics of ABT-530 has been evaluated up to 600 mg QD. ABT-530 reached a T_{max} around 3 to 5 hours, with an elimination half-life of 12 to 17 hours. ABT-530 exposures increased in a greater than dose-proportional manner across the 1.5 mg to 120 mg dose range and approximately dose proportionally from the 120 mg to 600 mg single doses. The mean percentages of the ABT-530 dose excreted as unchanged drug in urine were less than 0.004%, indicating minimum renal elimination for ABT-530.

In Phase 2a Study M13-595, preliminary results showed same dose ABT-530 exposures in subjects with HCV infection were similar to those observed in healthy subjects.

Antiviral potency of ABT-530 monotherapy for 3 days in HCV GT1-infected patients was evaluated over a range of doses up to 400 mg QD of ABT-530. Preliminary data show that the 40 mg and 120 mg doses of ABT-530 provide similar strong anti-viral potency (e.g., greater than 3 $\log_{10}$ decline of HCV plasma RNA in all available patients) and were selected as ABT-530 doses to be further evaluated in Phase 2 studies.

In general ABT-530 has been well tolerated when administered to over 320 healthy volunteers and 40 HCV GT1-infected subjects. To date, most AEs reported were Grade 1 in severity, demonstrated no pattern or resulted in study drug discontinuation. Additionally, no pattern of laboratory abnormalities has been observed.

In summary, ABT-530 has the potential to address an unmet need in the treatment of chronic HCV infection. A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[28]

ABT-493 and ABT-530

Additive or synergistic in vitro anti-HCV activity has been demonstrated with the combination of ABT-493 and ABT-530.

When ABT-493 was given in combination with ABT-530 in healthy volunteers, preliminary results showed ABT-493 exposures were not significantly changed when co-administered with ABT-530 (≤ 31% difference); however, the exposure of ABT-530 increased in an ABT-493-dose-dependent manner (from 1.5-fold at 100 mg ABT-493 up to 3- to 4-fold at 400 mg ABT-493).

Drug-drug interaction (DDI) studies have also been conducted to evaluate the co-administration effects of ABT-493 and ABT-530 on substrates of P-gp, BCRP, OATP1B1/1B3, OAT3 and CYP3A4. Studies are summarized in the investigator brochures.[27,28]

The safety profile of co-administered ABT-493 and ABT-530 in healthy volunteers is consistent with that of the individual compounds, also as described in the investigator brochures.[27,28]

3.1 Differences Statement

This is the first study evaluating the long-term durability of SVR, persistence of DAA resistance, and clinical outcomes for subjects who received AbbVie Next Generation DAA regimen compounds (ABT-493 and/or ABT-530) in efficacy trials. In addition, the duration of follow-up in this study is significantly longer than the follow-up duration for current and planned phase 2 and 3 studies for ABT-493 and ABT-530.

3.2 Benefits and Risks

There are no expected direct benefits for subjects who enroll in this study, except that early identification of relapse may allow initiation of other treatment. Subjects may experience discomfort or inconvenience related to study procedures.

4.0 Study Objectives

The primary objectives of this study are as follows:

- Assess the durability of response for subjects who achieved SVR_{12} with a regimen including ABT-493 and/or ABT-530.
- Assess the persistence of specific HCV amino acid variants associated with drug resistance in subjects who experienced virologic failure.

The secondary objectives of the study are as follows:

- Summarize medical events related to progression of liver disease including but not limited to: events of hepatic decompensation, change in Child-Pugh classification, liver transplantation, hepatocellular carcinoma and/or, death.
- Summarize results of the following laboratory tests and scores: FibroTest, APRI, IP-10, alpha fetoprotein (if collected under a previous protocol version), FibroScan, and liver biopsy.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This Phase 2/3, multicenter study will be offered to subjects who received at least one dose of an ABT-493- and/or ABT-530-containing regimen at any dose level in an eligible prior AbbVie Phase 2 or 3 study for the treatment of chronic HCV and elect to enroll in this study. The subject must have completed the follow-up period of the prior eligible AbbVie study.

It is anticipated that approximately 400 subjects will participate in this study. An attempt will be made to enroll all virologic failures who will not receive immediate re-treatment with a regimen containing ABT-493/ABT-530.

At the Day 1 Visit, subjects will provide written (signed and dated) informed consent prior to any study specific procedures being performed. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 prior to enrollment in this rollover study.

Subjects will be followed for a total of approximately 3 years after their last dose of DAA in the previous HCV clinical study. The 3 years will be inclusive of any post-treatment period in the prior study, as well as any gaps between the end of the prior study and enrollment in this study. Subjects must complete the full post-treatment period of the prior study before enrolling into Study M13-576. Once a subject has reached 3 years post-DAA therapy, participation in this study will be completed, except for subjects enrolled with virologic failure who receive re-treatment with a HCV antiviral regimen other than investigational ABT-493/ABT-530. Subjects who are retreated with investigational ABT-493/ABT-530 are not allowed in this study. Subjects who are re-treated with HCV regimens other than investigational ABT-493/ABT-530 will have only one further assessment for treatment outcome 12 weeks after stopping that therapy or earlier if already known (in cases of treatment failure). (See Appendix C, Table B, Study Activities for Virologic Failures Receiving Re-Treatment).

Subjects who have not been re-treated will return to the study site for their scheduled visits on an outpatient basis as described in Section 5.3.1 until approximately 3 years after their last dose of DAA in the previous clinical study (See Appendix C, Table A, Study Activities for SVR and Non-SVR Subjects Not Receiving Re-Treatment).

Some of the study visits and visit activities (including but not limited to clinical laboratory tests and concomitant medication assessment) may be optionally conducted in the home or non-hospital/clinic environment as arranged by the Investigator with the agreement of the subject, and with the prior approval of the sponsor.

5.2 Selection of Study Population

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

5.2.1 Inclusion Criteria

A subject will be eligible for study participation if he or she meets the following criteria:

1. The subject is male or female 18 years of age or older.
2. The subject has received at least one dose of an ABT-493- and/or ABT-530 containing regimen in a prior AbbVie HCV Phase 2 or 3 study (see Appendix D for list of eligible prior studies).
3. The interval between the last dose of the AbbVie DAA therapy from the previous clinical study and enrollment in Study M13-576 must be no longer than 2 years for subjects who have not been retreated. Subjects who have been treated with a commercially-available anti-HCV treatment may be enrolled greater than 2 years after the last dose of the AbbVie DAA therapy from the previous clinical study.
4. The subject must voluntarily sign and date the informed consent form approved by an Independent Review Board or Ethics Committee prior to the initiation of any study-specific procedures.
5. Subject completed the post-treatment period of an eligible prior study.

Rationale for Inclusion Criteria

1, 2, 3 and 5	To select the appropriate subject population for evaluation
4	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

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

1. The investigator considers the subject unsuitable for the study for any reasons (e.g., failure to comply with study procedures in the prior AbbVie clinical study).
2. Receipt of any investigational HCV antiviral treatment after receiving ABT-493 and/or ABT-530 in the prior study.
3. Subjects who experienced non-virologic treatment failures due to premature discontinuation of study drug in the prior study of ABT-493/ABT-530.
4. Participation in AbbVie's Study M15-942 for re-treatment for virologic failures following the prior Phase 2 or 3 study.

Rationale for Exclusion Criteria

1 and 2	To ensure safety of the subjects throughout the study
3 and 4	To select the appropriate subject population for evaluation

5.2.3 Prior and Concomitant Therapy

The HCV drug treatment regimen and its duration given as a part of the subject's participation in the prior AbbVie HCV study, as well as all other past HCV treatment regimens and their durations received by the subject, will be recorded in the eCRF. Commercially available prescription medications for the treatment of HCV therapy, including regimens containing commercially available glecaprevir/pibrentasvir (GLE/PIB,

investigationally known as ABT-493/ABT-530), initiated after the completion of a subject's participation in the previous clinical study (either prior to or during participation in this study) are permitted, and the regimen received and duration will be recorded in the eCRF. Subjects enrolled with virologic failure who undergo re-treatment with a HCV antiviral regimen not containing investigational ABT-493/ABT-530 will be followed until completing the post-treatment Week 12 visit after receiving their re-treatment regimen, after which they will discontinue from the study. If a subject with virologic failure is enrolled into this study and later enrolls in the AbbVie Study M15-942, such subjects will discontinue from Study M13-576.

The use of investigational medications is not allowed during participation in this study. Subjects who are enrolled in the Study M13-576 and who take an investigational medicine as a participant in a separate trial will be required to discontinue participation in the Study M13-576.

Information regarding medication or vaccine use (including over-the-counter medications, vitamins, and/or herbal supplements) will not be collected in this study with the exception of:

- Prescription medications taken for the treatment of HCV since the completion or discontinuation of the previous clinical study (either prior to or during this study).
- Any medications taken for treatment of an SAE as defined in Section 6.0.

This information will be collected at each study visit and will be recorded in the electronic case report form (eCRF). The medication name along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency will be recorded.

The AbbVie Therapeutic Area Medical Director should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.3 Efficacy and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described in this protocol are summarized in Appendix C.

5.3.1.1 Study Procedures

Informed Consent

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

Medical History Relating to Liver Disease or HCV Infection

Documentation of any significant changes in the medical history related to liver disease and/or HCV infection that are considered to be clinically significant by the investigator and occur since the completion of the prior AbbVie clinical study will be collected at the Day 1 Visit and recorded on the appropriate Medical Events eCRF for all subjects, except for those subjects entering the study on a re-treatment regimen. For subjects entering the study on a re-treatment regimen, this information will be collected for changes that occurred since the prior AbbVie clinical study but before the start of the re-treatment regimen only. Significant events related to liver disease progression include the development of cirrhosis, events indicative of hepatic decompensation, (including: variceal bleeding, new ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepato-renal syndrome, hepatic hydrothorax or other evidence of hepatic decompensation considered to be significant by the investigator), change in the Child-Pugh category (e.g., change from Child-Pugh Class A to Child-Pugh Class B), the occurrence of hepatocellular carcinoma and/or liver transplantation. See Appendix E for details of Child-Pugh score and classification. In addition, history of past HCV drug treatment during the prior study and before the prior study will be collected at the Day 1 Visit.

Recording Medical Events Related to Liver Disease, HCV Infection or the Event of Death

Any events (i.e., diagnoses) related to liver disease progression and/or HCV infection that are considered to be clinically significant by the investigator and begin or worsen after Day 1 will be captured on the appropriate Medical Events eCRF until the end of the study or initiation of re-treatment for HCV (if applicable). Significant events related to liver disease progression include the development of cirrhosis, events indicative of hepatic decompensation, (including: variceal bleeding, new ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepato-renal syndrome, hepatic hydrothorax or other evidence of hepatic decompensation considered to be significant by the investigator), change in the Child-Pugh category (e.g., change from Child-Pugh Class A to Child-Pugh Class B), the occurrence of hepatocellular carcinoma, liver transplantation and/or death.

Collection of Liver Diagnostic Results

Any results from liver diagnostic testing performed outside of the study (i.e., FibroScan, Liver U/S, and/or Liver Biopsy) will be collected at the study visits indicated in Appendix C for all subjects, until the end of the study or initiation of re-treatment for HCV (if applicable).

Hepatocellular Carcinoma Screening: Liver Ultrasound

HCC screening will be required as a protocol-specified study procedure only at the Final visit, as indicated in Appendix C, for subjects with cirrhosis only. At any other time during the study, HCC screening should be performed according to standard of care.

At the Final visit, subjects with cirrhosis will be required to perform a liver ultrasound to screen for HCC, unless the subject has a liver ultrasound, CT or MRI performed for HCC screening within 3 months prior to that visit, in which case the result of that US, CT or MRI will be used as the result for the Study Visit assessment. A positive ultrasound result suspicious of HCC will be confirmed with CT scan or MRI. Alternate methods of screening for HCC (i.e., MRI or CT) at a study visit should be discussed with the TA MD.

Clinical Laboratory Tests

Samples will be obtained for the clinical laboratory tests, including FibroTest and APRI, IP-10, and quantitative HCV RNA PCR, INR and serum Albumin at the visits specified in Appendix C for all subjects, until the end of the study or initiation of re-treatment for HCV (if applicable).

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

Sites should refer to the laboratory manual provided by the central laboratory, AbbVie, or its designee for instructions regarding the collection, processing, and shipping of all laboratory samples. The certified laboratory chosen for this study is Covance. Depending on the location of the study site, samples will be sent initially to one of the following addresses, where the specimen will be analyzed or sent to a different location for analysis or storage:

Covance
8211 SciCor Drive
Indianapolis, IN 46214 USA

Covance
7 rue Marcinhes
1217 Geneva
Meyrin Switzerland

Covance
1 International Business Park
#05-12A/B The Synergy
Singapore 609917

Table 1. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Additional Tests
Platelet count[a,c]	Total bilirubin[b] GGT[b] Alpha2-macroglobulin[b] Aspartate aminotransferase (AST)[a] Alanine aminotransferase (ALT) Haptoglobin[b] Apolipoprotein A1[b]	IP-10 HCV-RNA INR Serum Albumin

a. Performed for APRI.

b. Performed for FibroTest and Child-Pugh assessment.

c. Platelet count may be done as part of complete blood count (cbc).

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

A plasma sample for IP-10 testing will be collected at the study visits indicated in Appendix C for all subjects, until the end of the study or initiation of re-treatment for HCV (if applicable).

HCV RNA Levels

A plasma sample for HCV RNA levels will be collected as indicated in Appendix C until the end of the study or initiation of re-treatment for HCV (if applicable). Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. For this assay, the lower limit of quantification (LLOQ) is 15 IU/mL for all HCV genotypes.

If a subject's HCV RNA level changes from < LLOQ to ≥ LLOQ during the study, confirmatory testing should be completed as soon as possible but no later than 2 weeks after the study visit corresponding with the possible HCV RNA relapse.

HCV Resistance Testing Sample

A plasma sample for HCV resistance testing will be collected at the study visits, indicated in Appendix C for all subjects, until the end of the study or initiation of re-treatment for HCV (if applicable).

Archive Plasma Sample

An archive plasma sample should be collected at the study visits, indicated in Appendix C for all subjects, until the end of the study or initiation of re-treatment for HCV (if applicable). Archive plasma samples are being collected for possible additional analyses, including but not limited to, viral load, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by AbbVie.

Documentation of Medications for the Treatment of HCV or Treatment of an SAE

All prescription medications taken for the treatment of HCV since the completion of the previous study (either prior to or during this study) or any medications taken for the treatment of an SAE related to study procedures in this study or reasonably related to exposure to ABT-493 and/or ABT-530 in the prior study will be recorded in the subject's source documentation at each visit beginning with the Day 1 Visit and captured on the appropriate eCRF.

5.3.2 Efficacy Variables

The primary efficacy outcome variables are:

1. The percentage of subjects who maintain SVR out of those who achieved SVR_{12} in the prior study with an ABT-493- and/or ABT-530-containing regimen.
2. The percentage of subjects who relapse or have new HCV infection at any time up to the last follow-up in this study out of subjects who achieved SVR_{12} in the previous study and enroll in this study.

5.3.3 Resistance Variables

The primary resistance outcome variables are: The persistence of resistance-associated amino acid variants will be assessed by population and/or deep sequencing for a period up to 3 years after the subject's last dose of DAA therapy in the prior AbbVie clinical study.

5.3.3.1 Clinical Variables

Clinical Variables

The Clinical variables (secondary outcomes) are:

- Variables related to liver disease progression will be monitored and summarized as described in the study procedures (Section 5.3.1.1), including but not limited to:
  - Events of hepatic decompensation (as described in Section 5.3.1.1),
  - Change in Child-Pugh classification,
  - Liver transplantation,
  - Hepatocellular carcinoma,
  - Death.

Results of the following laboratory tests and studies will be summarized: IP-10, FibroTest, APRI, alpha fetoprotein, (if collected under a previous protocol version) FibroScan, liver biopsy. FibroScan and liver biopsy will not be performed as study procedures, but any available results from source documents will be summarized.

5.3.4 Safety Variables

Only serious adverse events related to study procedures or those that meet seriousness criteria outlined in Section 6.0 and are considered reasonably related to ABT-530 and/or ABT-493 drug exposure in a prior study (Appendix D) by the investigator will be collected. Events that are considered related to underlying disease, events that are accidental (i.e., road traffic accidents), and elective procedures (i.e., hip replacement)

would not be routinely considered related to ABT-530 and/or ABT-493 exposure in the previous study.

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 a serious adverse event or noncompliance with the protocol. In the event that a subject withdraws or is discontinued from the study, the reasons for the discontinuation from the study will be recorded in the eCRF and an assessment of serious adverse events as described in Section 6.0 will be performed as soon as possible after discontinuation from the study.

Subjects who experienced virology failure in the prior study and have received HCV re-treatment will be followed until the Post-Treatment Week 12 visit for assessment of SVR_{12}, and then discontinued from the study.

If a subject is discontinued from the study with an ongoing serious adverse event as described in Section 6.0, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the serious adverse event is achieved.

5.4.2 Discontinuation of Entire Study

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

5.5 Treatments

Treatment will not be provided to subjects as part of this study.

5.5.1 Method of Assigning Subject ID Numbers

For subjects enrolling from a Phase 2 study, subjects will receive a new subject number for this study which will be composed of a single digit (1, 2, 3, …) used to identify the prior AbbVie study and the subject number assigned to them from the prior AbbVie clinical study. For subjects enrolling from the Phase 3 studies, subjects will retain their subject number as assigned to them from the prior AbbVie clinical study.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This is a rollover study to assess resistance and durability of response to ABT-493 and/or ABT-530 in subjects who have participated in Phase 2 or 3 clinical studies with these agents for the treatment of chronic HCV. No AbbVie study drug will be administered in this study. As such, the absence of randomization, blinding or control groups is appropriate. No quantitative analyses or tests of statistical significance are planned; statistical analyses will be purely descriptive.

5.6.2 Appropriateness of Measurements

Standard laboratory procedures will be utilized in this study.

5.6.3 Suitability of Subject Population

The intention of this study is to assess the durability of response in subjects who had previously achieved SVR and the emergence and persistence of resistance-associated amino acid variants selected by exposure to AbbVie DAA treatment in subjects who fail previous treatment. Therefore, subjects who received at least one dose an ABT-493- and/or ABT-530-containing regimen in a prior eligible AbbVie Phase 2 or 3 trial (Appendix D), for the treatment of HCV are eligible to participate. This population is

appropriate because all such subjects will have been well described clinically and virologically prior to starting AbbVie DAA treatment and the duration and magnitude of their exposure to AbbVie DAA treatment will be well documented.

6.0 Adverse Events

As this is a non-drug interventional study, only serious adverse events that the investigator considers reasonably related to interventional study procedures (i.e., venipunctures) or those considered reasonably related to ABT-530 and/or ABT-493 exposure in the prior study (Appendix D) by the investigator will be collected. Events that are considered related to underlying disease, events that are accidental (i.e., road traffic accidents), and elective procedures (i.e., hip replacement) would not be routinely considered related to ABT-530 and/or ABT-493 drug exposure.

The investigator will assess and record any such serious adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), and any action(s) taken. For adverse events to be considered intermittent, the events must be of similar nature and severity. Serious adverse events related to study procedures or reasonably related to exposure to ABT-493 and/or ABT-530 in the prior study, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be collected.

These serious adverse events will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

An adverse event (AE) in this study is defined as any untoward medical occurrence in a patient or clinical investigation subject that occurs as a result of a study procedure, or is considered by the investigator to be reasonably related to exposure to ABT-493 and/or ABT-530 in the previous study. Worsening in severity of a reported adverse event should be reported as a new adverse event.

6.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria and is causally related to study procedures (i.e., venipunctures) or those considered by the investigator to be reasonably related to exposure to ABT-493 and/or ABT-530 in the previous study, 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 rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4).

The table of clinical toxicity grades "National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4" is available from the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf and is to be used in the grading of adverse events. Below are the general grading categories. However, the investigator should always search NCI CTC AE for a given diagnostic/symptomatic AE term to identify and apply specific grading details for that AE entity.

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

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

ADL = Activities of Daily Living

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

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

6.3 Relationship to Study Procedures or Study Drug Exposure in the Prior Study

The investigator will use the following definitions to assess the relationship of the adverse event to a study procedure or to exposure to ABT-530 and/or ABT-493 in the previous study:

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study procedure or ABT-530 and/or ABT-493 exposure in the previous study and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study procedure or ABT-530 and/or ABT-493 exposure in the previous study and the adverse event.

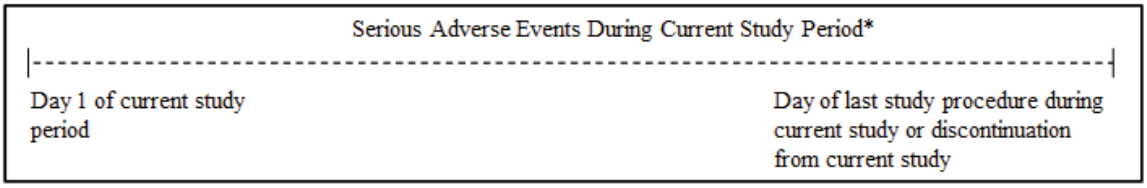
For causality assessments, events assessed as having a reasonable possibility of being related to a study procedure, or to ABT-530 and/or ABT-493 exposure in the previous study will be considered "associated." Events assessed as having no reasonable possibility of being related to a study procedure or ABT-530 and/or ABT-493 exposure in the previous study will be considered "not associated."

6.4 Adverse Event Collection Period

All serious adverse events that occur during the current study period, and are considered related to a study procedure (like an SAE related to venipuncture), or reasonably related to exposure to ABT-530 and/or ABT-493 that was administered during the previous study period (note: no study drugs are administered during the current study period) will be collected from the time of the Day 1 Visit of the current study period through the last study procedure or discontinuation from study, whichever is later.

Serious adverse event information will be collected as shown in Figure 1.

Figure 1. Serious Adverse Event Collection



* Serious adverse events considered related to study procedures (like an SAE due to venipuncture), or considered related to drugs that were administered during the prior study period (no study drugs administered during the current study period).

6.5 Adverse Event Reporting

In the event of a serious adverse event (as described in Section 6.4), the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable should be faxed to AbbVie Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

FAX to:	[redacted]
Email:	

For safety concerns, contact the Antiviral Safety Team at:

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

Office: [redacted]
eFax:
Email:

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

Therapeutic Area Medical Director:

[redacted]
Antiviral Clinical Project Team
1500 Seaport Boulevard
Redwood City, CA 94063
USA

Telephone Contact Information:
Office: [redacted]
eFax:
Fax:
Mobile:
Email:

Should, in case of subject safety concerns or medical emergencies, the Therapeutic Area Medical Director be unavailable, please call the following central back-up number:

Phone: [redacted]

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with

Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

6.6 Pregnancy

In the event of a subject entering Study M13-576, within 7 months of the last dose of study medication in the prior study, who is pregnant, the pregnancy must be reported to AbbVie as an occurrence relating to the prior study, and according to the requirements of that study. The pregnancy will not be reported in Study M13-576.

7.0 Protocol Deviations

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

Primary Contact:

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

Office: [redacted]
Fax:
Email:

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. AbbVie will assess all protocol deviations and determine if the deviation requires reporting to the Regulatory

Authority(ies), if required by local regulations, as a serious breach of GCP and the protocol. Protocol waivers are not permitted.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

Analyses will be conducted on all subjects who enroll in this study without receiving re-treatment prior to enrolling in this study, denoted as the full analysis set. Subjects who are virologic failures who receive re-treatment prior to enrollment in this study will be summarized separately and are excluded from the full analysis set.

Descriptive statistics will be provided for demographic variables for all subjects in the full analysis set.

8.1.1 Efficacy

Efficacy analyses will be conducted in all enrolled subjects as specified above including data up to the last follow-up in this study prior to any HCV re-treatment. The number and percentage of subjects in the full analysis set who maintain SVR in this study will be summarized out of subjects in the full analysis set who achieved SVR_{12} in the previous study. The number and percentage of subjects who relapse or have new HCV infection will be summarized out of subjects in the full analysis set who achieved SVR_{12} in the previous study. The time to relapse or new infection from the end of DAA treatment for subjects who achieved HCV RNA < LLOQ at the end of treatment in the previous study will be displayed graphically using Kaplan-Meier curves. Similarly, the time to relapse or new infection from SVR_{12} time point for the subset of subjects who achieved SVR_{12} in the previous study will also be displayed graphically using Kaplan-Meier curves. These summaries will be separate for subjects who have probable relapse as distinguished from subjects who have probable new HCV infection based on AbbVie's evaluation of DNA sequence of HCV drug target genes.

For subjects in the full analysis set, HCV RNA measurements taken after the start of another anti-viral HCV treatment (after completion of AbbVie DAA treatments in previous study) will be excluded from the analyses.

A listing of subjects who are re-treated will be provided summarizing HCV treatment regimen and SVR outcome.

8.1.2 Resistance

The following subjects in the full analysis set will have resistance testing conducted: (1) those with on-treatment virologic failure (VF) in the previous study; (2) those with post-treatment relapse prior to enrollment in Study M13-576; and (3) those who become viremic (with HCV) during Study M13-576.

A listing by subject will be produced for all subjects entering Study M13-576 who experienced VF (as defined above) that includes HCV subtype, IL28B genotype, time point of VF, HCV RNA level at each evaluated time point, time point(s) sequenced, and assessment of possibility of new infection. The study report will include a description of the methods and results used to distinguish between virologic relapse and new infection in subjects suspected to have a new infection.

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of the products of amplification. For subjects who experience VF before or during Study M13-576, the sample closest in time after the failure with an HCV RNA level ≥ 1000 IU/mL will be used if the HCV RNA level at the time of VF is < 1000 IU/mL.

The regions of interest for population and/or deep sequencing from all evaluated time points in this study are those encoding complete NS3/4A, and/or NS5A (based on regimen received in the earlier study). Subtype-specific prototypic reference strains for sequence analyses will be utilized.

For each DAA target, signature resistance-associated amino acid positions will be identified by AbbVie Clinical Virology.

The following definitions will be used in the resistance analyses:

- Baseline sample: sample collected before the first dose of DAA study drug in the previous study.
- Baseline variant: a variant (by population or deep sequencing) in the 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 (NS3/4A or NS5A).
- Post-baseline variant by population or deep sequencing: an amino acid variant in a post-baseline time point sample that was not detected at baseline and is detectable by population or deep sequencing in a given DAA target (NS3/4A or NS5A).

For all subjects who experience VF (whether before or during enrollment in Study M13-576), 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/or NS5A as appropriate).

For all subjects who experience VF (whether before or during enrollment in Study M13-576), the HCV amino acid sequence as determined by population or deep sequencing at available post-baseline time points (including previous study and Study M13-576) with an HCV RNA level of $\geq$ 1000 IU/mL will be compared to the baseline and appropriate prototypic reference amino acid sequences. A listing by subject and time point of all post-baseline variants detected by population or deep sequencing relative to the baseline amino acid sequences will be provided for each DAA target (NS3/4A and/or NS5A as appropriate). A listing by subject and time point of all post-baseline variants (by population or deep sequencing) at signature resistance-associated amino acid positions relative to the appropriate prototypic reference amino acid sequences will be provided.

The number and percentage of subjects with post-baseline variants at signature amino acid positions by population or deep sequencing, listed by amino acid position and variant within a DAA target at Post-Treatment Week 24, 48 or time points up to Post-Treatment Week 144 (3 years) compared to baseline will be summarized, along with the number of subjects for whom sequence information was obtained for each DAA target and overall. Additionally, the number and percentage of subjects in whom a signature variant persisted at Post-Treatment Week 24, 48 or time points up to Post-Treatment Week 144 (3 years), out of the total number of subjects with that variant at the VF time point and at Post-Treatment Week 24, 48 or time points up to post-treatment Week 144 (3 years) will be summarized by DAA target (NS3 and/or NS5A, as appropriate), and variant. If a signature variant is detectable in a sample by population or deep sequencing at a later time point, then the variant is imputed as being detectable at earlier time windows even if the sample from the earlier time window from that subject is not sequenced.

If no resistance-associated variants are detected by population or deep sequencing in a given target for a subject either at the time of failure or in a post-treatment sample, then that target may not be sequenced in subsequent samples from that subject.

Time to loss of key resistance-associated variants will be summarized.

8.1.3 Safety

Serious adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class (SOC) and preferred term (PT).[1] A summary of medical events related to the progression of liver disease and shifts in laboratory measurements will be provided.

8.2 Determination of Sample Size

No sample size determination was conducted for this study. The objective of the study is to characterize the persistence of amino acid variants in subjects enrolled in AbbVie DAA studies who experienced virologic failure, and the durability of response in subjects who achieved SVR. Thus, the number of subjects enrolled in the current trial will be partially

based on the number of subjects who experienced virologic failure in prior studies with AbbVie DAA therapies and subsequently agree to participate in the current trial.

The sample size is being increased under protocol Amendment 2 to allow for inclusion of a representative sample of subjects from additional studies as listed in Appendix D.

9.0 Ethics

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

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

Any amendments to the protocol will require IEC/IRB approval and approval by Regulatory Authority(ies), if required by local regulations, prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

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

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

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

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

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

10.2 Case Report Forms

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

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

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

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from

investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

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

12.0 Use of Information

All information concerning AbbVie DAA therapies 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.

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 AbbVie DAA therapy. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and 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 and documents for study-related monitoring, audits, IRB review, 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. AbbVie will provide the Clinical Study Report to Regulatory Authority(ies), if required by local regulations.

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 regulatory authority guidance.

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-493 and ABT-530.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy (ABT-493 and/or ABT-530) in Subjects Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection
Protocol Date:	09 October 2017

Signature of Principal Investigator Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

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

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

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

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

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Clinical
		Statistics

Appendix C. Study Activities A and B

Table A. SVR and Non-SVR Subjects Not Receiving Re-Treatment

Activity	Day 1[a]	Month 3[b,c]	Month 6[b,c]	Month 12[b,c]	Month 18[b,c]	Month 24[b,c]	Month 30[b,c]	Month 36[b,c]
Informed Consent	X							
Medical History (related to liver disease/HCV infection) including past HCV drug treatments (during the prior study and before prior study)	X							
Assessment of Medical Events Related to Liver Disease/HCV Infection		X	X	X	X	X	X	X
Child-Pugh Score and Classification (cirrhotic subjects only)[d]	X		X	X	X	X	X	X
INR	X		X	X	X	X	X	X
Serum Albumin	X		X	X	X	X	X	X
IP-10 Sample	X	X	X			X	X (if final visit)	X
Clinical Chemistry Tests including FibroTest and APRI (see Table 1 for details)	X	X	X	X[f]	X[f]	X	X (if final visit)	X
Platelets (for APRI)	X	X	X			X	X (if final visit)	X
HCV RNA Sample	X	X	X	X	X	X	X	X
HCV Resistance Sample	X	X	X	X	X	X	X	X
Archive Plasma Sample	X	X	X	X	X	X	X	X
Collection of Liver Diagnostic Results	X	X	X	X	X	X	X	X
HCC Screening Liver ultrasound for subjects with cirrhosis only (at Final visit only)	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]

Activity	Day 1[a]	Month 3[b,c]	Month 6[b,c]	Month 12[b,c]	Month 18[b,c]	Month 24[b,c]	Month 30[b,c]	Month 36[b,c]
Assess for SAE related to Study Procedures or to Exposure to ABT-493 and/or ABT-530 in the prior study	X	X	X	X	X	X	X	X
Documentation of Medications for the Treatment of HCV or Treatment of an SAE Related to Study Procedures or to Exposure to ABT-493 and/or ABT-530 in the Prior Study	X	X	X	X	X	X	X	X
Collection of re-treatment regimen information and dosing dates (if applicable)[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]

a. The interval between the last dose of DAA therapy in the prior AbbVie clinical study and the Day 1 Visit of Study M13-576 must be no longer than 2 years.

b. Once a subject has reached approximately 3 years post-DAA therapy, participation in Study M13-576 will be completed. The study visit which falls closest to 3 years since the subject's last dose of AbbVie DAA will be registered as their final visit.

c. Visit window interval. Study visits should ideally take place within 3 weeks of the planned visit date. If the Month 3 visit is more than 6 weeks later than planned it should be registered instead as the Month 6 visit. If a Month 6, 12, 18, 24, 30 or 36 visit is more than 12 weeks later than planned it should be registered as the next visit in the schedule.

d. Child-Pugh Score and Category should be assessed on all cirrhotic subjects (those cirrhotic upon enrollment and those who become cirrhotic during the study) after approval of Amendment 2 at the site.

e. Subjects who are virologic failures and begin a re-treatment regimen during participation in the Study M13-576 will begin following the Study Activities Table B for re-treated subjects at the time re-treatment begins.

f. Total bilirubin only will be collected at Month 12 and Month 18 for the Child-Pugh Score for cirrhotic subjects only.

g. HCC Screening Liver ultrasound will be performed on subjects with cirrhosis at the visit considered the Final visit for the subject, unless the subject has a liver ultrasound, CT or MRI performed for HCC screening within 3 months prior to that visit, in which case the result of that US, CT or MRI will be used as the result for Final Study Visit assessment.

Table B. Virologic Failures Receiving Re-Treatment (Prior to or During Enrollment in Study M13-576)

Activity	Day 1[a]	SVR_{12} for Virologic Failures Re-Treated During Study M13-576[b,c]
Informed Consent	X	
Medical History (related to liver disease/HCV infection) occurring since the end of the prior AbbVie HCV clinical study but before starting a re-treatment regimen	X[d]	
Assessment of Medical Events Related to Liver Disease/HCV Infection that occurred after the prior AbbVie HCV clinical study but before starting a re-treatment regimen	X[d]	
Collection of re-treatment regimen information and dosing dates for HCV	X	X
Collection of re-treatment outcome		X
HCC Screening Liver ultrasound for subjects with cirrhosis		X[e]

a. The interval between the last dose of DAA therapy in the prior AbbVie clinical study and the Day 1 Visit of Study M13-576 must be no longer than 2 years.

b. Subjects who are virologic failures in the prior Phase 2 or 3 study may participate in Study M13-576 and be re-treated at any time after their last dose of study drug in the prior study. They will be followed in Study M13-576 until 12 weeks after the last dose (SVR_{12}) of the re-treatment regimen.

c. SVR_{12} assessment may be done by clinic visit or by telephone. Documentation of the re-treatment outcome will be recorded in the eCRF and supported by an appropriate entry in the subject's source document. Cirrhotic subjects should have a liver ultrasound done at the final visit, therefore conducting the SVR_{12} assessment should be done by clinic visit not by telephone.

d. Subjects who begin a re-treatment regimen during participation in Study M13-576 will have already had these activities done at Day 1 upon enrollment into the study. They do not need to be repeated when they begin their re-treatment regimen.

e. HCC Screening Liver ultrasound will be performed on subjects with cirrhosis at the visit considered the Final visit for the subject, unless the subject has a liver ultrasound, CT or MRI performed for HCC screening within 3 months prior to that visit, in which case the result of that US, CT or MRI will be used as the result for Final Study Visit assessment.

Appendix D. List of Prior Eligible Studies

Subjects who have received at least one dose of an ABT-493 and/or ABT-530-containing regimen in any of the following eligible AbbVie HCV Phase 2 or 3 studies meet inclusion criteria number 1:

- M14-213
- M14-867
- M14-868
- M15-410
- M13-590
- M15-464
- M13-594
- M13-583
- M14-172
- M15-462

Appendix E. Child-Pugh Score and Category

The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments). Child-Pugh score will be determined only for subjects with cirrhosis at the visits indicated in Appendix C.

Table 2. 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.

The Child-Pugh Classification is defined in terms of the sum of the scores for the five parameters:

- A score of 5 or 6 indicates Child-Pugh Category A (mild hepatic impairment).
- A score of 7, 8, or 9 indicates Child-Pugh Category B (moderate hepatic impairment).
- A score of 10 through 15 indicates Child-Pugh Category C (severe hepatic impairment).

Appendix F. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.2 Synopsis
Subsection Phase of Development:
Previously read:

2

Has been changed to read:

2/3

Section 1.2 Synopsis
Subsection Objectives:
Second paragraph, last bullet previously read:

Summarize results of the following laboratory tests and scores: FibroTest, APRI, IP-10, alpha fetoprotein, FibroScan, and liver biopsy.

Has been changed to read:

Summarize results of the following laboratory tests and scores: FibroTest, APRI, IP-10, alpha fetoprotein (if collected under a previous protocol version), FibroScan, and liver biopsy.

Section 1.2 Synopsis
Subsection Diagnosis and Main Criteria for Inclusion/Exclusion:
Heading "Main Inclusion:"
Criterion 2 previously read:

The interval between the last dose of the AbbVie DAA therapy from the previous clinical study and enrollment in Study M13-576 must be no longer than 2 years.

Has been changed to read:

The interval between the last dose of the AbbVie DAA therapy from the previous clinical study and enrollment in Study M13-576 must be no longer than 2 years for subjects who have not been retreated. Subjects who have been treated with a commercially-available anti-HCV treatment may be enrolled greater than 2 years after the last dose of the AbbVie DAA therapy from the previous clinical study.

Section 4.0 Study Objectives
Second paragraph, last bullet previously read:

Summarize results of the following laboratory tests and scores: FibroTest, APRI, IP-10, alpha fetoprotein, FibroScan, and liver biopsy.

Has been changed to read:

Summarize results of the following laboratory tests and scores: FibroTest, APRI, IP-10, alpha fetoprotein (if collected under a previous protocol version), FibroScan, and liver biopsy.

Section 5.1 Overall Study Design and Plan: Description
Fourth paragraph, fourth and fifth sentence previously read:

Once a subject has reached 3 years post-DAA therapy, participation in this study will be completed, except for subjects enrolled with virologic failure who receive re-treatment with a new HCV antiviral regimen that does not contain ABT-493/ABT-530. Subjects who are re-treated with HCV regimens other than ABT-493/ABT-530 will have only one further assessment for treatment outcome 12 weeks after stopping that therapy or earlier if already known (in cases of treatment failure).

Has been changed to read:

Once a subject has reached 3 years post-DAA therapy, participation in this study will be completed, except for subjects enrolled with virologic failure who receive re-treatment with a HCV antiviral regimen other than investigational ABT-493/ABT-530. Subjects

who are retreated with investigational ABT-493/ABT-530 are not allowed in this study. Subjects who are re-treated with HCV regimens other than investigational ABT-493/ABT-530 will have only one further assessment for treatment outcome 12 weeks after stopping that therapy or earlier if already known (in cases of treatment failure).

Section 5.2.1 Inclusion Criteria
Criterion 3 previously read:

The interval between the last dose of the AbbVie DAA therapy from the previous clinical study and enrollment in Study M13-576 must be no longer than 2 years.

Has been changed to read:

The interval between the last dose of the AbbVie DAA therapy from the previous clinical study and enrollment in Study M13-576 must be no longer than 2 years for subjects who have not been retreated. Subjects who have been treated with a commercially-available anti-HCV treatment may be enrolled greater than 2 years after the last dose of the AbbVie DAA therapy from the previous clinical study.

Section 5.2.3 Prior and Concomitant Therapy
First paragraph, second and third sentence previously read:

Commercially available prescription medications for the treatment of HCV therapy initiated after the completion of a subject's participation in the previous clinical study (either prior to or during participation in this study) are permitted, and the regimen received and duration will be recorded in the eCRF. Subjects enrolled with virologic failure who undergo re-treatment with a new HCV antiviral regimen not containing ABT-493/ABT-530 will be followed until completing the post-treatment Week 12 visit after receiving their re-treatment regimen, after which they will discontinue from the study.

Has been changed to read:

Commercially available prescription medications for the treatment of HCV therapy, including regimens containing commercially available glecaprevir/pibrentasvir (GLE/PIB, investigationally known as ABT-493/ABT-530), initiated after the completion of a subject's participation in the previous clinical study (either prior to or during participation in this study) are permitted, and the regimen received and duration will be recorded in the eCRF. Subjects enrolled with virologic failure who undergo re-treatment with a HCV antiviral regimen not containing investigational ABT-493/ABT-530 will be followed until completing the post-treatment Week 12 visit after receiving their re-treatment regimen, after which they will discontinue from the study.

Section 5.3.1.1 Study Procedures
Section Hepatocellular Carcinoma Screening: Liver Ultrasound
Add: new section title and text

Hepatocellular Carcinoma Screening: Liver Ultrasound

HCC screening will be required as a protocol-specified study procedure only at the Final visit, as indicated in Appendix C, for subjects with cirrhosis only. At any other time during the study, HCC screening should be performed according to standard of care.

At the Final visit, subjects with cirrhosis will be required to perform a liver ultrasound to screen for HCC, unless the subject has a liver ultrasound, CT or MRI performed for HCC screening within 3 months prior to that visit, in which case the result of that US, CT or MRI will be used as the result for the Study Visit assessment. A positive ultrasound result suspicious of HCC will be confirmed with CT scan or MRI. Alternate methods of screening for HCC (i.e., MRI or CT) at a study visit should be discussed with the TA MD.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
First paragraph previously read:

Samples will be obtained for the clinical laboratory tests, including FibroTest and APRI, IP-10, AFP and quantitative HCV RNA PCR, INR and serum Albumin at the visits

specified in Appendix C for all subjects, until the end of the study or initiation of re-treatment for HCV (if applicable).

Has been changed to read:

Samples will be obtained for the clinical laboratory tests, including FibroTest and APRI, IP-10, and quantitative HCV RNA PCR, INR and serum Albumin at the visits specified in Appendix C for all subjects, until the end of the study or initiation of re-treatment for HCV (if applicable).

Table 1. Clinical Laboratory Tests
Column "Clinical Chemistry"
Delete:

Alpha Fetoprotein

Section 5.3.3.1 Clinical Variables
Subsection Clinical Variables
Last paragraph, first sentence previously read:

Results of the following laboratory tests and studies will be summarized: IP-10, FibroTest, APRI, alpha fetoprotein, FibroScan, liver biopsy.

Has been changed to read:

Results of the following laboratory tests and studies will be summarized: IP-10, FibroTest, APRI, alpha fetoprotein, (if collected under a previous protocol version) FibroScan, liver biopsy.

Section 5.3.4 Safety Variables
First sentence previously read:

Only serious adverse events related to study procedures or those that meet seriousness criteria outlined in Section 6.0 and are considered reasonably related to ABT-530 and/or ABT-493 drug exposure in a prior study (Appendix D) by the investigator will be reported as serious adverse events.

Has been changed to read:

Only serious adverse events related to study procedures or those that meet seriousness criteria outlined in Section 6.0 and are considered reasonably related to ABT-530 and/or ABT-493 drug exposure in a prior study (Appendix D) by the investigator will be collected.

Section 6.0 Adverse Events
First paragraph, first sentence previously read:

As this is a non-drug interventional study, only serious adverse events that the investigator considers reasonably related to interventional study procedures (i.e., venipunctures) or those considered reasonably related to ABT-530 and/or ABT-493 exposure in the prior study (Appendix D) by the investigator will be reported as serious adverse events.

Has been changed to read:

As this is a non-drug interventional study, only serious adverse events that the investigator considers reasonably related to interventional study procedures (i.e., venipunctures) or those considered reasonably related to ABT-530 and/or ABT-493 exposure in the prior study (Appendix D) by the investigator will be collected.

Section 6.0 Adverse Events
Second paragraph, last sentence previously read:

Serious adverse events related to study procedures or reasonably related to exposure to ABT-493 and/or ABT-530 in the prior study, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

Has been changed to read:

Serious adverse events related to study procedures or reasonably related to exposure to ABT-493 and/or ABT-530 in the prior study, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be collected.

Section 6.5 Adverse Event Reporting
Add: new last paragraph

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

Section 7.0 Protocol Deviations
First paragraph, last sentence previously read:

If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie representatives:

Has been changed to read:

If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) and the following AbbVie representatives:

Section 7.0 Protocol Deviations
Last paragraph
Add: new second and third sentence

AbbVie will assess all protocol deviations and determine if the deviation requires reporting to the Regulatory Authority(ies), if required by local regulations, as a serious breach of GCP and the protocol. Protocol waivers are not permitted.

Section 9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Second paragraph, first sentence previously read:

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design.

Has been changed to read:

Any amendments to the protocol will require IEC/IRB approval and approval by Regulatory Authority(ies), if required by local regulations, prior to implementation of any changes made to the study design.

Section 13.0 Completion of the Study
First paragraph
Add: new last sentence

AbbVie will provide the Clinical Study Report to Regulatory Authority(ies), if required by local regulations.

Section 15.0 Reference List
Add: new Reference 29

The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating hepatitis C. Last updated: 12 April 2017. Available from: http://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/HCVGuidance_April_12_2017_b.pdf.

Appendix B. List of Protocol Signatories
Previously read:

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

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Clinical
		Statistics

Appendix C. Study Activities A and B
Table A. SVR and Non-SVR Subjects Not Receiving Re-Treatment
Activity "Clinical Chemistry Tests including FibroTest and APRI (see Table 1 for details)" previously read:

Activity	Day 1[a]	Month 3[b,c]	Month 6[b,c]	Month 12[b,c]	Month 18[b,c]	Month 24[b,c]	Month 30[b,c]	Month 36[b,c]
Clinical Chemistry Tests including FibroTest and APRI (see Table 1 for details)	X	X	X			X	X (if final visit)	X

Has been changed to read:

Activity	Day 1[a]	Month 3[b,c]	Month 6[b,c]	Month 12[b,c]	Month 18[b,c]	Month 24[b,c]	Month 30[b,c]	Month 36[b,c]
Clinical Chemistry Tests including FibroTest and APRI (see Table 1 for details)	X	X	X	X[f]	X[f]	X	X (if final visit)	X

Appendix C. Study Activities A and B
Table A. SVR and Non-SVR Subjects Not Receiving Re-Treatment
Add: Activity "HCC Screening Liver ultrasound for subjects with cirrhosis only (at Final visit only)"

Activity	Day 1[a]	Month 3[b,c]	Month 6[b,c]	Month 12[b,c]	Month 18[b,c]	Month 24[b,c]	Month 30[b,c]	Month 36[b,c]
HCC Screening Liver ultrasound for subjects with cirrhosis only (at Final visit only)	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]

Appendix C. Study Activities A and B
Table A. SVR and Non-SVR Subjects Not Receiving Re-Treatment
Add: new table note "f." and "g."

f. Total bilirubin only will be collected at Month 12 and Month 18 for the Child-Pugh Score for cirrhotic subjects only.

g. HCC Screening Liver ultrasound will be performed on subjects with cirrhosis at the visit considered the Final visit for the subject, unless the subject has a liver ultrasound, CT or MRI performed for HCC screening within 3 months prior to that visit, in which case the result of that US, CT or MRI will be used as the result for Final Study Visit assessment.

Appendix C. Study Activities A and B
Table B. Virologic Failures Receiving Re-Treatment (Prior to or During Enrollment in Study M13-576)
Add: Activity "HCC Screening Liver ultrasound for subjects with cirrhosis"

Activity	Day 1[a]	SVR_{12} for Virologic Failures Re-Treated During Study M13-576[b,c]
HCC Screening Liver ultrasound for subjects with cirrhosis		X[e]

Appendix C. Study Activities A and B
Table B. Virologic Failures Receiving Re-Treatment (Prior to or During Enrollment in Study M13-576)
Table note "c."
Add: new last sentence

Cirrhotic subjects should have a liver ultrasound done at the final visit, therefore conducting the SVR_{12} assessment should be done by clinic visit not by telephone.

Appendix C. Study Activities A and B
Table B. Virologic Failures Receiving Re-Treatment (Prior to or During Enrollment in Study M13-576)
Add: new table note "e."

HCC Screening Liver ultrasound will be performed on subjects with cirrhosis at the visit considered the Final visit for the subject, unless the subject has a liver ultrasound, CT or MRI performed for HCC screening within 3 months prior to that visit, in which case the result of that US, CT or MRI will be used as the result for Final Study Visit assessment.