

1.0 Title Page

Clinical Study Protocol M13-596

**A Single-Arm, Open-Label, Multicenter Study to
Evaluate the Safety and Efficacy of
ABT-493/ABT-530 in Adult Post-Liver or Post-Renal
Transplant Recipients with Chronic Hepatitis C Virus
Genotype 1 – 6 Infection (MAGELLAN-2)**

Incorporating Amendments 1 and 2

AbbVie Investigational Product: ABT-493/ABT-530

Date: 21 June 2016


Development Phase: 3

Study Design: This is an open label, multicenter study

EudraCT Number: 2015-005616-14

Investigators: Multicenter. Investigator information is on file at AbbVie.

Sponsor: AbbVie Inc. (AbbVie)*

Sponsor/Emergency Contact: 

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

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

Confidential Information

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1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	28 January 2016
Amendment 1	26 May 2016

The purpose of this amendment is to:

- Update Section 3.0, Introduction, and Section 5.2.3.2, Management of Immunosuppressant Agent Dosing.

Rationale: *The protocol has been updated to provide clarification regarding cyclosporine dose adjustment during the Treatment Period for subjects requiring maintenance titration as per usual transplant standard of care. The dosing recommendation of 100 mg total daily dose is based upon the Phase 1 drug-drug interaction studies (Studies M13-584, M13-605) that examined cyclosporine doses of 100 mg and 400 mg, as described within the protocol. Stable dosing at or below cyclosporine 100 mg/day was selected as the entry criteria (Inclusion Criterion 14), as this dose demonstrated only mild increases in ABT-493 exposure when coadministered with ABT-493 and ABT-530. Although larger increases in ABT-493 exposure were observed with the cyclosporine 400 mg dose, all study drugs were well tolerated in both studies and no safety signals were identified. Coadministration with ABT-493 and ABT-530 did not affect exposure of cyclosporine at either dose level.*

While the recommended dose of cyclosporine at the time of entry into the study (Inclusion Criterion 14) remains the same, clarification is needed for a subject who has entered into the study at a daily cyclosporine dose of 100 mg or less and requires an increase in the maintenance cyclosporine dose during the period of ABT-493/ABT-530 administration to > 100 mg/day. Cyclosporine doses > 400 mg have not been formally evaluated in DDI studies with ABT-493 and ABT-530, and cyclosporine doses should not exceed 400 mg/day when coadministered with ABT-493/ABT-530 under any circumstances. Contact with the Therapeutic Area MD should be made for any case requiring titration of the cyclosporine maintenance dose to greater than 100 mg to

discuss proper management of concurrent therapies in order to prevent unnecessary discontinuation of study drug and risk of resistance development due to incomplete therapy.

- Update Section 5.2.2, Exclusion Criteria, Criterion 7.

Rationale: *Clarification that concurrent liver disease other than HCV as an exclusionary criteria is applicable in the post-transplant period.*

- Update Section 5.1.2, Treatment Period, and Section 5.3.1.1, Study Procedures.

Rationale: *To clarify that the Immunosuppressive dosing diary completion begins during the screening period.*

- Update Appendix B, List of Protocol Signatories.

Rationale: *To correct the typographical error.*

- Minor clerical updates made throughout the protocol.

Rationale: *For clarification and consistency throughout the protocol.*

An itemized list of all changes made to the protocol under this amendment can be found in [Appendix E](#).

1.2 Synopsis

AbbVie Inc.	Protocol Number: M13-596
Name of Study Drug: ABT-493/ABT-530 100 mg/40 mg tablets (ABT-493/ABT-530)	Phase of Development: 3
Name of Active Ingredient: ABT-493, ABT-530	Date of Protocol Synopsis: 21 June 2016
Protocol Title: A Single-Arm, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of ABT-493/ABT-530 in Adult Post-Liver or Post-Renal Transplant Subjects with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (MAGELLAN-2)	
Objectives: The primary objectives of this study are to compare the 12-week sustained virologic response, SVR ₁₂ (HCV RNA < LLOQ 12 weeks following therapy) of 12 weeks of treatment with the ABT-493/ABT-530 combination regimen in adults with HCV genotype 1 – 6 infection who are post primary orthotopic liver transplant or renal transplant to a pre-defined threshold, based on the historical SVR ₁₂ rates for the current standard of care regimens (sofosbuvir/ledipasvir plus ribavirin or sofosbuvir plus daclatasvir plus RBV) and to assess the safety of treatment with the ABT-493/ABT-530 combination regimen for 12 weeks in adults with HCV genotype GT1 – 6 infection and post primary orthotopic liver transplant or renal transplant.	
Investigators: Multicenter	
Study Sites: Approximately 30 sites globally	
Study Population: Adults at least 18 years of age with chronic HCV genotype (GT) 1 – 6 infection who are post primary liver or renal transplant.	
Number of Subjects to be Enrolled: Approximately 90 subjects (including a minimum of 15 post-renal transplant subjects) and a maximum of approximately 50 subjects with HCV GT1 infection).	
<p>Methodology:</p> <p>This is a Phase 3, single arm, open-label, multicenter study to evaluate the safety and efficacy of ABT-493/ABT-530 for 12 weeks in chronic HCV GT1 – 6 infected subjects who have received a primary liver or renal transplant, and who are either HCV treatment-naïve or prior treatment experienced with IFN or pegIFN with or without RBV or sofosbuvir with RBV with or without pegIFN (except GT3 infected subjects, who must be treatment-naïve).</p> <p>The study will consist of 2 periods:</p> <p><u>Treatment Period:</u></p> <p>Eligible subjects will be enrolled to receive 12 weeks of ABT-493/ABT-530 300 mg/120 mg once daily (QD) for 12 weeks.</p> <p>Scheduled visits for subjects in the Treatment Period consist of Day 1, Day 3 and Weeks 1, 2, 4, 6, 8, and 12. Study procedures, including assessment of adverse events, vital signs, study drug adherence, concomitant medications, HCV RNA, HCV resistance, ABT-493/ABT-530 and immunosuppressant concentrations, pharmacokinetic assays, and clinical laboratory tests, will be conducted at each visit.</p> <p><u>Post-Treatment Period:</u></p> <p>Subjects who complete or prematurely discontinue the Treatment Period will be followed for 24 weeks to monitor safety, HCV RNA levels, and the emergence and persistence of resistant viral variants.</p>	

Methodology (Continued):	
During the Post-Treatment Period, all subjects will have visits at Day 3 and Weeks 1, 2, 4, 8, 12, and 24 following completion of the Treatment Period. Study procedures to monitor safety, HCV RNA, and the emergence and persistence of resistant virus will be conducted during these visits.	
Diagnosis and Main Criteria for Inclusion/Exclusion:	
Main Inclusion:	
<ol style="list-style-type: none"> 1. Male or female, at least 18 years of age at time of screening. 2. Screening laboratory result indicating HCV GT1 – 6 infection. 3. Subject is a recipient of a cadaveric or living donor liver transplant which was a consequence of HCV infection \geq 3 months prior to screening Or Subject received a cadaveric or living donor kidney at least \geq 3 months before screening. 4. Subjects must be documented as non-cirrhotic. 5. Subject is currently taking a stable immunosuppression regimen based on tacrolimus, sirolimus, everolimus, mycophenolate mofetil (MMF), mycophenolic acid, azathioprine and/or cyclosporine. 	
Main Exclusion:	
<ol style="list-style-type: none"> 1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug. 2. Clinical history of fibrosing cholestatic hepatitis post-transplant. 3. Re-transplantation of the liver or kidney. 4. Steroid resistant rejection of the transplanted liver or kidney, or a history of rejection treated with high dose steroid within 3 months of screening. 5. History of post-transplant complications related to hepatic or renal vasculature. 	
Investigational Products:	ABT-493/ABT-530 100 mg/40 mg Film-coated tablet
Dose:	ABT-493/ABT-530: 300 mg/120 mg QD (3 tablets)
Mode of Administration:	Oral with food
Reference Therapy:	N/A
Dose:	N/A
Mode of Administration:	N/A
Duration of Treatment: Subjects will receive ABT-493/ABT-530 for 12 weeks.	
Criteria for Evaluation:	
Safety:	
Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests, and vital signs.	
Efficacy:	
Plasma HCV RNA (IU/mL) will be assessed at each Treatment and Post-Treatment Visit.	

Criteria for Evaluation (Continued):

Pharmacokinetic:

Individual plasma concentrations of ABT-493 and ABT-530, and possible metabolites of ABT-493 and ABT-530 will be tabulated and summarized. Individual blood concentrations of immunosuppressants; cyclosporine, sirolimus, everolimus, and/or tacrolimus, will also be tabulated and summarized.

Patient Reported Outcomes (PROs):

Health state utility will be measured using the EuroQoL-5-Dimensions-3 Level (EQ-5D-3L) instrument. The Fatigue Severity Scale (FSS) will be used to measure the severity of fatigue and its effect on lifestyle and activities. The Short Form 36 Version 2 Health Status Survey (SF-36v2) will be used to assess the functional health and well-being of subjects.

Resistance:

The following information will be tabulated and summarized: 1) for all subjects with available samples, the variants at baseline at signature resistance-associated amino acid positions relative to the appropriate prototypic reference sequence; and 2) for subjects who do not achieve SVR₁₂, post-baseline variants relative to baseline.

Statistical Methods:

Efficacy:

The primary efficacy endpoint is the percentage of subjects with SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) for all intent-to-treat (ITT) subjects treated with ABT-493/ABT-530. Non-inferiority of the SVR₁₂ rate for the ABT-493/ABT-530 regimen compared to the historical SVR₁₂ rate for the current standard of care regimens (based on SVR₁₂ rates for SOF/ledipasvir (LDV) plus RBV or SOF plus daclatasvir (DCV) plus RBV [REDACTED]) will be tested. The number and percentage of subjects achieving SVR₁₂ will be summarized and a two-sided 95% confidence interval will be calculated using the Normal approximation to the binomial distribution unless the SVR₁₂ rate for the primary is 100%, where the Wilson's score method will be used for the confidence intervals instead. The lower confidence bound of the 2-sided 95% CI (LCB) for the percentage of subjects achieving SVR₁₂ must exceed 86% to achieve non-inferiority.

The secondary efficacy endpoints are:

- The percentage of subjects with on-treatment virologic failure,
- The percentage of subjects with post-treatment relapse.

The number and percentage of subjects meeting each secondary efficacy endpoint will be summarized along with 95% Wilson score confidence intervals.

Additional efficacy endpoints include: percentage of subjects with HCV RNA < LLOQ at each post-baseline visit during treatment period, percentage of DAA naïve subjects with on-treatment virologic failure and relapse, SVR₄, SVR₂₄, and the percentage of subjects who relapsed after achieving SVR₁₂; the number and percentage of subjects meeting each additional efficacy endpoint will be summarized along with 95% Wilson score confidence intervals.

Statistical Methods (Continued):

Pharmacokinetic:

Plasma concentration of ABT-493, ABT-530, and their possible metabolites will be tabulated for each subject. Summary statistics will be computed for each time and visit. Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach. Individual blood concentrations of immunosuppressants, cyclosporine, sirolimus, everolimus, and/or tacrolimus, will also be tabulated and summarized.

PROs:

Change from baseline in the patient reported outcome summary measures will be summarized descriptively. In addition, the proportion of patients achieving a minimal important difference will be identified.

Resistance:

For all subjects receiving study drug, the HCV variants at signature resistance-associated amino acid positions at baseline identified by population or deep sequencing and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving study drugs who do not achieve SVR₁₂ and who have a post-baseline sample with HCV RNA \geq 1000 IU/mL: 1) the amino acid variants in available post-baseline samples identified by population or deep sequencing and comparison to the baseline sequences, 2) the amino acid variants in available post baseline samples at signature resistance-associated positions identified by population or deep sequencing, and comparison to the appropriate prototypic reference sequence, and 3) the persistence of post-baseline viral resistance by population or deep sequencing.

Safety:

All subjects who receive at least one dose of study drug will be included in the safety analyses. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug) will be tabulated by primary System Organ Class (SOC) and MedDRA preferred term. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by severity grade and relationship to study drug. Change from baseline in laboratory tests and vital signs measurements to each time point of collection will be summarized, and values that are potentially clinically significant, according to predefined criteria, will be summarized.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

Ab	Antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APRI	Aminotransferase/platelet ratio index
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	Twice Daily
BMI	Body Mass Index
BUN	Blood urea nitrogen
CNI	Calcineurin Inhibitors
CPK	Creatine phosphokinase
CR/CL	Creatinine clearance
CRF	Case report form
CT	Computed Tomography
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DCV	Daclatasvir
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EQ-5D-3L	EuroQol 5 Dimensions 3 Levels Health State Instrument
EU	European Union
FSS	Fatigue Severity Scale
GAM	Generalized additive method
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GT	Genotype

HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
Hemoglobin A1c	Glycated hemoglobin
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon
IL28B	Interleukin 28B
IMP	Investigational Medical Product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International units
IUD	Intrauterine device
LDV	Ledipasvir
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NONMEM	Non-linear mixed-effect modeling
MMF	Mycophenolate mofetil
mTOR	Mammalian target of rapamycin
NS5A	Nonstructural viral protein 5A
NS5B	Nonstructural viral protein 5B
PCR	Polymerase Chain Reaction
PegIFN	Pegylated-interferon alfa-2a or alfa-2b
PegIFN/RBV	Combination of pegylated-interferon alfa-2a or alfa-2b and ribavirin
PI	Protease Inhibitor
PK	Pharmacokinetic

POR	Proof of Receipt
PRO	Patient Reported Outcome
PR	pegIFN/RBV
PT	Post-Treatment
QD	Once daily
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
ROC	Receiver Operating Characteristic
SAE	Serious adverse event
SF-36v2	Short Form 36-Version 2 Health Status Survey
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOF	Sofosbuvir
SOC	System Organ Class/Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
SVR ₄	Sustained virologic response 4 weeks post dosing
SVR ₁₂	Sustained virologic response 12 weeks post dosing
SVR ₂₄	Sustained virologic response 24 weeks post dosing
ULN	Upper limit of normal
VAS	Visual Analog Scale
V/F	Apparent Volume of distribution
Wk	Week
WBC	White blood cells
WOCBP	Women of Child Bearing Potential
WPAI	Work Productivity and Activity Index

Pharmacokinetic and Statistical Abbreviations

AUC	Area under the plasma concentration-time curve
AUC ₂₄	AUC for the 24-hour dosing interval
β	Apparent terminal phase elimination rate constant
CI	Confidence Interval
CL/F	Apparent oral plasma clearance
C _{max}	Maximum observed plasma concentration
C _{trough}	Pre-dose trough plasma concentration
LCB	Lower confidence bound
ITT	Intent-to-Treat
SD	Standard Deviation
t _{1/2}	Terminal phase elimination half-life
T _{max}	Time to maximum observed plasma concentration (C _{max})

Definition of Terms

Study Drug	ABT-493, ABT-530
Study Day 1	First day of study drug dosing
Treatment Period	Day 1 through last dose of study drug
Post-Treatment Period	Day after the last dose of study drug through Post-Treatment Week 24 or Post-Treatment Discontinuation

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3.0 Introduction

End stage liver disease due to chronic hepatitis C virus (HCV) infection is a common indication for liver transplantation, accounting for up to 30% of all liver transplants.¹ In HCV-infected individuals, recurrent infection of the new graft occurs in almost all liver transplant recipients. HCV infection is typically more aggressive in the post-transplant population than in other HCV-infected populations, with 30% of transplant recipients developing cirrhosis within 5 years, and is a frequent cause of graft loss. HCV infection significantly impacts both patient and allograft survival in the liver transplant population, a trend that is also seen in the renal transplant population.²⁻⁶ Within the renal transplant population, HCV seroprevalence is up to 22% in kidney recipients, and those who are HCV positive have lower long term survival rates when compared to the HCV negative renal transplant population, with 15 year survival rates of 78% versus 94.5%, respectively. Thus, safe and effective treatment of HCV in the post-renal and liver transplant populations is of clinical importance.

HCV infection is a global health problem, with over 130 – 184 million individuals infected worldwide.⁷ There are 7 identified HCV genotypes,⁸ with genotype 1 (GT1) being most prevalent worldwide, including in the United States. Depending on various risk factors, between 10% and 40% of patients with chronic HCV infection will develop cirrhosis.⁹ 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.⁹ Patients diagnosed with hepatocellular carcinoma have a 33% probability of death during the first year.⁹ 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.^{10,11}

Interferon (IFN)-based therapies in the post-liver transplant setting have historically been associated with low SVR rates, partly due to the treatment limiting toxicities associated with IFN and ribavirin (RBV)¹² though even these regimens are associated with improved long-term outcomes. In the renal transplant setting, IFN can be deleterious to the

allograft, and should be avoided.⁶ Currently approved interferon (IFN)- and, in some cases, ribavirin (RBV)-free combination regimens consisting of 2 or more potent direct acting antiviral agents (DAAs) represent overall substantial progress in the treatment of HCV infection compared with previous IFN-based therapy for most HCV populations outside of the transplant population. The current IFN-free DAA combination treatment regimens have substantially increased SVR₁₂ rates in pegIFN/RBV-naïve and -experienced patients, shortened the duration of treatment, and improved the safety and tolerability of treatment relative to IFN-containing regimens. Improved SVR, shorter treatment durations and improved safety and tolerability have also been described in the post-transplant population with these regimens.¹³⁻¹⁶

Despite the advances in IFN-free regimens, not all are equally potent across all HCV genotypes and subtypes, and across all subpopulations, including patients who have failed previous DAA-based regimens, patients with severe renal impairment, post-transplant patients and patients with decompensated cirrhosis, leaving important medical needs unaddressed. Currently available treatments in the transplant populations still require RBV for most recommended regimens,¹⁷ and can potentially be associated with significant drug interactions, particularly with calcineurin inhibitors (CNIs).

In addition, more convenient and tolerable regimens are also needed in order to improve patient compliance and by extension, increase the chances of cure. Features of such a regimen include low pill burden and once daily dosing, pan-genotypic coverage and RBV-free dosing. AbbVie is currently developing two "next generation" DAAs, ABT-493 (NS3/4A PI) and ABT-530 (NS5A inhibitor), as combination therapy for chronic HCV infection. These DAAs are denoted as "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 resistant variants.

ABT-493 and ABT-530

ABT-493 is an NS3/4A PI with potent and pan-genotypic activity. It demonstrates a high genetic barrier to resistance with activity against common variants that emerge following

exposure to first generation PIs. ABT-530 is an NS5A inhibitor with pan-genotypic activity and a high genetic barrier to resistance maintaining 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 single key resistance-associated variants. Additive or synergistic in vitro anti-HCV activity has been demonstrated with the combination of ABT-493 and ABT-530, depending on the concentrations tested.

In general, ABT-493 and ABT-530 in combination has been well tolerated when administered to over 250 healthy volunteers and 270 HCV-infected subjects. When ABT-493 was given in combination with ABT-530 in healthy volunteers, results showed that ABT-493 exposures were not significantly changed when co-administered with ABT-530 ($\leq 31\%$ 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).

Studies M14-867 and M14-868^{18,19} are Phase 2b studies designed to assess the efficacy, safety and pharmacokinetics of the combination of ABT-493 and ABT-530 in non-cirrhotic subjects with HCV GT1 – 6 infection. In these studies, subjects received 12 weeks of ABT-493 and ABT-530 with or without ribavirin.

In Study M14-867 Part 1, the combination of ABT-493 and ABT-530 demonstrated high rates of SVR₁₂ in treatment-naïve (98%) and treatment-experienced (100%) HCV GT1-infected subjects. In Study M14-868, preliminary results across dose regimens in GT2 and GT3 demonstrated SVR₁₂ of 89% – 97% (excluding non-virologic failures). To date, safety data across 274 subjects in Part 1 of Studies M14-867 and M14-868 encompassing 274 subjects show that the most frequently reported adverse events were fatigue, nausea, and headache (occurring in > 5% of subjects) with the majority being Grade 1 or 2 in severity. Among these 274 subjects, there have been 4 (1.5%) treatment-emergent SAEs reported (all assessed as not related to ABT-493 or ABT-530): pneumonia, atrial fibrillation, B-cell lymphoma, and metastatic prostate cancer. Two subjects (0.7%; 2/274) had treatment-emergent adverse events leading to treatment

discontinuation. One subject with history of irritable bowel disease discontinued for Grade 2 AE of abdominal pain assessed as having a reasonable possibility of relatedness to both the DAAs and RBV. The abdominal pain for this subject resolved after discontinuation from study drugs. The other subject discontinued for the aforementioned Grade 4 SAE of B-cell lymphoma for the purposes of initiating chemotherapy.

In both Studies M14-867 and M14-868, in all subjects with baseline ALT elevations, the ALT levels showed a trend toward normal or became normal with DAA treatment, and there have been no on-treatment ALT elevations above baseline. Other laboratory abnormalities were infrequent and were primarily associated with well-described hemolytic effect of RBV, manifesting as Grade 1 anemia in a total of 4 subjects, all occurring in the RBV-containing arms Study M14-868. Observed total bilirubin elevations were Grade 1 or 2 with predominantly indirect fraction, were mostly isolated occurrences, and normalized or stabilized with continued DAA therapy. Total bilirubin elevations were primarily observed in the RBV-containing arms.

In Part 2 of Study M14-867,¹⁸ a total of 34 GT1-infected subjects without cirrhosis received ABT-493 and ABT-530 for 8 weeks. Among enrolled subjects, there are 29 treatment-naïve subjects. Thirty-three of the 34 (97%) subjects achieved SVR₁₂. One subject discontinued from study drug due to the non-DAA related SAE of adenocarcinoma but did achieve SVR₄; the subject subsequently died due to the aforementioned SAE prior to the post-treatment Week 12 visit. There have been no other SAEs, discontinuations due to adverse events or deaths. Adverse events have been mostly Grade 1 or Grade 2, with the most frequently reported adverse events being fatigue, diarrhea and nausea. There have been no on-treatment ALT elevations above baseline. This study also contains arms to evaluate genotypes 4 – 6 (total 34 patients), who received ABT-493 and ABT-530 for 12 weeks, and have achieved SVR₄ of 100%.

DDI STUDIES WITH CYCLOSPORINE AND TACROLIMUS

Phase 1 drug-drug interaction studies of ABT-493/ABT-530 have been conducted with tacrolimus and cyclosporine (CsA) in healthy volunteers. The pharmacokinetic results from these studies are summarized below:

Tacrolimus Phase 1 Data (Study M13-592): The effect of the combination of 300 mg ABT-493 and 120 mg ABT-530 at steady-state on the pharmacokinetics of a single dose of 1 mg tacrolimus and vice-versa was evaluated in healthy subjects. A single dose of 1 mg tacrolimus did not affect the steady-state exposures of 300 mg ABT-493 and 120 mg ABT-530. Tacrolimus exposures increased by 50% when co-administered with ABT-493 and ABT-530. All study drugs were well-tolerated and no safety concerns were identified. Based on these results, the following dosing recommendations for tacrolimus management during treatment with ABT-493 and ABT-530 are recommended in this study:

- For subjects who are initiating therapy with tacrolimus, the initial dose should be selected from the lower end of the recommended range as per the tacrolimus label (e.g., 0.10 mg/kg/day for adult liver transplant recipients).
- For subjects already taking tacrolimus, dosing should continue with close monitoring of tacrolimus trough levels and tacrolimus dose adjustment as needed.

Cyclosporine Phase 1 Data (Studies M13-584 and M13-605): Study M13-584 evaluated the effect of co-administration of single-dose and multiple-doses of 300 mg ABT-493 and 120 mg ABT-530 with a single dose of 100 mg cyclosporine. Pharmacokinetic results showed that a single dose of cyclosporine modestly increased the steady-state exposures of ABT-493 by 30% – 34% and of ABT-530 by 11% – 26%. The exposures of cyclosporine following a single dose of 100 mg were minimally affected by co-administration of single or steady-state doses of ABT-493 and ABT-530 ($\leq 14\%$ increase). All study drugs were well-tolerated and no safety concerns were identified.

Study M13-605 evaluated the interaction between a single dose of 300 mg ABT-493 and 120 mg ABT-530 and a single dose of 400 mg cyclosporine in healthy subjects.

Preliminary pharmacokinetic results from this study showed that cyclosporine exposures were not affected by co-administration with ABT-493 and ABT-530. However, the exposures of ABT-493 increased 4.5 to 5.1-fold, and for ABT-530 increased 22% to 88% following co-administration of a single dose of 400 mg cyclosporine. All study drugs were well-tolerated and no safety concerns were identified.

Based on pharmacokinetic results from these two studies, the following recommendations are made for cyclosporine management during treatment with ABT-493 and ABT-530:

- The dose of cyclosporine with ABT-493/ABT-530 (300/120 mg QD) should not exceed 100 mg once daily for entry into the study. If the cyclosporine maintenance dose needs to be increased to a total daily dose greater than 100 mg during the Treatment Period, discussion with the Therapeutic Area Medical Director should occur. Dosages of cyclosporine > 400 mg are not allowed during the Treatment Period.

Study M13-596 is a single-arm, multi-center, open label, Phase 3 study intended to evaluate the safety and efficacy of ABT-493/ABT-530 administered for 12 weeks in adult post-liver or post-renal transplant subjects with chronic HCV GT1 – 6 infection who are treatment-naïve or treatment-experienced with pegIFN or IFN with or without RBV or sofosbuvir with RBV with or without pegIFN (except GT3 infected subjects who must be treatment naïve). Additional discussion and justification of study design may be found in Section 5.6.1.

A detailed discussion of the preclinical pharmacology and toxicology, in vitro virology and metabolism, drug-drug interaction and clinical data can be found in the ABT-493/ABT-530 Fixed-Dose Combination Investigator's Brochure.²⁰

3.1 Differences Statement

The current study (Study M13-596) is the first study to evaluate the safety and efficacy of the ABT-493/ABT-530 combination regimen in chronic HCV GT1 – 6 infected, post-primary orthotopic liver or renal transplant subjects. The ongoing Phase 2b studies (Studies M14-867 and M14-868) were designed to assess the efficacy, safety and pharmacokinetics of the combination regimen of ABT-493 and ABT-530 administered for 12 and 8 weeks in subjects with HCV GT1 – 6 infection and provide the main supporting data and rationale of the advancement of the ABT-493/ABT-530 fixed dose combination regimen into this Phase 3 study. Study M13-596 will evaluate the co-formulated, fixed dose combination tablet of ABT-493/ABT-530 intended for marketing. Other ongoing Phase 3 studies within the program, including other special populations, exclude post-transplant subjects, thus the need for a dedicated study in this population.

3.2 Benefits and Risks

Preliminary efficacy data in Studies M14-867 and M14-868 demonstrated high rates of SVR₁₂ (89% to 100% SVR₄ or SVR₁₂) in subjects with HCV GT1 – 6 infection without cirrhosis who received ABT-493 in combination with ABT-530 for 12-weeks.

One hundred percent of subjects (n = 40) who received ABT-493 200 mg + ABT-530 120 mg × 12 weeks in Study M14-867 achieved SVR₁₂. Preliminary safety data across the GT1 – 3 arms in Part 1 of Studies M14-867 and M14-868 using a regimen containing ABT-493 at a 300 mg dose (n = 89) demonstrate an acceptable safety profile.

In the post liver and renal transplant population, the risks associated with ABT-493 and ABT-530, including the risks of toxicity and virologic failure, are anticipated to be limited and manageable based on the results of the Phase 2 trials which are summarized in the Introduction (Section 3.0). The efficacy of this regimen has not yet been defined in this population, and it is possible that the treatment failure rate may be higher than what was observed in the Phase 2 trials for the non-immunosuppressed populations. Although the present study is limited to subjects without cirrhosis, hepatic decompensation and/or graft failure can still occur in the post-transplant population. Other risks include the potential

for alterations in immunosuppressant exposures, specifically tacrolimus, sirolimus, and everolimus, though the risk will be mitigated with close monitoring of immunosuppressant drug levels. However, as RBV-free treatment options are limited within this patient population, the potential benefits of treatment outweigh the potential risks.

Adverse events that are known, and those not previously described, may occur with the combination of the two DAAs, as detailed in the informed consent for this study. In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures. Additional safety data for each DAA alone and the combination of ABT-493 and ABT-530 are detailed in Section 3.0 and in the Investigator's Brochure.

Given the potential high SVR rate in populations of HCV-infected subjects, the benefit-risk profile for co-administered ABT-493 and ABT-530 as treatment for chronic HCV infection is favorable.

4.0 Study Objective

4.1 Primary Objective

The primary objectives of this study are to compare the 12-week sustained virologic response, SVR₁₂ (HCV RNA < LLOQ 12 weeks following therapy) of 12 weeks of treatment with the ABT-493/ABT-530 combination regimen in adults with HCV genotype GT1 – 6 infection who are post primary orthotopic liver transplant or renal transplant to a pre-defined threshold, based on the historical SVR₁₂ rates for the current standard of care regimens (sofosbuvir/ledipasvir plus ribavirin or sofosbuvir plus daclatasvir plus RBV) and to assess the safety of treatment with the ABT-493/ABT-530 combination regimen for 12 weeks in adults with HCV genotype GT1 – 6 infection and post primary orthotopic liver transplant or renal transplant.

4.2 Secondary Objective

The secondary objectives are to assess:

- The percentages of subjects with on-treatment virologic failure.
- The percentages of subjects with post-treatment relapse.

Additional objectives are to assess pharmacokinetics and emergence/persistence of viral variants in these treatment regimens.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

The study was designed to enroll approximately 90 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled. The number of GT1 subjects included will be a maximum of approximately 50 subjects for the overall study to ensure enrollment of other genotypes. A minimum of 15 post-renal transplant subjects will be included in the study.

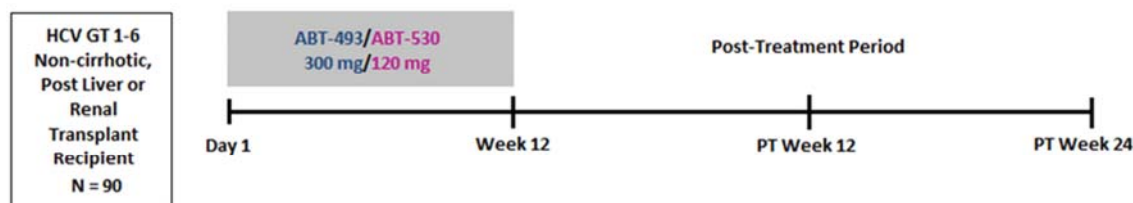
This is a Phase 3, single arm, open-label, multicenter study to evaluate the safety and efficacy of ABT-493/ABT-530 in chronic HCV GT1 to 6-infected non-cirrhotic (F0-F3) subjects who have received a primary orthotopic liver or renal transplant who are either HCV treatment-naïve or prior treatment-experienced with IFN or pegIFN with or without RBV or sofosbuvir with RBV with or without pegIFN (except GT3-infected subjects who must be treatment-naïve).

This study consists of 2 Periods:

- Treatment Period: Enrolled subjects will receive 12 weeks of ABT-493/ABT-530.
- Post-Treatment Period: Subjects who complete or prematurely discontinue the treatment period will be followed for 24 weeks after their last dose of study drug to evaluate efficacy and to monitor HCV RNA and the emergence and persistence of viral variants.

A study schematic is shown below in [Figure 1](#).

Figure 1. Study Schematic



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

5.1.1 Screening

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study specific procedures will receive a unique subject number via the Interactive Response Technology (IRT) system and will undergo the study procedures identified in Section 5.3.1.1. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through Study Day 1 prior to dosing, and will record the results of this assessment and the details of the informed consent process in the subject's medical records. Eligible subjects have up to 42 days following the Screening Visit to enroll into the study.

An immunosuppression regimen diary will be provided to subjects during screening to begin recording all cyclosporine, sirolimus, everolimus, and/or tacrolimus (CNI/mTOR) dosing information including date, time, and dose.

For subjects who do not meet the study eligibility criteria or for eligible subjects that are not able to enroll due to enrollment being completed, the site personnel must register the subject as a screen failure in both IRT and EDC systems.

5.1.1.1 Retest/Rescreening

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

- A positive Hepatitis B surface antigen (HBsAg);
- A positive HIV-1 Ab test;
- HCV genotype indicating co-infection with more than one HCV genotype;
- A positive serum pregnancy test (if female).

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

Retesting:

Subjects who have exclusionary laboratory parameter(s) per Exclusion Criterion 9, Section 5.2.2 are allowed to retest on the related panel(s) (e.g., exclusionary ALT requires a repeat chemistry panel) within the same screening period and must meet all other eligibility laboratory criteria on the panel that is repeated. If the retest result(s) are also exclusionary, the subject may only be rescreened or retested again with approval from the Primary Therapeutic Area Medical Director.

Rescreening:

Subjects that exceed the initial 42-day screening period should be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary at the first screening attempt (with the exception of HIV, HBV, HCV genotype and subtype, follicle stimulating hormone (FSH), which do not need to be repeated). The FibroScan and liver biopsy do not need to be repeated for rescreened subjects provided that the date of the liver biopsy is within 6 months of the rescreening date and the FibroScan is within 3 months of the rescreening date (Section 5.1.1).

The Primary Therapeutic Area Medical Director should be contacted for approval prior to rescreening. Subjects that are beyond the initial 42-day screening period may still be allowed to enroll within a reasonable time period if they continue to meet all eligibility

criteria and have received approval by the Primary Therapeutic Area Medical Director. If rescreened, the 42 day screening period restarts, and subjects retain their initial subject number.

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

5.1.2 Treatment Period

After meeting the eligibility criteria, subjects will be enrolled via IRT on Study Day 1. Subjects will be administered study drugs at the site on Study Day 1, and given instructions about the administration of study drugs, immunosuppression medication and dosing schedule.

Subject immunosuppression dosing regimen diaries will be maintained throughout the trial, for all subjects taking cyclosporine, sirolimus, everolimus, and/or tacrolimus during the Screening, Treatment and Post-Treatment periods. All doses of these medications are to be recorded in the diary, including dosage strength, date, and time. The information collected in the diaries will be reviewed during each study visit and recorded in the eCRF in addition to the local laboratory immunosuppression level results. Diaries should be dispensed, collected and reviewed at each study visit as indicated in [Appendix C](#) and [Appendix D](#). Subjects should be reminded to bring the diary to each study visit.

At any time during the treatment period, the investigator may perform supplemental immunosuppression level testing as an unscheduled visit.

Refer to Section [5.2.3.2](#) (Management of Immunosuppressive Agent Dosing) for details regarding management of the immunosuppressive regimen (CNI and mTOR) during the treatment period.

Study visits and procedures during the Treatment Period are detailed in [Appendix C](#). Safety and tolerability will be assessed throughout the study. Laboratory testing will

include chemistry, hematology, coagulation panel and urinalysis as specified in [Table 2](#). Plasma samples for pharmacokinetic analysis (including optional samples for intensive PK analysis) and HCV RNA analysis will be collected as detailed in [Section 5.3.1.1](#) and [Section 5.3.2](#), respectively. Blood samples for optional pharmacogenetic analysis will be collected as detailed in [Appendix C](#).

All subjects will continue to return to the site on an outpatient basis as outlined in [Appendix C](#). Sites should ensure that subjects adhere to all the study visits. Subjects who cannot complete their study visit per the visit schedule should ensure that they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate study drug exposure.

The virologic failure criteria will be evaluated and applied by the investigator as detailed in [Section 5.4.1.1](#).

Subjects who prematurely discontinue from the Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined in [Appendix C](#) and as described in [Section 5.4.1](#). Subjects who prematurely discontinue from study treatment will continue to be followed in the Post-Treatment Period (see [Section 5.1.3](#)).

5.1.3 Post-Treatment Period

All subjects who received at least one dose of study drug will be monitored in the Post-Treatment Period for safety, HCV RNA and the emergence and persistence of viral variants for an additional 24 weeks following the last dose of study drug. The Post-Treatment Period will begin the day following the last dose of study drug treatment. Study visits during the Post-Treatment period are detailed in [Appendix D](#) and [Section 5.3.1.1](#).

On Day 1 of the Post-Treatment Period, it is recommended that the pre-study dose of immunosuppressants tacrolimus, sirolimus, everolimus and cyclosporine be resumed. Further modifications in tacrolimus, sirolimus, everolimus and cyclosporine dosing or

dose frequency should be guided by measuring trough level testing. During the post-treatment period, the investigator may need to monitor and adjust the dosing of cyclosporine, tacrolimus, everolimus, and sirolimus for study subjects.

Subjects who prematurely discontinue the Post-Treatment Period should return to the site for a Post-Treatment discontinuation visit as outlined in [Appendix D](#).

5.2 Selection of Study Population

The study population will consist of chronic HCV-infected GT1 – 6 males and females, who have received a primary orthotopic liver transplant or primary renal transplant, are non-cirrhotic (F0-F3), and who are either HCV treatment-naïve or prior treatment-experienced with IFN or pegIFN with or without RBV or sofosbuvir with RBV with or without pegIFN (except for GT3 subjects who must be treatment-naïve).

5.2.1 Inclusion Criteria

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

1. Male or female at least 18 years of age at time of Screening.
2. If female, subject must be either postmenopausal (defined in Section [5.2.4](#)), OR permanently surgically sterile OR for Women of Childbearing Potential practicing at least one protocol specified method of birth control (see Section [5.2.4](#)), starting at Study Day 1 through at least 30 days after the last dose of study drug.

For male subjects, no contraception is required.

3. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section [5.2.4](#)) at Screening do not require pregnancy testing.
4. Screening laboratory result indicating HCV GT 1, 2, 3, 4, 5 or 6 infection.

5. Subject has positive anti-HCV Ab and plasma HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.
6. Chronic HCV infection defined as one of the following:
 - Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, or
 - A liver biopsy consistent with chronic HCV infection, or
 - Abnormal alanine aminotransferase (ALT) levels for at least 6 months before Screening.
7. Subject must be HCV treatment-naïve (i.e., subject has not received a single dose of any approved or investigational anti-HCV medication) or HCV treatment-experienced (subject has failed prior treatment with IFN or pegIFN with or without RBV or sofosbuvir with RBV with or without pegIFN), pre- or post-transplant. Previous HCV treatment must have been completed ≥ 2 months prior to screening. GT3 subjects must be treatment-naïve.
8. Body Mass Index (BMI) is ≥ 18.0 kg/m² at the time of Screening. BMI is calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m).
9. Subjects must be documented as non-cirrhotic defined as meeting one of the following criteria:
 - A liver biopsy within 6 months prior to or during Screening demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of ≤ 3 , Ishak fibrosis score of ≤ 4 ; or
 - A FibroScan[®] score of < 12.5 kPa within 3 months of Screening or during the Screening Period;
 - Subjects with indeterminate FibroScan[®] score ($12.5 \leq \text{score} < 14.6$), must have a qualifying liver biopsy; or
 - A screening FibroTest score of ≤ 0.48 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) < 1 .

- Subjects with indeterminate FibroTest ($0.48 < \text{result} < 0.75$), or conflicting FibroTest and APRI results (e.g., $\text{FibroTest} \leq 0.48$, but $\text{APRI} \geq 1$) must have a qualifying liver FibroScan[®] or biopsy.

Liver biopsy results will supersede Fibrotest[®]/APRI or FibroScan[®] results and be considered definitive. FibroScan[®] results will supersede Fibrotest[®]/APRI results for the determination of absence of cirrhosis.

10. Subjects must voluntarily sign and date an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to the initiation of any screening or study-specific procedures.
11. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.
12. Subject is a recipient of a cadaveric or living donor liver transplant which was a consequence of HCV infection ≥ 3 months prior to screening Or Subject received a cadaveric or living donor kidney at least ≥ 3 months before screening.
13. For subjects with a history of hepatocellular carcinoma (HCC): Subject is a recipient of a cadaveric or living donor liver transplant ≥ 3 months prior to screening as a consequence of hepatocellular carcinoma (HCC) in the setting of chronic HCV will be eligible if there is not a clinical diagnosis of recurrent HCC post-liver transplant.
14. Subject is currently taking a stable immunosuppressant regimen based on tacrolimus, sirolimus, everolimus, mycophenolate mofetil (MMF), azathioprine, cyclosporine and/or mycophenolic acid. Corticosteroids such as prednisone or prednisolone are permitted as components of the immunosuppressant regimen providing the dose is no more than 10 mg/day at the time of screening. Cyclosporine must be at a maintenance dose of 100 mg or less per day.

Rationale for Inclusion Criteria

- 1, 4 – 7, 9, 12, 13 In order to select the appropriate subject population with appropriate disease characteristics for evaluation

8, 14	For the safety of study subjects
2, 3	The impact of ABT-493 and ABT-530 on pregnancies is unknown
10, 11	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

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

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol in the opinion of the investigator.
3. Positive test result at Screening for hepatitis B surface antigen (HBsAg) or anti human immunodeficiency virus antibody (HIV Ab).
4. HCV genotype performed during screening indicating co-infection with more than one HCV genotype or if HCV genotype is indeterminate.
5. Requirement for and inability to safely discontinue the medications or supplements listed in [Table 1](#) the protocol (Section [5.2.3.4](#)) at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of any study drug.
6. Clinically significant abnormalities, other than HCV infection, that make the subject an unsuitable candidate for this study in the opinion of the investigator, including, but not limited to:
 - Active or suspected malignancy.
 - Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric, metabolic, or other medical disease or disorder, which is unrelated to the existing HCV infection.

- Uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% at the Screening Visit.
7. Any cause of liver disease post transplantation other than chronic HCV infection including but not limited to the following:
 - Hemochromatosis
 - Alpha-1 antitrypsin deficiency
 - Wilson's disease
 - Autoimmune hepatitis
 - Alcoholic liver disease
 - Steatohepatitis on liver biopsy considered to be the primary cause of the liver disease rather than concomitant/incidental with HCV infection.
 8. Clinical history of Fibrosing cholestatic hepatitis at any time post-transplant.
 9. Screening laboratory analyses showing any of the following abnormal laboratory results:
 - ALT and AST > 10 × ULN
 - Albumin < 3.5 g/dL
 - Hemoglobin < 10 g/dL
 - Platelets < 70,000
 - Calculated creatinine clearance (using Cockcroft-Gault method) of < 30 mL/min
 - Direct bilirubin > 2 mg/dL
 - International Normalized Ratio (INR) > 1.5 ULN
 10. Clinical history of acute renal failure in the 3 months prior to screening.
 11. Re-transplantation of the liver or kidney.
 12. Recipient of liver or kidney from a donor with known HIV infection and/or HBV surface antigen positive.
 13. Steroid resistant rejection of the transplanted liver or kidney, or a history of rejection treated with high dose steroid within 3 months of screening.
-

14. History of post-transplant complications related to hepatic or renal vasculature.
15. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks (whichever is longer) prior to study drug administration.
16. Receipt of any other investigational or commercially available direct acting anti-HCV agents other than sofosbuvir (e.g., telaprevir, boceprevir, simeprevir, paritaprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir or dasabuvir).
17. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-493/ABT-530.
18. History of severe, life-threatening or other significant sensitivity to any excipients of the study drugs.
19. Subjects who cannot participate in the study per local law.

Rationale for Exclusion Criteria

1, 6, 9, 11, 13 – 19	In order to ensure safety of the subjects throughout the study
2, 5, 10, 12	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications
3, 4, 7, 8, 12	To exclude subjects with HIV or liver diseases other than chronic HCV GT1 – 6 infection

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving from the time of signing consent, or received during the study, through the Treatment Period and 30 days after study drugs are stopped, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route

and frequency. The investigator should review all concomitant medications for any potential drug-drug interactions.

During the Post-Treatment Period, all medications taken will be recorded until 30 days following the last dose of study drugs. After 30 days post-treatment, during the Post-Treatment Period, only antiviral therapies related to the treatment of HCV and medications prescribed in association with a serious adverse event (SAE) will be recorded in EDC.

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

5.2.3.1 Prior HCV Therapy

Subjects must be HCV treatment-naïve or treatment-experienced, with the exception of HCV GT3 treatment-experienced subjects who will not be eligible. Subjects will be considered treatment-experienced, if they have previously received HCV treatment with IFN or pegIFN with or without RBV or sofosbuvir with RBV with or without pegIFN. Receipt of any other investigational or commercially available direct acting anti-HCV agents other than sofosbuvir is not allowed.

Subjects will be categorized as:

- Treatment-naïve: subject has never received any treatment for HCV infection.
- Subjects with **an allowed prior treatment** will be categorized as:
 - **Non-responder:** HCV RNA detected at the end of a prior treatment course (except for breakthrough, which is captured separately). These subjects are further categorized as:
 - Null responder: failed to achieve a 1 log₁₀ IU/mL reduction in HCV RNA by Week 4 or a 2 log₁₀ IU/mL reduction in HCV RNA by Week 12 during a prior treatment course;

- Partial responder: achieved at least a 2 log₁₀ IU/mL reduction in HCV RNA by Week 12 during a prior treatment course but failed to achieve HCV RNA undetectable at the end of treatment;
- Unknown or unable to specify: insufficient data to categorize as null or partial responder.
- **Breakthrough:** confirmed ≥ 1 log₁₀ IU/mL increase from nadir or achieved HCV RNA undetectable (or unquantifiable) during a prior treatment course but HCV RNA was quantifiable during or at the end of treatment.
- **Relapse:** achieved HCV RNA undetectable at the end of a prior treatment course but HCV RNA was detectable following cessation of therapy.
- **Other:** subject received a prior treatment course and reason for not achieving SVR is other than above.
- **Unknown:** subject received a prior treatment course and reason for not achieving SVR is unknown.

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

5.2.3.2 Management of Immunosuppressant Agent Dosing

Drug-drug interaction studies have been conducted for ABT-493/ABT-530 co-administered with cyclosporine or tacrolimus and are detailed, along with the dosing recommendations during the Treatment Period as follows:

Dosing recommendations for tacrolimus management during treatment with ABT-493 and ABT-530 in this study are:

- For subjects who are initiating therapy with tacrolimus, the initial dose should be selected from the lower end of the recommended range as per the tacrolimus label (e.g., 0.10 mg/kg/day for adult liver transplant recipients).
- For subjects already taking tacrolimus, dosing should continue with close monitoring of tacrolimus trough levels and tacrolimus dose adjustment as needed.

Dosing recommendations for cyclosporine management during treatment with ABT-493 and ABT-530 in this study are:

- The dose of cyclosporine with ABT-493/ABT-530 (300/120 mg QD) should not exceed 100 mg once daily for entry into the study. If the cyclosporine maintenance dose needs to be increased to a total daily dose greater than 100 mg during the Treatment Period, discussion with the Therapeutic Area Medical Director should occur. Dosages of cyclosporine > 400 mg are not allowed during the Treatment Period.

For mTOR inhibitors, as the metabolic profile for both sirolimus and everolimus are similar to tacrolimus, management of sirolimus and everolimus will be similar to tacrolimus (refer to Section 3.0 for additional information).

- For subjects who are initiating therapy with sirolimus or everolimus, the initial dose should be selected from the lower end of the recommended range as per the sirolimus and everolimus labels.
- For subjects already taking sirolimus or everolimus, dosing should continue with close monitoring of drug trough levels and dose adjustment as needed.

During this study, the dosing of tacrolimus, cyclosporine, sirolimus and everolimus will be informed by scheduled blood level testing. Tacrolimus, cyclosporine, sirolimus and everolimus blood level testing may be performed at any time during the study at the investigator's discretion. Where possible, it is recommended that CNI and mTOR medications be taken with study drugs in the morning with food. Based on in vitro drug-drug interaction studies, no potential interaction is expected with azathioprine, MMF and mycophenolic acid. Subjects may be on azathioprine, MMF, and/or mycophenolic acid as per the investigator's discretion. Monitoring of azathioprine, MMF, and/or mycophenolic acid levels beyond what is standard and clinically indicated is not required.

CNI dosing in the study is guided by the recommended dose reductions based on healthy volunteer data and modeled to achieve trough levels appropriate in the post-transplant setting. Clinical experience suggests some differences may be observed between patients

in relation to cyclosporine or tacrolimus dosing and associated trough levels. Therefore CNI and mTOR dosing will be guided by frequent trough level estimates, particularly during the first weeks of treatment administration, and by the investigators clinical experience in the management of CNI and mTOR medications in liver or renal transplant recipients.

On Day 1 of the Post-Treatment Period, it is recommended that the pre-study dose of immunosuppressants tacrolimus, sirolimus, everolimus and cyclosporine be resumed. Further modifications in tacrolimus, sirolimus, everolimus and cyclosporine dosing or dose frequency should be guided by measuring trough levels.

5.2.3.3 Concomitant Therapy

Subjects should be on a stable dose of concomitant medications for at least 2 weeks prior to initiation of study drugs. The investigator should confirm that a concomitant medication/supplement can be safely administered with study drugs. Some medications may require dose adjustments due to the potential for drug-drug interactions.

During the Post-Treatment Period, investigators should reassess concomitant medications/supplements and subjects may resume previously prohibited medications/supplements or revert to pre-study doses, 30 days following discontinuation of study drugs, if applicable.

5.2.3.4 Prohibited Therapy

Subjects must be able to safely discontinue any prohibited medications or supplements listed in [Table 1](#) at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of any study drug and not use these during the entire Treatment Period and for 30 days following discontinuation of study drugs.

Table 1. Prohibited Medications and Supplements

Medication or Supplement Name
Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin*
Astemizole, cisapride, terfenadine

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drugs. Subjects receiving these statins should either switch to pravastatin or rosuvastatin prior to the first dose of study drugs or may interrupt statin therapy throughout the treatment period and until 30 days after the last dose of study drug, based on investigator's judgment. If switching to or continuing pravastatin or rosuvastatin, it is recommended to reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drugs.

Use of ethinyl estradiol containing oral contraceptives with ABT-493 and ABT-530 combination was associated with ALT increases in some healthy female subjects. Hormonal contraceptives (including oral, topical [including vaginal rings], injectable, or implantable varieties) containing ethinyl estradiol may not be used from 2 weeks prior to the first dose of ABT-493/ABT-530 until 30 days after the end of ABT-493/ABT-530 dosing. Progestin-only contraceptives, such as those containing norethindrone, desogestrel, or levonorgestrel, without ethinyl estradiol, may be used with ABT-493/ABT-530. Post-menopausal hormone replacement therapy i.e., estradiol, esterified or conjugated estrogens, as long as they do not contain ethinyl estradiol, may be used with ABT-493/ABT-530 at the discretion of the Investigator.

The chronic use of systemic immunosuppressants other than those from the anti-rejection regimen is prohibited from 2 weeks prior to the first dose of study drug and until 30 days after the last dose of study drug including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), or monoclonal antibodies (e.g., infliximab).

5.2.4 Contraception Recommendations and Pregnancy Testing

If female, subject must be either postmenopausal defined as:

- Age \geq 55 years with no menses for 12 or more months without an alternative medical cause.
- Age $<$ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level $>$ 40 IU/L.

OR

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
- Practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.
 - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
 - Bilateral tubal occlusion/ligation.
 - Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.
 - Intrauterine device (IUD).
 - Intrauterine hormone-releasing system (IUS).
 - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 1 month prior to Study Day 1.
 - Male or female condom with or without spermicide. Condom without spermicide is acceptable only in countries where spermicide is not available.
 - Cap, diaphragm or sponge with spermicide.
 - A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier method).
 - True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

For male study subjects no contraception is required.

5.3 Efficacy Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in [Appendix C](#) (Treatment Period) and [Appendix D](#) (Post-Treatment Period).

5.3.1.1 Study Procedures

Informed Consent

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

Medical History

A complete medical history, including date of transplant, type of donor (deceased or living), history of tobacco, alcohol and drug use, will be taken at Screening. The subject's medical history will be updated at the Study Day 1 Visit. This updated medical history will serve as the baseline for clinical assessment.

For all subjects, prior IFN-based HCV treatment history and type of prior treatment response should be collected and recorded in source documentation according to the categories listed in Section [5.2.3.1](#). Data should be collected and recorded for each subject for both pre and post renal and liver transplant settings. Reasonable effort should be made to obtain and document this information.

Physical Examination

A complete physical examination will be performed at visits specified in [Appendix C](#), or upon subject discontinuation. A symptom-directed physical examination may be performed at any other visit, when necessary.

The physical examination performed on Study Day 1 will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after the first dose will be recorded as adverse events.

Height will be measured only at Screening.

Vital Signs and Weight

Body temperature, blood pressure, pulse and body weight will be measured at each study visit as specified in [Appendix C](#) and [Appendix D](#) or upon subject discontinuation. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes. The subject will wear lightweight clothing and no shoes during weighing.

12-Lead Electrocardiogram

A 12-lead resting ECG will be obtained at Screening. The ECG should be performed prior to blood collection.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign, and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

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

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

Local Therapeutic Monitoring for Cyclosporine, Sirolimus, Everolimus, and/or Tacrolimus

Blood samples for immunosuppressant trough level estimation will be submitted to the investigative site's local laboratory for subjects taking cyclosporine, tacrolimus, everolimus and sirolimus as indicated in [Appendix C](#) and [Appendix D](#) and at any other time points that the investigator deems necessary. For each immunosuppressant level blood draw, the result, the date and time of the sample collection and details regarding immunosuppressant dosing will be recorded in the electronic case report form (eCRF).

Investigators will use the local laboratory results for management of immunosuppressant related adverse events or dose modifications during the study. A central laboratory will be utilized to process and provide results for all other clinical laboratory tests.

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in [Table 2](#) at the visits indicated in [Appendix C](#) and [Appendix D](#).

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

clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

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

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

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

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

Covance (Asia) Pte Ltd
1 International Business Park
[REDACTED] The Synergy
Singapore 609917
(For sites in Asia Pacific)

Table 2. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Other Tests
Hematocrit	Blood Urea Nitrogen (BUN)	HBsAg ^c
Hemoglobin	Creatinine	Anti-HCV Ab ^c
Red Blood Cell (RBC) count	Direct and indirect bilirubin	Anti-HIV Ab ^c
White Blood Cell (WBC) count	Total bilirubin	Opiates ^c
Neutrophils	Albumin	Barbiturates ^c
Bands	Aspartate aminotransferase (AST)	Amphetamines ^c
Lymphocytes	Alanine aminotransferase (ALT)	Cocaine ^c
Monocytes	Alkaline phosphatase	Benzodiazepines ^c
Basophils	Calcium	Alcohol ^c
Eosinophils	Inorganic phosphate	Phencyclidine ^c
Platelet count (estimate not acceptable)	Sodium	Propoxyphene ^c
Reticulocyte count	Potassium	Methadone ^c
Prothrombin Time/INR	Cholesterol	Urine and Serum
Activated partial thromboplastin time (aPTT)	Low Density Lipoproteins (LDL) ^{a,b}	Human Chorionic Gonadotropin (hCG) for females ^d
	High Density Lipoprotein (HDL) ^b	
	Chloride	FSH ^h
Urinalysis	Bicarbonate	HCV RNA
Specific gravity	Magnesium	Hepatitis B Panel ^e
Ketones	Total Insulin	Hemoglobin A1C ^c
pH	Total protein	IL28B
Protein	Glucose	HCV genotype and subtype ^c
Blood	Triglycerides	Pharmacogenetic sample (optional)
Glucose	Gamma-glutamyl transferase (GGT)	Alpha2-macroglobulin ^f
Urobilinogen	Creatinine clearance (Cockcroft-Gault calculation)	Haptoglobin ^f
Bilirubin		Apolipoprotein A1 ^f
Leukocyte esterase		Alpha fetoprotein ^c
Microscopic (reflex)		Cyclosporine level ^g
		Tacrolimus level ^g
		Everolimus level ^g
		Sirolimus level ^g

- a. Directly measured.
- b. Performed only at Baseline.
- c. Performed only at Screening.
- d. Pregnancy testing is not required for females of non-childbearing potential.
- e. Performed for management of transaminase elevation (Section 6.1.7.1).
- f. Component of FibroTest and collected only if needed during the Screening Period.
- g. Therapeutic monitoring only performed locally during the study for purposes of immunosuppression dose management.
- h. Only performed if requested during screening for post-menopausal women < 55 to verify FSH level if site does not have one available.

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

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

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

Pregnancy Test

A serum pregnancy test will be performed for all female subjects of childbearing potential at Screening. Additional urine pregnancy tests will be performed at all visits indicated in [Appendix C](#). Pregnancy testing is not required for females of non-childbearing potential. Determination of postmenopausal status will be made during the Screening period, based on the subject's history.

Hepatitis and HIV Screen

HBsAg (hepatitis B surface antigen), anti-HCV Ab and anti-HIV Ab will be performed at Screening. The investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report these results per local regulations, if necessary. The HIV results will not be reported by the central laboratory to the clinical database.

Urine Screens for Drugs of Abuse

Urine specimens will be tested at the Screening Visit for the presence of drugs of abuse. The panel for drugs of abuse will minimally include the drugs listed in [Table 2](#). Any positive result must be assessed for clinical significance.

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

Liver Diagnostic Testing

At Screening, it is recommended that subjects should otherwise meet all of the inclusion criteria and none of the exclusion criteria before undergoing a liver biopsy.

Subjects who have not had a qualifying liver biopsy within the previous 6 months or who have not had a qualifying FibroScan within the previous 3 months but otherwise meet all of the inclusion criteria and none of the exclusion criteria will undergo liver biopsy or non-invasive testing (FibroTest and APRI or FibroScan) for assessment of cirrhosis prior to enrollment. Selection of liver biopsy or non-invasive testing performed should be based on local standard practice.

Subject will be considered to be non-cirrhotic and eligible for the study if they meet at least one of the criteria listed in the Inclusion Criterion 9 (Section 5.2.1).

Patient Reported Outcomes (PRO) Instruments (Questionnaires)

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

PRO instruments should be consistently presented as listed in [Appendix C](#) and [Appendix D](#), so that subjects complete the questionnaires in the following order: the SF-36v2, FSS and EQ-5D-3L. The PRO instruments should be completed prior to study

drug administration on Day 1 and prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels.

Short Form 36 (SF-36) – Version 2 Health Survey

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

Fatigue Severity Scale (FSS)

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

EuroQol-5 Dimensions-3 Level (EQ-5D-3L)

The EQ-5D-3L is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-3L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on 3 levels of severity (no problems, some problems, unable to do/extreme problems). Responses to the 5 items encode a discrete health state which is mapped to a preference (utility) specific for different societies. Subjects also rate their perception

of their overall health on a separate visual analogue scale (VAS). The EQ-5D-3L should require approximately 5 minutes to complete.

Enrollment and Assignment of Subject Numbers

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

Subject numbers will be unique 6-digit numbers and will begin with 100301 with the first three digits representing the investigative site, and the last three digits representing the subjects at that site. Enrolled subjects will keep their subject number throughout the study.

Study Drug Compliance for Kits

Individual bottles of ABT-493/ABT-530 will be provided for subject dosing to the site. Each subject will have compliance documented by the site in the subject's source notes for ABT-493/ABT-530. At each Study Drug Accountability Visit listed in [Appendix C](#), the overall number of tablets of ABT-493/ABT-530 remaining in each bottle will be recorded and entered in the IRT system along with the date of reconciliation.

Additional information regarding treatment compliance can be found in Section [5.5.6](#).

HCV Genotype and Subtype

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

HCV RNA Levels

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

HCV Resistance Testing Sample

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

Archive Plasma Sample

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

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

Immunosuppression Regimen Dosing Diary

A subject immunosuppression regimen dosing diary will be provided to all subjects taking cyclosporine, sirolimus, everolimus, and/or tacrolimus during Screening and for 30 days into the Post-Treatment period. All doses of these immunosuppressive medications will be recorded in the diary by study subjects, including dosage strength, date, and time. The information collected in the diaries will be reviewed during each study visit and recorded

in the eCRF along with the local laboratory therapeutic monitoring laboratory results. Site personnel will provide training on its proper use and subjects will be instructed to complete the required information and ensure that entries are accurate and current at all times.

Diaries should be dispensed, collected and reviewed at each study visit as appropriate as indicated in [Appendix C](#) and [Appendix D](#). Subjects should be reminded to bring the completed diary to each study visit.

Study Drug Dosing Card

Subjects will be provided with self-administration instructions and study drug dosing cards to record the exact date, time (record to the nearest minute) and number of tablets of study drug administration (ABT-493/ABT-530) for the last 2 doses of each study drug taken prior to the scheduled pharmacokinetic sample collection during the Treatment Period.

The site staff will record the information about the last 2 doses taken prior to the scheduled pharmacokinetic sample collection from the study drug dosing card into the eCRF. In the event that the dosing card is not available, the site may obtain dosing information via patient interview and record this information in the source notes.

To facilitate proper dosing of study drug before pharmacokinetic evaluation blood samples are taken, the following procedures should be performed:

- The study coordinator should make sure the subject is given the dosing card at the visits listed in [Appendix C](#) and that instruction is provided to the subject regarding proper study drug administration relative to the pharmacokinetic blood collection and documentation of dosing times on the dosing card.
- The completed dosing card will be collected by the Investigator or designee on the day of the visit and be kept as a source record of dosage administration times documented in the eCRF.

5.3.1.2 Meals and Dietary Requirements

Study drug (i.e., ABT-493/ABT-530) tablets should be dosed together and taken with food. When an immunosuppressant medication is scheduled to be taken, per direction from the investigator, the medication should be administered with the study drug.

5.3.1.3 Collection and Handling of Pharmacogenetic Exploratory Research Samples

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

IL28B Sample

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

5.3.1.4 Optional Sample for Pharmacogenetic Exploratory Research

Subjects will have the option to provide samples for optional pharmacogenetic exploratory research. Subjects may still participate in the main study even if they decide not to participate in this optional exploratory research.

An optional whole blood sample for DNA isolation will be collected on Day 1 from each subject who consents to provide samples for exploratory research. If the sample is not collected on Day 1, the sample may be collected at any time throughout the study.

AbbVie (or people or companies working with AbbVie) will store the optional pharmacogenetic exploratory research samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABT-493/ABT-530 (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion. The procedure for

obtaining and documenting informed consent for exploratory research samples is discussed in Section 9.3.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic assays of ABT-493, ABT-530 and their possible metabolites will be collected by venipuncture at each study visit indicated below and in [Appendix C](#).

Subjects who do not participate in Optional Intensive PK sampling:

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

Subjects who consent to participate in Optional Intensive PK sampling:

- On Study Day 1 and the Week 4 visit, subjects will have their dose administered by study site personnel with food. Blood samples will be collected on Study Day 1 at 2, 4 and 6 hours post-dose and at the Week 4 Visit immediately prior to dose (0 hour) and 2 and 4 hours post-dose.
 - The date and time of site-administered dose, blood sample collection and the two previous doses of study drug (for Week 4 Visit only) will be recorded to the nearest minute in the source documents. Additionally, the date and time of the site-administered dose and two previous doses (for Week 4 Visit only) will be recorded in the eCRF.
- At all other Treatment Period visits, a single blood sample (3 mL) will be collected without regard to the time of dosing.
 - The date and time of blood sample collection and the two previous doses of the study drug will be recorded to the nearest minute in the source

documents. Additionally, the date and time of the two previous doses of the study drug will be recorded to the nearest minute on the eCRF.

5.3.2.2 Handling/Processing of Samples

Specific instructions for collection of blood samples and subsequent preparation and storage of the plasma samples for the pharmacokinetic assays of ABT-493 and ABT-530 will be provided by the central laboratory, the Sponsor, or its designee.

5.3.2.3 Disposition of Samples

The frozen plasma samples for the pharmacokinetic assays of ABT-493, ABT-530, their possible metabolites and archive plasma samples will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory.

The central laboratory will then ship the ABT-493 and ABT-530 samples to the reference laboratories following separately provided instructions.

5.3.2.4 Measurement Methods

Plasma concentrations of ABT-493 and ABT-530 will be determined using validated assay methods under the supervision of the Drug Analysis Department at AbbVie. Plasma concentrations of possible metabolites of any analytes listed above may also be determined using either validated or non-validated methods.

5.3.3 Efficacy Variables

Virologic response will be assessed by plasma HCV RNA levels in IU/mL at various time points from Day 1 through 24 weeks after completion of treatment.

5.3.3.1 Primary Variable

The primary efficacy variable is SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

5.3.3.2 Secondary Variable(s)

The secondary efficacy variables are on-treatment virologic failure and post-treatment relapse.

Additional efficacy variables include: SVR₄, SVR₂₄, and the percentage of subjects who relapsed after achieving SVR₁₂.

5.3.4 Resistance Variables

For all subjects receiving ABT-493/ABT-530, the variants at signature resistance-associated amino acid positions at baseline identified by population or deep sequencing and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving ABT-493/ABT-530 who do not achieve SVR₁₂ and who have a post-baseline sample with HCV RNA \geq 1000 IU/mL: 1) the amino acid variants in available post-baseline samples identified by population or deep sequencing and comparison to the baseline sequence, 2) the amino acid variants in available post-baseline samples at signature resistance associated positions identified by population or deep sequencing and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral resistance by population or deep sequencing.

5.3.5 Safety Variables

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

5.3.6 Pharmacokinetic Variables

Individual plasma concentrations of ABT-493 and ABT-530 and possible metabolites of ABT-493 and ABT-530 will be tabulated and summarized. Individual blood

concentrations of immunosuppressants, cyclosporine, sirolimus, everolimus, and/or tacrolimus, will also be tabulated and summarized.

5.3.7 Pharmacogenetic Exploratory Research Variables

IL28B status will be determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. These IL28B GT results may be analyzed as part of a multi-study assessment of IL28B and response to ABT-493, ABT-530, or drugs of these classes. The results may also be used for the development of diagnostic tests related to IL28B and study treatment, or drugs of these classes. The results of additional IL28B pharmacogenetic analyses may not be reported with the clinical study report.

Optional pharmacogenetic samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the study drug (or drugs of the same or similar class) or the development and progression of the subjects' disease or related conditions. The samples may also be used to develop new diagnostic tests, therapies, research methods or technologies. The results from these analyses are exploratory in nature and may not be included with the study report.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

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

If, during the course of study drug administration, the subject prematurely discontinues, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in [Appendix C](#). Ideally this should occur on the day of study drug

discontinuation, but no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment. The last dose of any study drug and reason for discontinuation will be recorded in the EDC (electronic data capture) system. The subject should then begin the Post-Treatment Period where the subject will be monitored for 24 weeks for HCV RNA and the emergence and persistence of resistant viral variants.

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

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

For subjects who are receiving study drugs and experience an episode of rejection of the transplanted liver or kidney that is presumed or histologically confirmed, the Primary Therapeutic Area Medical Director should be contacted to discuss the planned evaluation and/or treatment plan. Subjects who are receiving study drugs and experience an episode of rejection of the transplanted liver or kidney that is presumed or histologically confirmed may continue the study drugs per investigator discretion. Should there be a need to discontinue the study drugs, the subject should enter the Post-Treatment Period. Treatment(s) of a rejection episode, e.g., by use of corticosteroids or other agents, will be

captured in eCRF as part of the adverse event reporting. Alternative management of study drug in this setting requires Primary Therapeutic Area Medical Director approval.

For subjects discontinuing study drugs, investigators should be aware of the potential for consequent alterations in immunosuppressant levels and should ensure that a plan is in place for appropriate immunosuppressant dose modification in the PTP and this plan should be discussed with the study subject. See Section 5.2.3.2 for further information on the management of immunosuppressants.

5.4.1.1 Virologic Failure Criteria

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

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

When confirmatory testing is required, it should be completed as soon as possible and the subject should remain on study treatment until the virologic failure criteria has been confirmed. Subjects meeting the virologic failure criteria will be discontinued from study drug and will continue to be followed in the Post-Treatment Period for the emergence and persistence of resistant viral variants until 24 weeks post-treatment.

5.4.2 Discontinuation of Entire Study

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

concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

The study drug (ABT-493/ABT-530) will be dispensed in the form of co-formulated tablets at the visits listed in [Appendix C](#). Subjects will be instructed to take study drugs at the same time every day with food. Prior to all visits with pharmacokinetic sampling, the date and time of the two previous doses will be recorded to the nearest minute in the source documents and the eCRF.

ABT-493/ABT-530 will be provided by AbbVie as 100 mg/40 mg Film-coated tablets. ABT-493/ABT-530 will be taken orally at ABT-493 300 mg/ABT-530 120 mg (three × ABT-493 100 mg/ABT-530 40 mg tablets) QD and with food.

Subjects will be instructed to take study medication at the same time(s) every day. All compounds including cyclosporine, sirolimus, everolimus, tacrolimus, azathioprine, MMF, and mycophenolic acid should be taken together with food. This is important as taking the DAAs in combination with the immunosuppressants at different times can significantly impact the levels of the immunosuppressant medications.

Investigators should inform subjects in advance of Study Day 1 of the plan for cyclosporine, sirolimus, everolimus or tacrolimus management during the study, e.g., an investigator may wish to instruct a subject not to take their morning CNI/mTOR dose prior to the site visit on Study Day 1.

Beginning with Study Day 1, the site will use the IRT system to obtain the study drug kit numbers to dispense at the study visits specified in [Appendix C](#). Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. The site will also contact the IRT

system to provide study drug return information for each kit at the visits specified in [Appendix C](#). At the end of the Treatment Period or at the Premature D/C Visit from the Treatment Period, the site will contact the IRT system to provide the discontinuation visit date information and study drug return information for each kit.

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

5.5.2 Identity of Investigational Products

Information about the study drugs to be used in this study is presented in [Table 3](#).

Table 3. Identity of Investigational Products

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
ABT-493/ABT-530	AbbVie	Oral	Film-coated Tablet	100 mg/40 mg

5.5.2.1 Packaging and Labeling

All study drugs will be supplied in bottles.

Each bottle will be labeled as required per country requirements.

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

5.5.2.2 Storage and Disposition of Study Drug

Study Drug	Storage Conditions
ABT-493/ABT-530 bottles	15° to 25°C (59° to 77°F)

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

5.5.3 Method of Assigning Subjects to Treatment

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

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

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

5.5.4 Selection and Timing of Dose for Each Subject

Study drug dosing will be initiated at the Study Day 1 Visit. ABT-493/ABT-530 will be dosed every morning with food. Study drug and allowed immunosuppressants (cyclosporine, everolimus, sirolimus, tacrolimus, azathioprine, MMF, and mycophenolic acid) should be taken together with food at approximately the same times in the morning every day. This is important as taking the DAAs in combination with the immunosuppressants at different times can significantly alter the level of the immunosuppressants.

Selection of the doses for this study is discussed in Section [5.5.4](#).

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with

the protocol. The study drug must not be used for reasons other than that described in the protocol.

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

At each study visit after Day 1 during the Treatment Period, subjects will be instructed to bring all bottles of study drug (full, partial or empty) for assessment of treatment compliance. At post-baseline dispensing visits denoted in [Appendix C](#), study site personnel will assess subject compliance by inspecting the contents of the bottles and recording the status of each one, the site will record the exact number of remaining tablets of ABT-493/ABT-530 in IRT. Treatment compliance will be based on the number of tablets dispensed, as recorded in IRT, and the number of remaining tablets. If poor compliance is noted, the subject should be counseled and this should be documented in the subject's source.

5.5.7 Drug Accountability

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

During the study, should an enrolled subject misplace or damage a study drug bottle of ABT-493/ABT-530 the IRT system must be contacted and informed of the misplaced or

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

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

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design

This is a multicenter, Phase 3 single arm, open-label study in treatment naïve and prior IFN and/or pegIFN with or without RBV or sofosbuvir with RBV with or without pegIFN treatment-experienced, HCV GT1 – 6-infected adult subjects without cirrhosis designed to evaluate the safety and efficacy of ABT-493/ABT-530 300/120 mg administered QD for 12 weeks in subjects who are post primary liver or post renal transplant. Evaluation for the 12 week treatment duration in the current study is supported by preliminary data from the Phase 2b Studies M14-867 and M14-868, with high SVR in GT1 – 6 non-cirrhotic populations. Drug-drug interactions between ABT-493/ABT-530 and tacrolimus and cyclosporine have been evaluated in multiple Phase 1 studies. Active comparator and Placebo controlled trials are ongoing in current Phase 3 Studies M15-464 and M13-594.

As this study is to evaluate the safety and efficacy of the combination in the Post-transplant subpopulation, a single arm study was chosen, as placebo or active comparator arms may not yield additional information from that being obtained by the aforementioned ongoing studies. In addition, the potential to eradicate HCV infection while avoiding the limitations and toxicities of both IFN and RBV could represent a significant advance in treatment options in this population. Given these considerations, the absence of randomization, blinding, and control groups is appropriate.

Efficacy for the 12-week regimen in this study will be established by demonstrating non-inferiority to a historical control regimen because the SVR₁₂ rate for the current standard of care regimens of SOF/LDV plus RBV or SOF plus DCV plus RBV for 12 weeks in the post-transplant population is sufficiently high (95%). The justification of the historical control SVR₁₂ rate and the non-inferiority margin of 8% is described in Section 8.2.1.

This study will evaluate the potential to eradicate HCV starting in the early post-transplant period by treating subjects as early as 3 months post-transplant. Given the universal recurrence of HCV after transplantation and the accelerated rate of fibrosis and disease course, it is desirable to have the option to eradicate HCV before or after transplantation, e.g., in the post-transplant period. Treatment in the early post-transplant period, prior to onset of histologic disease, may be called preemptive therapy. Prior to transplant, individuals with Childs B or C stage cirrhosis who are awaiting transplantation may become too medically unstable, e.g., because of fluctuating hepatic and/or renal function, to complete a full treatment course prior to transplantation. Therefore, an important option for some patients would be to eradicate HCV soon after transplantation, preferably before there is evidence of graft fibrosis and potentially prior to detectable HCV induced hepatic injury. Histologic features of hepatitis develop in about 75% of recipients in the first 6 months following liver transplantation.⁶ Therefore, this study will evaluate the treatment of patients starting at 3 months post-transplant, after the immediate post-transplant period and when its attendant complications have been addressed and immunosuppression regimens are typically stable. In this setting with a recent hepatic

graft in situ, subjects are generally anticipated to have limited hepatic disease with a high likelihood of achieving SVR.

This study will also evaluate the potential to eradicate HCV in the post-renal transplant population. Given the impact of HCV nephropathy on the implanted graft, in addition to ongoing liver disease (which has not been treated, thus the liver would be susceptible to the natural course of HCV infection), it is desirable to have the option to eradicate HCV after transplantation, as up to 28% of renal transplant recipients will die of chronic liver disease. Given the high seroprevalence of HCV in the renal transplant population, there remains a need for HCV treatment, as the kidney is the most commonly transplanted organ.

5.6.2 Appropriateness of Measurements

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

The EQ-5D-3L, SF-36 v2 and the FSS instruments are standard in the literature and thoroughly validated.

5.6.3 Suitability of Subject Population

The selection of post-transplant liver and renal subjects infected with HCV GT1 – 6 will allow for the assessment of safety, efficacy and pharmacokinetics of the combination ABT-493/ABT-530 regimen for the duration of 12 weeks.

This study will enroll subjects who are naïve to HCV treatment or who have received prior treatment limited to sofosbuvir with RBV with or without pegIFN or IFN-based treatment for their HCV infection; this will include "pegIFN/RBV-null-responders" who have been considered the most difficult to cure amongst the IFN-experienced subjects. Preliminary data from Study M14-867 Part 1 shows no difference in efficacy in subjects with HCV GT1 when comparing treatment-naïve subjects (49 of 50 with SVR₁₂) and pegIFN/RBV null responders (28 of 28 with SVR₁₂). Similarly, preliminary data from

Study M14-867 Part 2 Arm K shows no difference in efficacy in HCV GT1 subjects when comparing treatment-naïve subjects (28 of 28 with SVR₁₂) and treatment-experienced subjects (5 of 5 with SVR₁₂) with available post-treatment Week 12 data. This study will specifically exclude subjects with any prior exposure to DAA treatment other than sofosbuvir as the effect of possible viral mutants on efficacy of ABT-493/ABT-530 is not fully understood.

This study will enroll HCV-infected subjects without cirrhosis based on the safety and efficacy of ABT-493/ABT-530 demonstrated in non-cirrhotic subjects in Phase 2b Studies M14-867 and M14-868. HCV GT 3, treatment-experienced subjects with cirrhosis are excluded from this study, as this sub-population of HCV-monoinfected subjects is currently being evaluated in the ongoing Part 3 of Study M14-868 to identify the optimal treatment duration in this sub-population.

The age range selected for this study, at least 18 years of age, is also intended to be representative of the target population. Similarly, a substantial portion of the HCV infected population have a relatively high BMI, and given the acceptable safety and pharmacokinetic profiles of ABT-493 and ABT-530 in Phase 1 and 2 studies, this protocol will enroll subjects with a BMI ≥ 18 kg/m².

HCV-infected subjects who are on stable opiate (methadone or buprenorphine/naloxone) maintenance therapy will be allowed to enroll in this study based on the results from Study M13-602 which evaluated the pharmacokinetic, pharmacodynamic, safety and tolerability of the co-administration of buprenorphine/naloxone or methadone and the DAAs (ABT-493 + ABT-530) in adult subjects on stable opioid maintenance therapy and demonstrated acceptable safety and no relevant pharmacokinetic or pharmacodynamic interactions.

5.6.4 Selection of Doses in the Study

High observed SVR rates ($\geq 96\%$) across HCV genotypes and cirrhotic and non-cirrhotic populations from the Phase 2b studies supported evaluating ABT-493 300 mg and

ABT-530 120 mg in HCV GT1 – 6, post-liver or post-renal transplant subjects. To date, the observed SVR rates are consistent with exposure-response model predicted values. Based on results from exposure-response analyses and clinical trial simulations, ABT-493/ABT-530 300/120 mg for 12 weeks is predicted to achieve high SVR in post-liver or post-renal transplant population. Adding ribavirin to the regimen or extending the duration to 16 weeks are not expected to significantly increase the SVR.

ABT-493 and ABT-530 regimens including the proposed 300 mg/120 mg ABT-493/ABT-530 QD regimen have been well-tolerated and safe across all Phase 2b study arms including cirrhotic subjects. All ABT-493 and ABT-530 doses studied had a similar safety profile. The most frequently reported adverse events were fatigue, nausea and headache and were mostly Grade 1 or 2 in severity. In all subjects with baseline ALT elevations, ALT levels normalized or trended toward normal with DAA treatment, and there have been no on-treatment ALT elevations above baseline grade.

- Clinical studies evaluating DDI between ABT-493 + ABT-530 and immunosuppressant drugs including tacrolimus and cyclosporine have been conducted. Results from these studies showed ABT-493 and ABT-530 did not affect cyclosporine exposure, but increased tacrolimus exposure by 50%. ABT-493 and ABT-530 exposures were not affected by tacrolimus. Cyclosporine 100 mg slightly increased exposure of ABT-493 by 37% and ABT-530 by 22%. High dose of cyclosporine (400 mg) significantly increased exposure of ABT-493 (up to 5.1-fold) and ABT-530 (up to 88%). This study will evaluate the treatment of patients in the early post-transplant period (> 3 months post liver transplant) but after the immediate post-transplant period and when its attendant complications have been addressed and CNI based immunosuppression is typically stable. As the recommended dose of cyclosporine used in this population is 75 to 150 mg BID, in order to maintain trough concentration (C_{trough}) of 75 to 125 ng/mL, no dose adjustment is needed for ABT-493 and ABT-530. A co-formulated bilayer tablet of ABT-493 and ABT-530 will be used in this Phase 3 study. Preliminary pharmacokinetic results of the Phase 3 HME bilayer tablet formulation administered under fasting conditions showed approximately 50% lower

bioavailability compared to the Phase 2 formulation at the ABT-493 300 mg + ABT-530 120 mg dose. When the Phase 3 HME bilayer tablet was administered under non-fasting conditions, exposures became relatively similar to the reference Phase 2 formulation. Hence, the Phase 3 co-formulated ABT-493 and ABT-530 HME Bilayer Tablet formulation should be administered with food (300/120 mg, 3 × 100/40 mg tablets) to provide DAA exposures that are similar to those of the Phase 2 formulations.

The maximum dose of ABT-493/ABT-530 will not exceed 300 mg/120 mg per day for 12 weeks.

5.6.4.1 Rationale for Duration Selections

Treatment duration of 12 weeks for this Phase 3 study is supported based on available data (all SVR₄ and available SVR₁₂ rates) from 12-week treatment groups receiving ABT-493/ABT-530 300 mg/120 mg combinations in Phase 2 Studies M14-867 and M14-868 in HCV GT1- to 6-infected non-cirrhotic patients. The combination of ABT-493/ABT-530 in these patients achieved > 93% SVR₄ or SVR₁₂. Study M14-867 also demonstrated efficacy with a shorter duration of 8 weeks of treatment, with 33 of 34 achieving SVR₁₂ (97%), in the GT1 infected subjects without cirrhosis. Though the 8 week treatment duration has demonstrated high SVR rates, as the post-transplant population has been associated with lower overall SVR rates historically compared to the non-transplant mono-infected population, the longer 12 week duration was selected for this study.

5.6.4.2 Risk of Development of Resistance Mutations During Combination DAA Trials

In subjects treated with a DAA, variants with amino acid substitution(s) in the targeted protein conferring resistance to the DAA can be selected. For example, in AbbVie HCV Phase 3 studies in which patients with GT1 infection were treated with the NS3/4A protease inhibitor paritaprevir and NS5A inhibitor ombitasvir, variants that conferred resistance to paritaprevir or ombitasvir were detected in patients experiencing virologic

failure. While data from patients treated with the combination of ABT-493 and ABT-530 are limited, it is expected that ABT-530, an NS5A inhibitor, will be able to suppress the appearance of virus containing resistance-associated variants in NS3 that confer resistance to ABT-493, because there should not be any cross-resistance in variants resistant to DAAs targeting different proteins. The converse is expected to be true as well – ABT-493 should be able to suppress the appearance of virus containing NS5A variants conferring resistance to ABT-530. In addition, in vitro resistant colony selection studies in HCV replicon cells containing GT1 – 6 NS5A demonstrated that ABT-530 had a high genetic barrier to resistance – very few colonies were selected, and those that were selected contained NS5A variants that conferred only modest levels of resistance to ABT-530. It remains to be seen whether the development of resistance in subjects treated with ABT-530 resembles that seen in vitro. Based on accumulated clinical and in vitro data to date, the risk of development of resistant variants during ABT-493 and ABT-530 combination trials is reduced when compared to treatment with first generation protease and NS5A inhibitors. For example, in Phase 2b Study M14-867 Part 1 evaluating the combination of ABT-493 and ABT-530 in 79 GT1-infected subjects without cirrhosis for a 12 week duration, only 1 subject experienced virologic failure, and preliminary sequencing results indicated that treatment-emergent NS5A RAVs were detected at the time of failure in this subject. These results support the prediction that the risk of development of resistance-associated variants with ABT-493 and ABT-530 combination treatment is low.

6.0 Complaints

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

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.8. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic

medical intervention, meets protocol specific criteria (see Section 6.1.7 regarding toxicity management) and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome

An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4).

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

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

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

ADL = Activities of Daily Living

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

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

6.1.3 Relationship to Study Drug

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

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

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

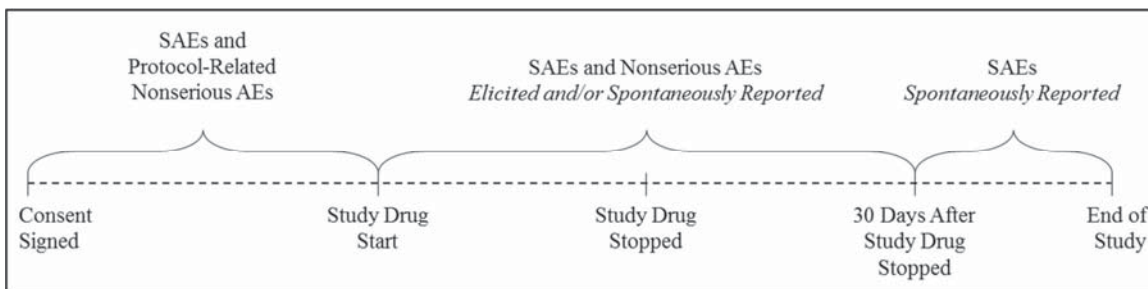
For serious adverse events, if an investigator's opinion of relatedness is "no reasonable possibility of being related to study drug" an "other" cause of event must be provided by the investigator.

6.1.4 Adverse Event Collection Period

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

Adverse event information will be collected as shown in [Figure 2](#).

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

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

Email:	[REDACTED]
FAX to	[REDACTED]

For safety concerns, contact the Antiviral Safety Team at:

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

Office: [REDACTED]
Email: [REDACTED]

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

Primary Therapeutic Area Medical Director:

[REDACTED]

Telephone Contact Information:
Office: [REDACTED]
Fax: [REDACTED]
Mobile: [REDACTED]
Email: [REDACTED]

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

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

6.1.6 Pregnancy

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

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

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

6.1.7 Toxicity Management

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

Specific toxicity management guidelines apply to the instances of increases in ALT (Section 6.1.7.1)

Because of the potential impact of interruption/discontinuation of study drugs on immunosuppressant levels, when an interruption/discontinuation is anticipated or required by protocol, investigators should ensure that a plan for appropriate immunosuppressant dose modification is in place and that this has been communicated with the subject. Similarly for those recommencing study drugs after an interruption, the investigator should ensure that a plan for appropriate immunosuppressant dose adjustment is in place and that this has been communicated with the subject. Where an interruption is required the study drugs should not be interrupted for more than 7 days. If study drugs need to be interrupted for more than 7 days, the Primary Therapeutic Area Medical Director should be contacted and consideration should be given to discontinue the subject.

6.1.7.1 Management of Increases in ALT

If a subject experiences a post-baseline increase in ALT to $> 5 \times \text{ULN}$ which is also $> 2 \times$ baseline value, the subject should have a confirmatory ALT measurement performed.

If the ALT increase is confirmed to be $> 5 \times \text{ULN}$ which is also $> 2 \times$ baseline value, the recommendations below should be followed:

- Evaluate for alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain additional testing as appropriate (e.g., hepatitis B panel).
- Manage the subject as medically appropriate.
- Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and INR within 1 week. Repeat liver chemistries as indicated until resolution.
- Discontinue study drugs if any of the following is observed at any time:
 - ALT level is $\geq 20 \times \text{ULN}$ in the absence of an alternate etiology.
 - Increasing direct bilirubin or INR or onset of symptoms/signs of hepatitis.
 - At the discretion of the investigator.

Alternate management of ALT increases is permitted with approval of the Primary Therapeutic Area Medical Director.

If at any time an investigator suspects rejection of the transplanted liver or kidney while the subject is receiving study drug, then dose adjustment of immunosuppressants may be performed per the investigator's usual practice and the event captured on eCRF. If the abnormality is non-responsive to immunosuppressant adjustment and/or if the investigator wishes to empirically augment the immunosuppressive regimen, e.g., by commencement of high dose steroids or to add specific anti-rejection agents but without the availability of a biopsy of the transplanted organ confirming rejection, then discontinuation of study drugs should be considered by the investigator. If the investigator wishes to pursue alternative management of study drugs in this setting the Primary Therapeutic Area Medical Director should be contacted to obtain approval.

If a biopsy of the transplanted organ is performed as part of the evaluation of rejection and the histologic findings are consistent with rejection as determined by the local pathologist, the investigator should follow the usual management of rejection and continuation of study drugs should be per investigator discretion. If the investigator wishes to pursue alternative management of study drugs in the setting of histologically confirmed rejection, then the Primary Therapeutic Area Medical Director should be contacted to obtain approval. Biopsy tissue from the transplanted organ obtained during the trial to evaluate rejection or other pathologic process should be read locally and the result recorded in the subject source documents. Because of the potential impact of discontinuation (or interruption) of study drugs on immunosuppressant levels, investigators should ensure that a plan for appropriate immunosuppressant dose modification is in place and that this plan is communicated to the subject.

If the findings of a liver biopsy are not consistent with liver rejection or if the clinical suspicion of rejection is low or the biopsy results are pending and the subject experiences an ALT level $\geq 5 \times$ ULN that is $\geq 2 \times$ baseline, confirmatory chemistry testing should be performed. If the ALT level is confirmed $\geq 5 \times$ ULN and $\geq 2 \times$ baseline and the HCV

RNA is declining or is undetectable, then management should be per above. If a liver biopsy has not been performed, consideration should be made to performing a liver biopsy.

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

6.1.8 Renal Transplant Management of Proteinuria

Renal transplant subjects will undergo a urinalysis at each study visit as part of the surveillance for renal injury including renal graft rejection. If new onset or increased proteinuria is identified it is recommended that this be evaluated further and in conjunction with the patient's nephrologist. If further work up confirms a new or increased proteinuria that is considered to be clinically significant, e.g., urine protein/creatinine ratio or 24-hour urine protein > 1 g on two or more occasions, then further evaluation for possible renal graft rejection or HCV associated renal disease is recommended and consideration should be given to the performance of an allograft biopsy with immunofluorescence and electron microscopy per KDIGO Clinical Practice Guidelines. In the setting of confirmed renal rejection, continuation of the study drugs should be per investigator discretion. If the investigator wishes to pursue alternative management of study drugs in the setting of histologically confirmed rejection, then the Primary Therapeutic Area Medical Director should be contacted to obtain approval. Biopsy tissue from the transplanted organ obtained during the trial to evaluate rejection or other pathologic process should be read locally and the result recorded in the subject source documents. Because of the potential impact of discontinuation (or interruption) of study drugs on immunosuppressant levels, if study drugs are discontinued or interrupted, investigators should ensure that a plan for appropriate immunosuppressant dose modification is in place and that this plan is communicated to the subject.

6.2 Product Complaint

6.2.1 Definition

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

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

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

6.2.2 Reporting

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

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

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

7.0 Protocol Deviations

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

Primary Contact:



Office:

Fax:



Alternate Contact:



Office:

Fax:



Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The primary analysis will occur after all subjects have completed the PT Week 12 Visit or prematurely discontinued the study. The data for the primary analysis will be locked after data cleaning. Data after PT Week 12 will be added to a new version of the database which will be cleaned and locked at the end of the study.

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

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

Sensitivity analyses of the primary endpoint, SVR₁₂, when applicable, will be performed on the ITT population modified to exclude subjects not of eligible genotypes (e.g., according to phylogenetic analyses) (mITT-GT), and on the mITT-GT population modified to exclude subjects who did not achieve SVR₁₂ for reasons other than virologic failure (mITT-GT-VF).

No data will be imputed for any efficacy or safety analysis except for analyses of SVR endpoints (HCV RNA data) and PRO questionnaires. HCV RNA values will be selected for the analyses of all SVR endpoints (e.g., SVR₄, SVR₁₂, and SVR₂₄) based on defined visit windows. A backward imputation method will be used to impute missing responses for SVR analyses. Imputation of missing responses on PRO questionnaires is described in Section 8.1.3.

8.1.1 Demographics

Demographics, baseline characteristics, study drug exposure and compliance will be summarized for the ITT population. Demographics will include age, weight, height, BMI, gender, race, and ethnicity. Baseline characteristics will be summarized as continuous variables (where appropriate) and as categorical variables, including all subgroup variables defined in Section 8.1.2.4, and include HCV genotypes and subtypes, IL28B genotype, prior HCV treatment history (including timing of prior HCV treatment, i.e., pre- or post-transplant), baseline HCV RNA level, fibrosis stage (F0-F1, F2, F3 or F4 [if applicable]), baseline homeostasis model of assessment – insulin resistance

(HOMA-IR), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, former injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no), use of stable opiate substitution, history of diabetes, baseline metabolic syndrome, history of bleeding disorders, history of depression or bipolar disorder, history of cardiovascular disease, type of transplant (liver or kidney), prior dialysis (hemodialysis, peritoneal dialysis, other) in renal transplant subjects, donor type (living or deceased), time since transplantation (months), immunosuppressant medication, and geographic region.

Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and BMI), and the number and percentage of subjects will be presented for categorical variables (e.g., sex and race).

Study drug exposure and compliance will be summarized for all treated subjects. Treatment compliance to study drug will be calculated based on the percentage of tablets taken relative to the total tablets expected to be taken. A subject is considered to be compliant if the percentage is between 80% and 120%. Compliance will be calculated for each subject and summarized with the mean, median, SD, minimum, and maximum. The percentage of compliant subjects will be summarized.

8.1.2 Efficacy

All efficacy analyses will be performed on the ITT population, unless otherwise specified.

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

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

8.1.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint is SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in the ITT population. The number and percentage of subjects in the ITT population achieving SVR₁₂ will be summarized with a two-sided 95% confidence interval, calculated using the normal approximation to the binomial distribution. If the SVR₁₂ rate is 100%, then the Wilson's score method will be used to calculate the confidence interval.

The lower confidence bound of the 2-sided 95% CI (LCB) for the percentage of subjects achieving SVR₁₂ must exceed 86% to achieve non-inferiority to the standard of care.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- the percentage of subjects with on-treatment virologic failure (defined as confirmed increase of > 1 log₁₀ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and
- the percentage of subjects with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment with HCV RNA < LLOQ at the end of treatment; subjects with reinfection will be summarized separately).

For the analysis of relapse, completion of treatment is defined as any subject with study drug duration of 77 days or greater.

The number and percentage of subjects will be summarized along with two-sided 95% Wilson score confidence intervals.

In addition, a summary of reason for SVR₁₂ non-response (e.g., on-treatment virologic failure, relapse, other) will be provided.

8.1.2.3 Sensitivity Analysis

As sensitivity analyses, the percentage of subjects in the mITT-GT and mITT-GT-VF populations achieving SVR₁₂, as applicable, will be summarized.

The Wilson score confidence interval will also be calculated as a sensitivity analysis for the primary endpoint of SVR₁₂.

8.1.2.4 Subgroup Analysis

The percentage of ITT subjects with SVR₁₂ will be calculated, as will the corresponding two-sided 95% Wilson score confidence intervals for the following subgroups.

- HCV genotype (1, 2, 3, 4, 5, or 6) and subtype;
- Prior HCV treatment history;
 - For treatment-experienced subjects, type of non-response to previous treatment (on-treatment nonresponder or breakthrough, post-treatment relapse, or unknown/other);
- Prior sofosbuvir (SOF) experience (DAA naïve, SOF experienced);
- Organ transplant type (liver or kidney);
- IL28B genotype (CC or non-CC) and (CC, CT, or TT);
- Sex (male or female);
- Age (< 65 or ≥ 65 years) and (< 75 or ≥ 75 years);
- Race (White, Black/African-American, Asian, or other) and (black or non-black);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- BMI (< 25, ≥ 25 to < 30, or ≥ 30 kg/m²);
- Baseline HCV RNA level (< 6,000,000 or ≥ 6,000,000 IU/mL) and (< 2,000,000, ≥ 2,000,000 to < 6,000,000, ≥ 6,000,000 to < 10,000,000, or ≥ 10,000,000 IU/mL);

- Baseline HOMA-IR (< 2 or ≥ 2 $\text{mU} \times \text{mmol/L}^2$) and (< 3 or ≥ 3 $\text{mU} \times \text{mmol/L}^2$);
- Baseline fibrosis stage (F0 – F1, F2, F3, or F4 [if applicable]);
- Baseline platelet count (< 100 or $\geq 100 \times 10^9/\text{L}$) and (< 120 or $\geq 120 \times 10^9/\text{L}$);
- Baseline albumin ($< \text{LLN}$ or $\geq \text{LLN}$);
- Baseline GGT ($\leq \text{ULN}$ or $> \text{ULN}$);
- Baseline LDL (< 88 , ≥ 88 to < 119 , or ≥ 119 mg/dL);
- Baseline APRI (< 1 or ≥ 1);
- Baseline FIB-4 (< 1.45 , ≥ 1.45 to ≤ 3.25 , or > 3.25);
- Baseline AST/ALT ratio (< 1 or ≥ 1);
- Geographic region (North America, Europe, Rest of world);
- Country (as appropriate);
- History of diabetes (yes/no);
- History of bleeding disorders (yes/no);
- History of depression or bipolar disorder (yes/no);
- History of cardiovascular disease (yes/no);
- Baseline metabolic syndrome (yes/no);
- Former injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no);
- Subject on stable opiate substitution (yes/no);
- Presence of baseline resistance-associated variants (yes/no);
- Compliance to study drug (yes/no).

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

8.1.2.5 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized for the ITT population:

- The percentage of subjects with HCV RNA $< \text{LLOQ}$ at each post-baseline visit in the Treatment Period (using data as observed);

- The percentage of DAA naïve subjects with on-treatment virologic failure;
- The percentage of DAA naïve subjects with post-treatment relapse;
- The percentage of subjects with SVR₄;
- The percentage of subjects with SVR₂₄;
- The percentage of subjects who relapse after achieving SVR₁₂.

In the above analyses for SVR and relapse, the percentage of subjects with a two-sided 95% Wilson score confidence interval will be summarized. The percentage of sofosbuvir experienced subjects achieving SVR₁₂ will be summarized as applicable.

8.1.3 Patient Reported Outcomes

The handling of missing data for patient reported outcomes (PROs) will be as follows. If a respondent answers at least 50% of the items in a multi-item scale of the SF-36v2, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing. The missing items of the FSS questionnaire will be imputed with the average score of the answered items as long as more than 50% of the items on the FSS are answered. For EQ-5D-3L index and VAS scores, no imputation will be performed for missing items.

The mean change from baseline to each applicable post-baseline time point in the SF-36v2 Mental Component Summary (MCS) and Physical Component Summary (PCS) scores; FSS total score; EQ-5D-3L health index score and VAS score will be summarized descriptively at each visit and for change from baseline to each visit.

The following analyses of PROs will be performed:

- Cumulative number and percentage of subjects who have ever experienced an increase from baseline up through each applicable time point of greater than or equal to 2.5 points in the SF-36 MCS and PCS;

- Cumulative number and percentage of subjects who have ever experienced an increase from baseline up through each applicable time point of greater than or equal to 5 points in the SF-36 domain scores;
- Cumulative number and percentage of subjects who have ever experienced an increase from baseline up through each applicable time point of greater than or equal to 0.7 in the FSS total score.

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

8.1.4 Resistance Analysis

The DNA encoding NS3 amino acids 1 – 181 and NS5A amino acids 1 – 215 will be sequenced by population or deep sequencing for analysis of baseline samples from all of the SVR-achieving subjects. For subjects who experienced virologic failure (on-treatment virologic failure or post-treatment relapse), full length NS3/4A and NS5A genes from their baseline samples will be sequenced by population or deep sequencing. For each DAA target, resistance-associated signature amino acid variants will be identified by AbbVie Clinical Virology. An appropriate prototypic reference sequence will be used for comparison with sequences from samples.

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore, if the HCV RNA level at the time of virologic failure or treatment discontinuation is < 1000 IU/mL, the sample closest in time after failure/discontinuation with an HCV RNA level ≥ 1000 IU/mL will be used. Included time points for analyses on samples from subjects who do not achieve SVR₁₂ are 1) the sample closest in time after failure/discontinuation with an HCV RNA level of ≥ 1000 IU/mL, and 2) 24 weeks post-DAA treatment, provided that resistance-associated variants were detected by either population or deep sequencing at the time of failure/discontinuation.

The following definitions will be used in the resistance analyses:

- Baseline variant: a variant (by population or deep sequencing) in a baseline sample determined by comparison of the amino acid sequence of the baseline sample to the appropriate prototypic reference amino acid sequence for a given DAA target.
- Post-baseline variant by population or deep sequencing: an amino acid variant detected by population or deep sequencing in a post-baseline time point sample that was not detected by population or deep sequencing at baseline in the subject.
- Enriched variant by deep sequencing: post-baseline variant that is enriched by at least 20% relative to baseline sequence (post-baseline % – baseline % \geq 20).
- Treatment-emergent variant: Enriched variant or a post-baseline variant.
- Emerged variant by population or deep sequencing: a treatment emergent variant that is observed in 2 or more subjects of the same HCV subtype by population or deep sequencing.
- Linked variant by population or deep sequencing: 2 or more signature resistance associated or emerged resistance-associated amino acid variants identified within a target by population or deep sequencing, and no mixture of amino acids is detected at either position.

The following analyses will be performed for all subjects:

- The HCV amino acid sequence as determined by population or deep sequencing at baseline will be compared to the appropriate prototypic reference amino acid sequence. A listing by subject of all baseline variants relative to prototypic reference sequence at signature resistance associated amino acid positions will be provided for each DAA target (NS3 and NS5A).

The following analyses will be performed for subjects who do not achieve SVR₁₂ and have post-baseline resistance data available:

- The HCV amino acid sequence as determined by population or deep sequencing on the sample closest in time after virologic failure or treatment discontinuation with an HCV RNA level of \geq 1000 IU/mL will be compared to the baseline and appropriate prototypic reference amino acid sequence.

Listings by subject 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 and NS5A). Listings by subject of all emerged variants by population or deep sequencing, by amino acid position and variants within a DAA target in a post-baseline sample relative to the baseline amino acid sequence will be provided for each DAA target. In addition, listings by subject 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 for each DAA target (NS3 and NS5A).

- Linkage between emerged or signature variants by population or deep sequencing will also be evaluated. A listing by subject and time point of the linked variants by population or deep sequencing for each target will be provided.
- The persistence of post-baseline variants at signature resistance-associated amino acid positions for each target (NS3 and NS5A) will be assessed by population or, deep sequencing at Post-Treatment Week 24. Listings by subject and time point of all post-baseline variants relative to the baseline amino acid sequence will be provided for each DAA target (NS3 and NS5A).
- If resistance-associated variants are not detected by either population or, deep sequencing in a given target for a subject at the time of failure/discontinuation, then that target may not be sequenced in subsequent samples from that subject.

Replicon EC₅₀ values may not be obtainable for all samples, but for samples where phenotype data are obtained, the fold change in EC₅₀ levels at each post-baseline time point where phenotypic analysis was performed will be compared both to baseline and prototypic standards.

Phylogenetic analysis will be conducted on HCV sequence from available baseline samples from all non-GT1 subjects in order to accurately determine their subtypes. The resulting subtype information will be presented in summaries of baseline characteristics and efficacy subgroup analyses.

8.1.5 Safety

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

8.1.5.1 Adverse Events

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

8.1.5.2 Clinical Laboratory Data

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

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

In addition, the number and percentage of subjects with post-baseline values meeting pre-specified criteria for Potentially Clinically Significant (PCS) laboratory values or toxicity grades will be summarized.

8.1.5.3 Vital Signs Data

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

8.1.6 Pharmacokinetic and Exposure-Response Analyses

Plasma concentrations of ABT-493 and ABT-530 and possible metabolites and pharmacokinetic parameter values for ABT-493 and ABT-530 will be tabulated for each subject and group. Blood concentrations of cyclosporine, tacrolimus, everolimus and sirolimus will be tabulated for each subject and group. Summary statistics will be computed for each time and visit.

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

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

- The objective function of the best model is significantly smaller than the alternative model(s).

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

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

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

$$TVCL_i = \text{Theta}(1) + \text{Theta}(2) (\text{Comedication } [1,2,\dots]) + \text{Theta}(3) (\text{WT}_i - \text{median value}) + \text{Theta}(4) (\text{AGE}_i - \text{median value}).$$

Where $TVCL_i$ = Typical value of clearance for an individual i , $\text{Theta}(1)$ is the intercept and $\text{Theta}(2) - (4)$ are regression parameters relating the fixed effects (weight and age centered on the median value) to clearance.

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

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

Logistic regression analyses will explore the relationship between exposure and one or more virologic endpoints (e.g., SVR₁₂, relapse following end of treatment and breakthrough on treatment).

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

8.2 Determination of Sample Size

It is planned to enroll approximately 90 subjects with a minimum of 15 post-renal transplant subjects and a maximum of approximately 50 subjects with HCV genotype 1 infection. The primary efficacy endpoint of SVR₁₂ will be assessed for the ITT population. For the primary efficacy endpoint of SVR₁₂, with a sample size of 90 subjects and assuming that 96% of the subjects will achieve SVR₁₂, this study has greater than 90% power to show non-inferiority to the historical SVR₁₂ rate of 94% (based on the lower bound of a normal approximation of a single binomial proportion confidence interval being above a threshold of 86%) using a one-sample test for superiority using EAST 6.3.

No adjustment for dropouts is applicable because subjects who do not have data at Post-Treatment Week 12 (after imputing) are counted as failures for SVR₁₂.

8.2.1 Justification of Success Criterion and Non-Inferiority Margin for SVR₁₂

The primary efficacy endpoint analysis of SVR₁₂ is a non-inferiority test of the SVR₁₂ rate in this study to the historical SVR₁₂ rate of 94% (based on the lower bound of a normal approximation of a single binomial proportion confidence interval being above a threshold of 86%) using a one-sample test for superiority.

The 86% threshold was established by applying an 8% non-inferiority margin to a historical SVR₁₂ rate of 94%.

[REDACTED]

The 8% non-inferiority margin is based on the paucity of data in non-GT1 liver transplant recipients and renal transplant recipients regardless of genotype and the potential benefit of a RBV-free regimen.

- Most data published on the post-transplant population to date, including the studies that were used to establish the historical control rate for this study, are in GT1 subjects who have received a liver transplant.
- The current standard-of-care regimens used for historical comparison all include RBV. Given the ABT-493/ABT-530 regimen is RBV-sparing, a slightly wider non-inferiority margin compared to the margin used in other AbbVie Phase 3 studies with ABT-494/ABT-530 was considered, as a small decrement in efficacy may be outweighed by an improvement in safety offered with the avoidance of RBV in a patient population more susceptible to RBV-related toxicity.

9.0 Ethics

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

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

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

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

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

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.

The optional pharmacogenetic and intensive PK analysis will only be performed if the subject has voluntarily signed and dated the IRB/IEC approved pharmacogenetic informed consent and intensive PK informed consent respectively, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The subject must provide consent specific to pharmacogenetic testing and intensive PK before the testing is performed. If the subject does not consent to the additional pharmacogenetic and/or intensive PK testing it will not impact the subject's participation in the study.

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

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

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

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

13.0 Completion of the Study

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

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

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

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

14.0 Investigator's Agreement

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

Protocol Title: A Single-Arm, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of ABT-493/ABT-530 in Adult Post-Liver or Post-Renal Transplant Recipients with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (MAGELLAN-2)

Protocol Date: 21 June 2016

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
		Pharmacokinetics
		Clinical
		Clinical
		Bioanalysis
		Statistics
		Clinical
		Global Drug Supply Management

Appendix C. Study Activities – Treatment Period

Activity	Screening	Day 1 ^a	Study Day 3	Wk 1	Optional Day 10 for Mgmt of Immunosuppressive Meds	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12 EOT or Premature D/C from Treatment ^b	Unscheduled Visit for Mgmt of Immunosuppressive Meds
Informed Consent ^c	X										
Medical History ^d	X	X									
Physical Exam	X	X								X	
Vital Signs, Weight, Height ^e	X	X	X	X	X	X	X	X	X	X	X
ECG	X										
Hematology/Chemistry/Urinalysis/Coagulation Panel	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test (serum [s] urine [u]) ^f	X (s)	X (u)					X (u)			X (u)	
HBsAg, Anti-HCV Ab, Anti-HIV Ab	X										
Drug/Alcohol Screen	X										
Alpha fetoprotein	X										
Hemoglobin A1C ^g	X										
HCV Genotype and Subtype	X										
FibroTest and APRI or FibroScan or Liver Biopsy ^h	X										
IL28B Sample ⁱ		X									
Optional Exploratory Pharmacogenetic Sample ^j		X									
Total Insulin		X									

Activity	Screening	Day 1 ^a	Study Day 3	Wk 1	Optional Day 10 for Mgmt of Immunosuppressive Meds	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12 EOT or Premature D/C from Treatment ^b	Unscheduled Visit for Mgmt of Immunosuppressive Meds
Sample for cyclosporine, tacrolimus, everolimus, sirolimus therapeutic drug monitoring (Local Lab) ^j	X ^j	X	X	X	X	X	X	X	X	X	X
Immunosuppressive Regimen Dose Modification Review		X	X	X	X	X	X	X	X	X	X
Immunosuppression Regimen Dosing Diary dispensation, review and collection ^k	X (Dispense only)	X	X	X	X	X	X	X	X	X	X
Study Drug Dosing Card dispensation, review and collection		X (Dispense only)	X	X	X	X	X	X	X	X	
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment ^l	X	X	X	X	X	X	X	X	X	X	X
Patient Reported Outcomes Instruments (PROs) ^m		X								X	
Study Drugs Dispensed		X					X		X		
HCV RNA Samples	X	X	X	X	X	X	X	X	X	X	
Study Drug Accountability and Review of Study Drug Adherence ⁿ			X				X		X	X	
HCV Resistance Sample		X	X	X	X	X	X	X	X	X	
Archive Plasma Sample	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic Samples DAA ^{c,p}		X ^o	X	X	X	X	X ^o	X	X	X	

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

- a. All procedures to be performed prior to first dose, with the exception of the additional (optional) post-dose pharmacokinetic intensive samples (Section 5.3.2.1).
- b. Subjects who prematurely discontinue from the study during the Treatment Period should return to the site to complete the Premature D/C from Treatment Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy).
- c. Subjects need to sign and date an IRB/IEC approved informed consent for the study (prior to performing any screening or study-specific procedures) and the optional pharmacogenetic and intensive pharmacokinetic sample(s), if applicable.
- d. A complete medical history will be taken at Screening and will be updated at the Study Day 1 Visit.
- e. Height will be measured at the Screening Visit only.
- f. Pregnancy testing is not required for women not of childbearing potential as defined in Inclusion Criterion 2.
- g. For subjects with history of Diabetes Mellitus.
- h. For subjects who have not had a qualifying liver biopsy within the previous 6 months or a qualifying FibroScan within the previous 3 months.
- i. If the IL28 sample or the optional Pharmacogenetic sample are not collected at Study Day 1, they may be collected at any other visit during the study.
- j. Sample for cyclosporine, tacrolimus, everolimus, or sirolimus, blood concentrations at screening may take place as an unscheduled visit so the subjects screening day CNI/mTOR dose is not interrupted.
- k. The Immunosuppression Regimen Dosing Diary will be provided to study subjects taking an immunosuppressive regimen containing cyclosporine, sirolimus, everolimus, and/or tacrolimus during the screening visit and subsequent visits as indicated. The diaries will be reviewed for completeness and accuracy between study visits and collected by site staff after review.
- l. See specific information regarding adverse event collection in Section 6.1.1.1.
- m. PROs should be administered before any study procedures and in the order listed as per Section 5.3.1.1.
- n. Subjects should bring all study drug to every visit for the site to review adherence. However, the site will record the number of tablets returned only at the Study Drug Accountability Visits at Weeks 4, 8 and 12 or Premature D/C.
- o. For subjects participating in Optional Intensive PK sampling, intensive PK samples will be drawn on Day 1 at 2, 4 and 6 hours post-dose and on Week 4 at 0 (immediately prior to dose), 2, and 4 hours post the dose administered during the visit. Subjects not participating in intensive PK will not have a sample drawn at Day 1.
- p. Detail regarding timing of samples is provided in Section 5.3.2.1.

Appendix D. Study Activities – Post-Treatment (PT) Period

Activity	PT Day 3	PT Wk 1	PT Wk 2	PT Wk 4	PT Wk 8	PT Wk 12	PT Wk 24 or PT D/C ^a	Unscheduled Visit for Mgmt of Immunosuppressive Meds
Vital Signs and Weight	X	X	X	X	X	X	X	X
Hematology/Chemistry/Urinalysis/Coagulation Panel	X	X	X	X			X	X
Pregnancy Test (urine) ^b				X (u)			X (u)	
PRO Instruments ^c						X	X	
Concomitant Medication Assessment	X	X	X	X ^d	X ^d	X ^d	X ^d	X ^d
Adverse Event Assessment ^{e,f}	X	X	X ^e	X	X	X	X	X
HCV RNA Samples			X	X	X	X	X	
HCV Resistance Sample			X	X	X	X	X	
Cyclosporine, tacrolimus, everolimus, sirolimus therapeutic drug monitoring (Local Lab)	X	X	X	X				X
Immunosuppression Regimen Dosing Diary dispensation, review and collection ^g	X	X	X	X				X
Archive Plasma Sample	X	X	X	X	X	X	X	

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

- a. Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C Visit procedures.
- b. Urine pregnancy testing is not required in the PT Period for women that are not of childbearing potential.
- c. PROs should be administered before any study procedures and in the order listed as per Section 5.3.1.1.
- d. Only medications taken for SAEs and for treatment of HCV will be collected after 30 days post-dosing.

- e. Nonserious AEs and all SAEs will be collected until 30 days post dosing.
- f. Only SAEs will be collected after the 30 days post dosing (see Section 6.1.4).
- g. The Immunosuppression Regimen Dosing Diary will be provided to study subjects taking an immunosuppressive regimen containing cyclosporine, sirolimus, everolimus, and/or tacrolimus during the screening visit and subsequent visits as indicated. The diaries will be reviewed for completeness and accuracy between study visits and collected by site staff after review.

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

Appendix E. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 3.0 Introduction

Subsection DDI STUDIES WITH CYCLOSPORINE AND TACROLIMUS

Fifth paragraph, bullet previously read:

The dose of cyclosporine with ABT-493/ABT-530 (300/120 mg QD) should not exceed 100 mg once daily

Has been changed to read:

The dose of cyclosporine with ABT-493/ABT-530 (300/120 mg QD) should not exceed 100 mg once daily for entry into the study. If the cyclosporine maintenance dose needs to be increased to a total daily dose greater than 100 mg during the Treatment Period, discussion with the Therapeutic Area Medical Director should occur. Dosages of cyclosporine > 400 mg are not allowed during the Treatment Period.

Section 5.1.2 Treatment Period

Second paragraph, first sentence previously read:

Subject immunosuppression dosing regimen diaries will be maintained throughout the trial, for all subjects taking cyclosporine, sirolimus, everolimus, and/or tacrolimus during both the Treatment and Post-Treatment periods.

Has been changed to read:

Subject immunosuppression dosing regimen diaries will be maintained throughout the trial, for all subjects taking cyclosporine, sirolimus, everolimus, and/or tacrolimus during the Screening, Treatment and Post-Treatment periods.

Section 5.2.1 Inclusion Criteria

Criterion 3, last sentence previously read:

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing.

Has been changed to read:

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing.

Section 5.2.2 Exclusion Criteria

Criterion 7 previously read:

Any cause of liver disease other than chronic HCV infection including but not limited to the following:

Has been changed to read:

Any cause of liver disease post transplantation other than chronic HCV infection including but not limited to the following:

Section 5.2.2 Exclusion Criteria

Criterion 9, second bullet previously read:

Albumin < 3.5 mg/dL

Has been changed to read:

Albumin < 3.5 g/dL

Section 5.2.3.2 Management of Immunosuppressant Agent Dosing

Third paragraph, bullet previously read:

The dose of cyclosporine with ABT-493/ABT-530 (300/120 mg QD) should not exceed 100 mg once daily.

Has been changed to read:

The dose of cyclosporine with ABT-493/ABT-530 (300/120 mg QD) should not exceed 100 mg once daily for entry into the study. If the cyclosporine maintenance dose needs to be increased to a total daily dose greater than 100 mg during the Treatment Period, discussion with the Therapeutic Area Medical Director should occur. Dosages of cyclosporine > 400 mg are not allowed during the Treatment Period.

Section 5.3.1.1 Study Procedures

Subsection Immunosuppression Regimen Dosing Diary

First paragraph, first sentence previously read:

A subject immunosuppression regimen dosing diary will be provided to all subjects taking cyclosporine, sirolimus, everolimus, and/or tacrolimus during the Treatment period and for 30 days into the Post-Treatment period.

Has been changed to read:

A subject immunosuppression regimen dosing diary will be provided to all subjects taking cyclosporine, sirolimus, everolimus, and/or tacrolimus during Screening and for 30 days into the Post-Treatment period.

Section 5.3.1.1 Study Procedures

Subsection Immunosuppression Regimen Dosing Diary

Last paragraph, last sentence previously read:

Subjects should be reminded to bring the diary to each study visit.

Has been changed to read:

Subjects should be reminded to bring the completed diary to each study visit.

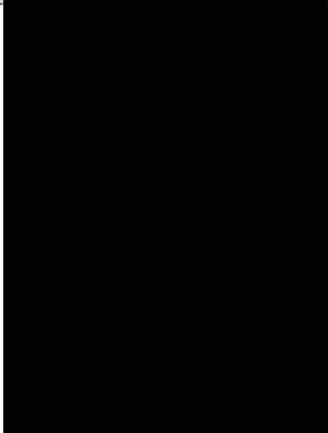
Document Approval

Study M13596 - A Single-Arm, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of
ABT-493/ABT-530 in Adult Post-Liver or Post-Renal Transplant Recipients with Chronic Hepatitis C Virus
Genotype 1 – 6 Infection (MAGELLAN-2) - Amendment 2 - EudraCT 2015-005616-14 - 21Jun2016

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Signed by:	Date:	Meaning Of Signature:
	21-Jun-2016 06:08:17 PM	Approver
	21-Jun-2016 07:17:33 PM	Approver
	21-Jun-2016 07:28:46 PM	Approver
	21-Jun-2016 07:46:19 PM	Approver
	21-Jun-2016 10:51:03 PM	Approver
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