1.0 Title Page

Clinical Study Protocol M14-730

A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection and Human Immunodeficiency Virus-1 (HIV-1) Co-Infection (EXPEDITION-2)

Incorporating Administrative Change 1 and Amendments 1, 2 and 3

AbbVie Investigational Product:	ABT-493/ABT-530
Date:	12 July 2016
Development Phase:	3
Study Design:	This is a non-randomized open-label, multicenter study.
EudraCT Number:	2015-005577-20
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc. (AbbVie)*
Sponsor/Emergency Contact:	[redacted]

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

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	28 January 2016
Amendment 1	01 March 2016
Amendment 2	21 March 2016
Administrative Change 1	23 May 2016

The purpose of this amendment is to:

- Add darunavir (DRV) coadministered with ritonavir (RTV), DRV/cobicistat (COBI), lopinavir/ritonavir (LPV/r), and elvitegravir + cobicistat (EVG/COBI) to the list of qualifying HIV-1 ART regimens and make updates throughout the protocol in alignment with the additions.

  Rationale: *Protocol updated to define permissive HIV-1 antiretrovirals based on either completed drug interaction studies, and or those HIV-1 antiretrovirals for which no significant interaction is predicted based upon metabolic and transporter pathways.*
- Update Section 1.2, Synopsis, and Section 1.3, List of Abbreviations and Definition of Terms.
- Update Section 3.0, Introduction.

  Rationale: *To ensure that the most up-to-date information is provided based on the most recent drug interaction data and to be consistent with AbbVie's ongoing HCV studies in support of the changes made to the study design throughout the protocol.*
- Update Section 3.2, Benefits and Risks.

  Rationale: *To include information about currently approved DAA regimens.*
- Update Section 5.1, Overall Study Design and Plan: Description, to increase the number of subjects to be enrolled in the study, increase the maximum number of HCV genotype 1/HIV-1 coinfected subjects and increase the minimum number of subjects with compensated cirrhosis that will be allowed in the study.

Rationale: *Overall sample size was increased to allow for enrollment of additional HCV genotype 1 subjects.*

- Update Section 5.2.1, Inclusion Criteria.

  Rationale: *Updated Criterion 3 to be consistent with the rest of the protocol. Updated the qualifying HIV-1 ART regimen in the Inclusion Criterion 13 to add DRV coadministered with RTV, DRV/COBI, LPV/r, and EVG/COBI based on data from recent drug-drug interaction studies. Revised Rationale for Inclusion Criteria to clarify the impact of ABT-493 and ABT-530 on pregnancies.*

- Update Section 5.2.3.2, Prior and Concomitant HIV-1 Therapy.

  Rationale: *To clarify cirrhotic subjects who are currently receiving the HIV-1 ART medications darunavir and lopinavir are not eligible for the study.*

- Update Section 5.6.3, Suitability of Subject Population and Section 5.6.4.1.1, ABT-493 and ABT-530 Dose.

  Rationale: *To be consistent with other updates made throughout the protocol related to allowable HIV-1 ART medications.*

- Update Section 8.2, Determination of Sample Size.

  Rationale: *To be consistent with other updates made throughout the protocol related to the increase in the number of subjects to be enrolled.*

- Incorporate Administrative Change 1.

  Rationale: *In accordance with AbbVie's protocol preparation procedures.*

- 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 F.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-730
Name of Study Drug: ABT-493/ABT-530	**Phase of Development:** 3
Name of Active Ingredient: ABT-493/ABT-530	**Date of Protocol Synopsis:** 12 July 2016
Protocol Title: A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection and Human Immunodeficiency Virus-1 (HIV-1) Co-Infection (EXPEDITION-2)	
Objectives: The primary objectives of this study are to compare the SVR_{12} rates (12-week sustained virologic response, SVR_{12} [HCV RNA < LLOQ 12 weeks following therapy]) of 8 or 12 weeks of treatment with ABT-493/ABT-530 combination in HCV genotype 1 – 6 infected subjects with HIV-1 co-infection to a pre-defined threshold, based on the historical SVR_{12} rate of the current standard of care (i.e., sofosbuvir/ledipasvir for 12 weeks or grazoprevir/elbasvir for 12 weeks) and to assess the safety of treatment with the combination regimen ABT-493/ABT-530 for 8 or 12 weeks in HCV genotype 1 – 6 infected subjects with HIV-1 co-infection with or without cirrhosis.	
Investigators: Multicenter	
Study Sites: Approximately 39 sites	
Study Population: Male and female adults aged 18 years or older with chronic HCV GT1 – 6 infection and HIV-1 co-infection without cirrhosis or with compensated cirrhosis (F0-F4; excluding GT3, treatment-experienced non-cirrhotics and cirrhotics), who are either HCV treatment-naïve or prior treatment-experienced (i.e., interferon [IFN] or pegylated-interferon [pegIFN] with or without ribavirin [RBV], or sofosbuvir [SOF] plus RBV with or without pegIFN).	
Number of Subjects to be Enrolled: Approximately 160 subjects	
Methodology: This is a Phase 3, open-label, multicenter study to evaluate efficacy and safety of ABT-493/ABT-530 for an 8 or 12 week treatment duration in HCV treatment-naïve or prior treatment-experienced (i.e., IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN) adults with chronic HCV GT1 – 6 infection and HIV-1 co-infection. Subjects must be naïve to treatment with any HIV-1 antiretroviral therapy (ART) or on a stable, qualifying HIV-1 ART regimen that contains rilpivirine (RPV), raltegravir (RAL), dolutegravir (DTG), or elvitegravir/cobicistat (EVG/COBI). Regimens that include darunavir coadministered with ritonavir (DRV+RTV) QD, darunavir/cobicistat (DRV/COBI) QD or lopinavir/ritonavir (LPV/r) BID will be allowed for non-cirrhotic subjects only. The study will consist of two periods: Treatment Period: Eligible subjects will be enrolled to receive ABT-493/ABT-530 (300 mg/120 mg) for an 8 (Arm A) or 12 (Arm B) week treatment duration based on cirrhosis status. Non-cirrhotic subjects will be allocated to Arm A and cirrhotic subjects will be allocated to Arm B. Scheduled visits for subjects in the Treatment Period who are assigned to the 8-week duration consist of Day 1 and Weeks 1, 2, 4 and 8. For subjects assigned to the 12-week duration scheduled visits in the Treatment Period consist of Day 1 and Weeks 1, 2, 4, 8 and 12.	

Methodology (Continued):

Study procedures, including assessment of adverse events, vital signs, study drug and ART regimen adherence, concomitant medications, HCV RNA, HIV RNA, HCV resistance, HIV resistance, ABT-493/ABT-530 pharmacokinetic assays, assessment of PROs and clinical laboratory tests, will be conducted.

Post-Treatment Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 24 weeks to monitor safety, HCV RNA levels, and to evaluate efficacy and the emergence and persistence of viral variants.

During the Post-Treatment Period, subjects will have visits at Weeks 2, 4, 8, 12 and 24 following completion of the Treatment Period. Study procedures to monitor safety, HCV RNA, the emergence and persistence of HCV viral variants, plasma HIV RNA, HIV drug resistance and assessment of PROs will be conducted during the Post-Treatment Period.

A mandatory whole blood sample for IL28B testing and an optional whole blood sample for DNA isolation will be collected for pharmacogenetic exploratory research at designated time points throughout the study.

A maximum of approximately 110 HCV GT1/HIV-1 co-infected subjects will be allowed to enroll in the study. A minimum of 10% (n = 16) of the overall study population will be subjects with compensated cirrhosis.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female, at least 18 years of age at time of Screening.
2. Screening laboratory result indicating HCV GT1-, 2-, 3-, 4-, 5-, or 6-infection.
3. Subject has positive anti-HCV Ab and plasma HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.
4. Subjects 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 IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN). GT3 subjects must be HCV treatment-naïve. Previous HCV treatment must have been completed ≥ 2 months prior to Screening.
5. Subjects naïve to ART must have CD4+ count ≥ 500 cells/mm^3 (or CD4+ % ≥ 29%) at Screening; or
   Subjects on a stable ART regimen must have the following:
   - CD4+ count ≥ 200 cells/mm^3 (or CD4+ % ≥ 14%) at Screening; and
   - Plasma HIV-1 RNA below LLOQ at Screening and at least once during the 12 months prior to Screening.

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

Main Exclusion:

1. 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.
2. Positive test result at Screening for hepatitis B surface antigen (HBsAg).
3. Positive Human Immunodeficiency virus, type 2 (HIV-2) Ab at Screening.
4. Receipt of any other investigational or commercially available direct acting anti-HCV agents other than sofosbuvir (e.g., telaprevir, boceprevir, simeprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir or dasabuvir).
5. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-493/ABT-530.

Investigational Products:	ABT-493/ABT-530: 100 mg/40 mg Film-coated tablet
Doses:	ABT-493/ABT-530: 300 mg/120 mg QD (3 tablets)
Mode of Administration:	Oral with food
Reference Therapy:	N/A
Doses:	N/A
Mode of Administration:	N/A

Duration of Treatment: Subjects will receive ABT-493/ABT-530 for 8 or 12 weeks.

Criteria for Evaluation:

Efficacy:

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

Pharmacokinetic:

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

Plasma concentrations of HIV-1 ARVs for an individual subject, a group of subjects or for the whole study will be analyzed based on HCV RNA and/or plasma HIV-1 RNA results and summarized.

Safety:

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

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 Survey (SF-36v2) will be used to assess the functional health and well-being of subjects.

Criteria for Evaluation (Continued):

Resistance:

The following information will be tabulated and summarized for HCV resistance: 1) for all subjects, 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 SVR_{12}, post-baseline variants relative to baseline.

HIV-1 drug resistance genotyping for protease (PR), reverse transcriptase (RT) and integrase (IN), as appropriate, will be performed for protocol-defined eligible specimens.

Statistical Methods:

Efficacy:

The primary efficacy endpoint is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) among HCV genotype 1 – 6 infected subjects with HIV-1 co-infection with or without cirrhosis treated for 8 or 12 weeks duration (ITT population). The number and percentage of subjects achieving SVR_{12} will be summarized and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial. If the SVR_{12} rate is 100%, then the Wilson's score method will be used to calculate the confidence interval.

The percentage of the subjects treated with ABT-493/ABT-530 with SVR_{12} will be non-inferior to the 96% SVR_{12} rate of the current standard of care (i.e., sofosbuvir/ledipasvir for 12 weeks [96%; 321/335] or grazoprevir/elbasvir for 12 weeks [96%; 210/218]) if the lower confidence bound of the 2-sided 95% confidence interval of the percentage of subjects with SVR_{12} is > 90%.

A summary of reason for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse, other) will be provided.

The secondary efficacy endpoints are:

- The percentage of subjects with on-treatment virologic failure (defined as confirmed increase of > 1 $\log_{10}$ 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),
- The percentage of subjects with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment).

For the secondary endpoints, the number and percentage of subjects will be summarized along with 95% Wilson score intervals.

Pharmacokinetic:

Plasma concentration of ABT-493, possible ABT-493 metabolites, ABT-530 and possible ABT-530 metabolites will be tabulated for each subject and group. 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.

Statistical Methods (Continued):

Safety:

All subjects who receive at least one dose of study drugs 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 grade and relationship to study drug. Change from baseline in laboratory tests (including CD4+ T-cell count and CD4+ T cell %) 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. Maintenance of HIV-1 suppression will be assessed.

PROs:

Change from baseline in the patient reported outcome summary measures will be summarized descriptively at each visit.

Resistance:

For all subjects receiving study drugs, 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 HCV resistance information will be analyzed for subjects receiving study drugs who do not achieve SVR_{12} 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 in 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 in comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral variants by population or deep sequencing.

HIV-1 drug resistance genotyping for protease (PR), reverse transcriptase (RT), and integrase (IN), as appropriate, will be performed for protocol-defined eligible specimens.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

3TC	Lamivudine
Ab	Antibody
ABC	Abacavir
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
APRI	Aminotransferase/platelet ratio index
aPTT	Activated partial thromboplastin time
ART	Antiretroviral Treatment
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area Under the Concentration Curve
BID	Twice Daily
BMI	Body Mass Index
BUN	Blood urea nitrogen
CFR	Code of Federal Regulation
CL/F	Apparent oral plasma clearance
COBI	Cobicistat
CrCl	Creatinine clearance
CRF	Case report form
CT	Computed Tomography
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DDI	Drug Drug Interaction
DNA	Deoxyribonucleic acid
DRV	Darunavir
DTG	Dolutegravir
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture

EMEA	European Agency for the Evaluation of Medicinal Products
EOT	End of treatment
EQ-5D-3L	EuroQol 5 Dimensions 3 Levels Health State Instrument
EU	European Union
EVG	Elvitegravir
FSH	Follicle Stimulating Hormone
FSS	Fatigue Severity Scale
FTC	Emtricitabine
GAM	Generalized additive method
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GT	Genotype
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular carcinoma
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HCV GT1 – 6	Hepatitis C virus genotype 1 – 6
Hemoglobin A1c	Glycated hemoglobin
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HIV-2	Human immunodeficiency virus type 2
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
ITT	Intent-to-Treat
IU	International units
IUD	Intrauterine device

IUS	Intrauterine hormone-releasing system
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
LPV	Lopinavir
LPV/r	Lopinavir and ritonavir
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mRNA	Messenger Ribonucleic Acid
MRI	Magnetic Resonance Imaging
NONMEM	Non-linear mixed-effect modeling
N(t)RTI	Nucleoside/Nucleotide reverse transcriptase inhibitor
NS3A	Nonstructural viral protein 3A
NS4A	Nonstructural viral protein 4A
NS5A	Nonstructural viral protein 5A
NS5B	Nonstructural viral protein 5B
OI	Opportunistic Infections
PCS	Physical Component Summary
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
PO	By mouth, orally
POR	Proof of Receipt
PRO	Patient Reported Outcome
PR	pegIFN/RBV
PT	Post-Treatment
QD	Once daily
RAL	Raltegravir
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
RPV	Rilpivirine

RTV or r	Ritonavir
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Standard Deviation
SF-36v2	Short Form 36-Version 2 Health Status Survey
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class/Standard of Care
SOF	Sofosbuvir
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
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
ULN	Upper limit of normal
VAS	Visual Analog Scale
VF	Virologic Failure
V/F	Apparent Volume of distribution
WBC	White blood cells
WOCBP	Women Of Childbearing Potential

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

2.0 Table of Contents

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3.0 Introduction

Hepatitis C viral (HCV) infection is a global health problem, with over 184 million individuals infected worldwide.[1] There are 7 identified HCV genotypes, with genotype 1 (GT1) being most prevalent worldwide. HCV genotypes 2 and 3 infections are more common in Latin America (5% to 30%), Europe (20% to 40%) and Asia (30% to 45%).[2-4] HCV GT4 is commonly found in parts of Africa and the Middle East, particularly in Egypt, GT5 is primarily found in South Africa, and GT6 is primarily found in south-east Asia.[5] Depending on various risk factors, between 10% and 40% of patients with chronic HCV infection will develop cirrhosis.[5] Those with HCV/HIV co-infection have poorer prognosis than HCV mono-infected patients, with acceleration of liver disease leading to cirrhosis (6 to 10 years versus 10 to 20 years) and hepatic decompensation. 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.[4] Patients diagnosed with hepatocellular carcinoma have a 33% probability of death during the first year.[4] Successful eradication of HCV has been shown to significantly reduce the risk of disease progression and related mortality as well as the development of hepatocellular carcinoma.[6,7]

HCV and HIV co-infection is associated with accelerated hepatic fibrosis progression and higher rates of liver decompensation and death compared to HCV monoinfection, and liver disease is a leading cause of non-AIDS-related mortality among HIV-infected patients.[8-10] New insights have revealed multiple mechanisms by which HCV and HIV lead to accelerated disease progression, specifically that HIV infection increases HCV replication, augments HCV-induced hepatic inflammation, increases hepatocyte apoptosis, increases microbial translocation from the gut and leads to an impairment of HCV-specific immune responses. Treatment of HIV with antiretroviral therapy and treatment of HCV have independently been shown to delay the progression of fibrosis and reduce complications from end-stage liver disease among co-infected patients.[11,12] However, rates of sustained virologic response with PEG-IFN and ribavirin have been

significantly inferior among co-infected patients compared with HCV-monoinfected patients, and treatment uptake has remained low given the limited efficacy and tolerability of current HCV regimens.[13-17] With multiple direct-acting antiviral agents in development to treat HCV, a unique opportunity exists to redefine the treatment paradigm for co-infected patients, which incorporates data on fibrosis stage as well as potential drug interactions with antiretroviral therapy.

Currently approved IFN- and, in some cases, RBV-free combination regimens consisting of 2 or more potent DAAs represent substantial progress in the treatment of HCV infection compared with IFN-based ones.[18-20] The combination of sofosbuvir/ledipasvir (Harvoni®), ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak® or Viekirax® + Exviera®) with and without RBV and grazoprevir/elbasvir (Zepatier®) are approved in the US and Europe for the treatment of chronic HCV GT1 infection and offer treatment options for the population of patients with compensated cirrhosis. These IFN-free first generation DAA combination treatment regimens substantially increased sustained virologic response rates 12 weeks post dosing (SVR_{12}) in pegIFN/RBV (PR)-naïve and -experienced patients, shortened the duration of treatment, and improved the safety and tolerability of treatment relative to IFN-containing regimens.

According to data from different trials, the effectiveness of DAA-based therapy appears to be similar between HCV mono-infected individuals and HCV/HIV co-infected individuals as shown in Table 1.[21] Per the most recent AASLD treatment guidelines, it is recommended that HCV/HIV co-infected patients be treated and re-treated the same as HCV mono-infected patients, albeit with attention paid to potential drug-drug interactions with anti-retroviral medications.[22]

Table 1. SVR Rates Observed in HCV-Mono-Infected and HCV/HIV Co-Infected Patients Treated with All-Oral HCV DAA Regimens

Study	Regimen, Duration, Population Studied	ITT SVR_{12} Rate in HCV/HIV-1 Co-Infected Population	ITT SVR_{12} Rate in Similar HCV Mono-Infected Population (Study or Studies)
TURQUOISE-I [19]	Ombitasvir/Paritaprevir/ritonavir + Dasabuvir + RBV, 12 weeks, GT1 HCV/HIV-1 Co-infection	94%	92% – 96% (SAPPHIRE-I and –II, TURQUOISE-II) [23-25]
ION-4 [26]	Sofosbuvir/Ledipasvir, 12 weeks, GT1, 4 HCV/HIV-1 Coinfection	96%	93% – 99% (ION-1, -2 and -3) [27-29]
ALLY-2 [30]	Sofosbuvir + Daclatasvir, 12 weeks, GT1 – 4 HCV/HIV-1 Coinfection	97%	95% (A1444040) [31]
C-EDGE CO-INFECTION [32]	Grazoprevir/Elbasvir, 12 weeks, GT1, 4, 6 HCV/HIV-1 Coinfection	96%	91% – 97% (C-EDGE TN, C-EDGE TE, C-WORTHY) [33,34]

Despite the progress, these IFN-free first generation regimens are not equally potent across all HCV genotypes and subtypes, and across all subpopulations, including, patients with severe renal impairment and post-transplant patients, leaving important medical needs unaddressed. Currently available treatments in some of these subpopulations still require co administration with RBV, necessitate longer treatment durations, and can potentially be associated with significant drug interactions. 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 (negating the need for baseline genotyping) and for certain subpopulations, further shortening of treatment durations while maintaining high SVR rates.

AbbVie is currently developing 2 "next generation" direct acting antiviral agents (DAAs), ABT-493, an HCV non-structural (NS) 3/4A protease inhibitor (PI) and ABT-530, an NS5A inhibitor, for use in combination for the treatment of chronic HCV infection,

including patients with compensated cirrhosis. 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 pangenotypic 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 pangenotypic 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 key resistance-associated variants.

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

In general, ABT-493 and ABT-530 combination has been well tolerated when administered to over 250 healthy volunteers and over 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 (≤ 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).

HCV-Infected Patients

Studies M14-867 and M14-868 are Phase 2b studies assessing efficacy, safety and pharmacokinetics of the combination of ABT-493 and ABT-530 in HCV GT1 (Study M14-867 Part 1) or GT2- or 3 infected (Study M14-868 Part 1) in treatment-naïve

(TN) and PR-experienced non-cirrhotic subjects, respectively, GT4 – 6 (Study M14-867) or GT2- or 3-infected (Study M14-868) treatment-naïve and PR-experienced subjects with and without cirrhosis.

In Part 1 of Study M14-867, 100% (40/40) of GT1-infected subjects without cirrhosis treated with ABT-493 200 mg QD + ABT-530 120 mg QD for 12 weeks and 97.4% (38/39) of subjects treated with ABT-493 200 mg QD + ABT-530 40 mg QD for 12 weeks achieved SVR_{12}. One subject in Arm B experienced relapse at Post-Treatment Week 4. In Part 2 of Study M14-867, 97% (33/34) of GT1-infected subjects without cirrhosis treated with ABT-493 300 mg QD + ABT-530 120 mg QD for 8 weeks achieved SVR_{12} (one subject discontinued due to metastatic cancer with HCV RNA undetectable at last visit).

Among 74 subjects with HCV GT2 infection in Part 1 of Study M14-868, no subject has experienced on treatment virologic failure or post-treatment relapse. Excluding one subject who was lost to follow-up, all 73 subjects with HCV GT2 infection achieved SVR_{12}. The SVR_{12} rates for each of the treatment regimens were 96% (24/25) (including a subject who was lost to follow-up) of subjects treated with ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks, 100% (24/24) of subjects treated with ABT-493 200 mg QD + ABT-530 120 mg QD for 12 weeks and 100% (25/25) of subjects treated with ABT-493 200 mg QD + ABT-530 120 mg QD + RBV for 12 weeks.

One hundred and twenty-one subjects (121) with HCV GT3 infection were treated in Part 1 of Study M14-868. Among all subjects receiving the regimen tested in this study, i.e., ABT-493 300 mg and ABT-530 120 mg without ribavirin for 12 weeks, 96.6% (28/29 subjects with available post-treatment data) achieved SVR_{12}. One subject in this arm experienced relapse at Post-Treatment Week 4.

Part 2 of Study M14-867 also has evaluated subjects infected with HCV GT4, GT5 or GT6. All subjects receiving treatment with ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks achieved SVR_{12} (34/34).

In Study M14-867 Part 2, GT1-infected treatment-naïve and PR-experienced subjects with compensated cirrhosis are being treated with ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks. Among the GT1 cirrhotic subjects, 96% (26/27) have achieved SVR_{12}, with one subject experienced relapse at Post-Treatment Week 4.

In Study M14-868 Part 2, among 29 treatment-naïve non-cirrhotic subjects with GT3 infection treated for 8 weeks with ABT-493 300 mg QD + ABT-530 120 mg QD, no subject experienced virologic failure. One subject prematurely discontinued from the study after Week 6 with an undetectable HCV RNA due to intolerance of blood draws, and did not return for follow up, thus is counted as a non-responder. The SVR_{12} rate for this cohort is 28/29 (96.6%). Among 24 treatment-naïve cirrhotic subjects with GT3 infection treated for 12 weeks with ABT-493 300 mg QD + ABT-530 120 mg QD, no subject experienced virologic failure. The SVR_{12} rate for this cohort is 24/24 (100%).

To date, safety data across all arms in Part 1 of Studies M14-867 and M14-868 encompassing 274 subjects treated with ABT-493 at doses 200 and 300 mg and ABT-530 at doses 40 and 120 mg (with and without RBV in Study M14-868) for 12 weeks show that the most frequently reported adverse events were fatigue, nausea, and headache (occurring in > 5% of subjects). Most of them were Grade 1 or 2 in severity. There were no increases in the frequency or severity of any adverse event associated between the different regimens of ABT-493 200 mg plus 40 mg or 120 mg ABT-530, and ABT-493 300 mg plus 120 mg ABT-530.

Of the 274 subjects, there have been 4 (1.5%) treatment-emergent SAEs reported in Studies M14-867 and M14-868 combined (all assessed as not related to ABT-493 or ABT-530): metastatic prostate cancer, pneumonia, atrial fibrillation, and B-cell lymphoma and one SAE that was not treatment-emergent (spontaneous abortion – also assessed as not related). Two subjects (0.7%; 2/274) had treatment-emergent adverse events leading to treatment discontinuation. Both were GT3-infected subjects in Arm F (ABT-493/ABT-530 [200 mg/120 mg] QD + RBV) of Study M14-868. 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. Baseline

ALT elevations for this subject normalized during treatment and there were no on-treatment ALT elevations above baseline; subject had total bilirubin elevations that were primarily indirect. 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 alanine aminotransferase (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. The ALT normalization pattern was similar across all arms (i.e., both ABT-493 and ABT-530 dose levels) in both studies. Other laboratory abnormalities were infrequent and were primarily associated with the well-described hemolytic effect of RBV, manifesting as Grade 1 anemia in a total of 4 subjects, all occurring in Study M14-868 RBV-containing arms. 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.

The safety of the combination regimen of ABT-493 and ABT-530 in subjects with compensated cirrhosis is investigated in Study M14-867 Part 2 (Arm F) and Study M14-868 Part 2 (Arms O and P) using a regimen of ABT-493 either 200 or 300 mg dose in combination with ABT-530 120 mg for 12 weeks without ribavirin. Based on 82 subjects with compensated cirrhosis enrolled in these arms who have received 4 weeks or more of treatment, the ABT-493 and ABT-530 regimen has demonstrated a favorable safety profile. The majority of adverse events have been Grade 1 or 2 and there have been no treatment discontinuations, serious drug-related AEs, or ALT elevations from baseline.

A detailed discussion of the preclinical pharmacology and toxicology, in vitro virology and metabolism, and clinical data for ABT-493, ABT-530 and the combination of ABT-493 and ABT-530 can be found in the ABT-493 and ABT-530 Fixed-Dose Combination Investigator's Brochure.[35]

ARV Drug-Drug Interaction Studies with ABT-493 and ABT-530

Phase 1 DDI studies of the ABT-493 + ABT-530 combination with HIV antiretroviral (ARV) drugs have been conducted in healthy volunteers and/or HIV-1 infected subjects.

The ABT-493 + ABT-530 combination had no clinically meaningful impact on the exposures (≤ 80%) of evaluated ARV regimens: ritonavir-boosted protease inhibitors (darunavir, lopinavir), rilpivirine, raltegravir, emtricitabine and tenofovir disoproxil fumarate (TDF). ABT-493 and ABT-530 exposures were not affected by rilpivirine and raltegravir.

Dolutegravir, lamivudine and abacavir (Triumeq®) coadministered with ABT-493 + ABT-530 has recently been evaluated in a DDI study (Study M15-584 Arm 2). Coadministration was safe and well tolerated with mild adverse events reported. ABT-493 and ABT-530 had no impact on dolutegravir, lamivudine and abacavir exposures. There was a mild decrease in ABT-493 and ABT-530 exposures of no clinical significance.

Efavirenz induces P-gp and exposures of ABT-493 and ABT-530 in the presence of efavirenz were approximately 3- and 2-fold lower, respectively, and thus will not be allowed in this study.

ABT-493 is a substrate of OATP and inhibition of OATP increases ABT-493 exposure. When ABT-493 + ABT-530 was administered with cyclosporine (400 mg), an OATP inhibitor, ABT-493 exposure was up to 5.1-fold of DAAs alone. The observed increase in exposures, however, was not associated with clinically significant safety findings.

Protease inhibitors as a class have potential to inhibit OATP, thus the larger exposure increases in ABT-493 with ritonavir boosted protease inhibitors than with ritonavir alone may result from interaction of ABT-493 with both the protease inhibitor and ritonavir components. Cobicistat has been shown in vitro and in vivo to have similar cytochrome P-450 enzyme and transporter inhibition potential as ritonavir.

When ABT-493 was administered with ritonavir, exposure of ABT-493 was 2-fold of ABT-493 exposure alone. Coadministration of ABT-493 + ABT-530 with ritonavir boosted protease inhibitors, darunavir QD or lopinavir BID resulted in increases in ABT-493 exposure of 3- to < 5-fold and < 2-fold exposure to ABT-530 without significant change in the LPV or DRV exposures. In spite of the increase in ABT-493 exposures while coadministered with DRV + RTV or LPV/r, co-administration of these agents were well tolerated with mild adverse events. Coadministration of ABT-493 + ABT-530 with ritonavir boosted atazanavir was studied in a DDI study [redacted]

A recently completed study (Study M15-584) evaluated the drug interaction profile when ABT-493 + ABT-530 was co-administered with Genvoya® (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, tenofovir alafenamide 10 mg QD). Coadministration was safe and well tolerated, with mild adverse events reported and one grade 3 neutropenia deemed related to the combination of Genvoya®, ABT-493 and ABT-530 in a black male subject with a low baseline ANC, leading to premature study drug discontinuation. The ABT-493 exposure increased 3-fold and the ABT-530 exposure increased 57%, with non-clinically significant increases in elvitegravir, cobicistat, tenofovir and emtricitabine exposures. Thus, cobicistat boosted elvitegravir will be allowed in Study M14-730.

In addition, ritonavir and cobicistat-boosted HIV-1 protease inhibitors (darunavir and lopinavir) will be allowed in the non-cirrhotic treatment arm only. As detailed in Section 5.6.4.1.1, these HIV-1 protease inhibitors will not be allowed in cirrhotic subjects, [redacted]

For a more detailed discussion of drug-drug interaction studies please refer to the ABT-493 and ABT-530 Fixed-Dose Combination Investigator's Brochures.[35]

Study M14-730 is an open-label, multicenter study to evaluate efficacy and safety of ABT-493/ABT-530 for an 8- or 12-week treatment duration in HCV treatment-naïve or prior treatment-experienced (i.e., IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN) adults with chronic HCV GT1-6 infection and HIV-1 co-infection, with and without cirrhosis. Additional discussion and justification of study design may be found in Section 5.6.

3.1 Differences Statement

This is the first dedicated study of ABT-493 and ABT-530 in HCV treatment-naïve or prior treatment-experienced (i.e., IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN) chronic HCV GT1 – 6 infected subjects with HIV-1 co-infection. Study M13-590 (Phase 3 evaluating the efficacy and safety of ABT-493/ABT-530 in adults with chronic HCV GT1 infection) will include subjects with HIV-1 co-infection and are non-cirrhotic. Study M14-730 is anticipated to provide additional safety and efficacy information in a more broadly representative HCV/HIV co-infected population.

3.2 Benefits and Risks

Potential benefits of treatment with ABT-493/ABT-530 include: Potent and pangenotypic antiviral activity in vitro, higher genetic barrier to development of drug resistance across genotypes compared to first generation protease and NS5A inhibitors, no need for RBV, 8 or 12 weeks of treatment, and a convenience of once daily regimen. Approved combination DAA regimens (sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir and dasabuvir, with or without RBV and grazoprevir/elbasvir) are not equally potent across all HCV genotypes and subtypes, and across subpopulations, including patients with HCV/HIV-1 co-infection, leaving important medical needs unaddressed. Currently available treatments in some subpopulations still require RBV, necessitate treatment durations longer than 12 weeks, and can potentially be associated with significant drug interactions. More convenient and tolerable regimens are also needed in order to improve patient compliance and, thereby, increase the chance of a sustained virologic response.

SVR rates among HCV/HIV-co-infected patients treated with new, all-oral HCV DAA regimens have been observed to be comparable to those observed in HCV-monoinfected patients, and this similar efficacy finding is anticipated following treatment with ABT-493/ABT-530. In addition, there is a risk of not treating HCV in HCV/HIV co-infected patients, since HCV and HIV co-infection is associated with accelerated hepatic fibrosis progression and higher rates of liver decompensation and death compared to HCV monoinfection, and liver disease is a leading cause of non-AIDS-related mortality among HIV-infected patients.[8-10]

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-530 and ABT-493 are detailed in the ABT-493/ABT-530 Fixed-Dose Combination Investigator's Brochure.[35]

Efficacy will be assessed on an ongoing basis during the study to determine if treatment should be extended from 8 to 12 weeks for subjects in Arm A who have not yet completed treatment, and if treatment should be extended for all subjects or only for certain subgroups. These safeguards are intended to minimize the risk of subjects failing with durable resistance to one or more drug classes, which could compromise future treatment options.

Risks associated with ABT-530 and ABT-493 co-administered including the risks of toxicity, virologic failure, and development of resistant mutations (Section 5.6.4), appear to be limited and manageable based upon the available data.

Given the potential high SVR rate in these populations of HCV-infected subjects, the benefit-risk profile for co-administered ABT-493 and ABT-530 as treatment for chronic HCV infection/HIV-1 co-infection is favorable.

4.0 Study Objective

4.1 Primary Objective

The primary objectives of this study are to are to compare the SVR_{12} rates (12-week sustained virologic response, SVR_{12} [HCV RNA < LLOQ 12 weeks following therapy]) of 8 or 12 weeks of treatment with ABT-493/ABT-530 combination in HCV genotype 1 – 6 infected subjects with HIV-1 co-infection to a pre-defined threshold, based on the historical SVR_{12} rate of the current standard of care (i.e., sofosbuvir/ledipasvir for 12 weeks or grazoprevir/elbasvir for 12 weeks) and to assess the safety of treatment with the combination regimen ABT-493/ABT-530 for 8 or 12 weeks in HCV genotype 1 – 6 infected subjects with HIV-1 co-infection.

4.2 Secondary Objective

The secondary objectives are to assess:

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

Additional objectives are:

- To estimate the pharmacokinetics of ABT-493 and ABT-530.
- To evaluate the percentage of HIV-1/HCV co-infected participants on stable ART who maintain HIV RNA suppression at the end of DAA treatment and at 12 week post DAA treatment.
- To evaluate the emergence of HCV resistance-associated variants among the participants who developed HCV virologic failure.
- To evaluate the emergence of HIV drug resistance-associated variants among the participants who developed HIV virologic failure.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, multicenter, open-label study to evaluate the efficacy and safety of the combination regimen ABT-493/ABT-530 in HCV treatment-naïve (i.e., subject has not received a single dose of any approved or investigational anti-HCV medication) or treatment-experienced (i.e., subject who has failed prior IFN or pegIFN with or without RBV therapy, or SOF plus RBV with or without pegIFN) adults with chronic HCV GT1 – 6 infection and HIV-1 co-infection with or without cirrhosis (F0-F4; excluding GT3 treatment-experienced subjects) for an 8-week (non-cirrhotics) or 12 week (cirrhotics) treatment duration.

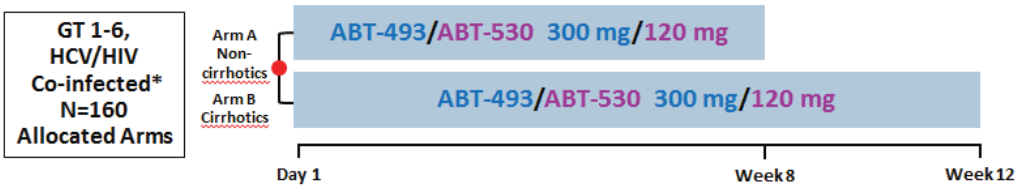
Subjects must be naïve to treatment with any HIV-1 antiretroviral therapy (ART) or on a stable, qualifying HIV-1 ART regimen that contains rilpivirine (RPV), raltegravir (RAL), dolutegravir (DTG), darunavir coadministered with ritonavir (DRV + RTV) QD, darunavir/cobicistat (DRV/COBI), lopinavir/ritonavir (LPV/r), BID or elvitegravir/cobicistat (EVG/COBI).

The study will consist of two periods:

- Treatment Period: Eligible subjects will be enrolled to receive ABT-493/ABT-530 300 mg/120 mg for an 8 or 12 week treatment duration based on cirrhosis status.
- Post-Treatment Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 24 weeks to monitor safety, assessment of PROs, HCV RNA, HIV RNA, HCV resistance, HIV resistance and the emergence and persistence of viral variants.

A study schematic is shown below in Figure 1.

Figure 1. Study Design



* HCV GT3 treatment-experienced subjects are not eligible for this study.

Approximately 160 eligible subjects will be allocated to one of the following treatment arms:

- Arm A: HCV GT1 – 6/HIV-1 co-infected non-cirrhotic subjects will be treated with ABT-493/ABT-530 300 mg/120 mg once a day (QD) for 8 weeks.
- Arm B: HCV GT1 – 6/HIV-1 co-infected subjects with compensated cirrhosis will be treated with ABT-493/ABT-530 300 mg/120 mg once a day (QD) for 12 weeks.

A maximum of approximately 110 GT1 subjects will be enrolled in the study. A minimum of 10% (n = 16) of the overall study population will be subjects with compensated cirrhosis.

The study was designed to enroll approximately 160 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 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 associated with the Screening Visit. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through Study Day 1 prior to dosing, and will record the results of this assessment and the details of the informed consent process in the subject's medical records. In addition, subject will be provided with an HIV-1 ARV dosing card as described in Section 5.3.1.1. Eligible subjects have up to 35 days following the Screening Visit to enroll into the study.

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 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-2 test;
- HCV genotype does not meet Inclusion Criterion 4, Section 5.2.1, or meets Exclusion Criteria 4 and 5, Section 5.2.2;
- 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 retest or rescreen.

Subjects who have exclusionary laboratory parameter(s) per Exclusionary Criterion 10, 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.

Subjects who are rescreened outside of the initial 35 day Screening period must be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary.

For subjects who rescreen or subjects who 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 assigned into either the 8 or 12 week treatment arms based on cirrhotic status via IRT. On Study Day 1 subjects will be administered study drugs at the site and given instructions about the study drugs and the dosing schedule.

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, and urinalysis as specified in Table 3. Plasma samples for pharmacokinetic analysis (including samples for intensive PK analysis) and HCV RNA analysis will be collected as detailed in Section 5.3.2 and Section 5.3.1.1, respectively. Blood samples for optional pharmacogenetic analysis will be collected as detailed in Appendix C. Patient Reported Outcomes (PROs) will also be assessed at the visits listed 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 drug exposure.

The HCV 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.

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, the emergence and persistence of HCV viral variants, plasma HIV-1 RNA, HIV drug resistance and assessment of PROs 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.

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

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 consists of male and female adults aged 18 years or older with chronic HCV GT1 – 6 infection and with HIV-1 co-infection, without cirrhosis or with compensated cirrhosis (F0-F4), who are treatment naïve (i.e., subject has never received a single dose of any approved or investigational anti-HCV medication) or treatment-experienced (i.e., subject who has failed prior IFN or pegIFN with or without RBV therapy, or SOF plus RBV with or without pegIFN). HCV GT3 treatment-experienced subjects are excluded from this study. Subjects who meet all the

inclusion criteria and none of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

1. Male or female, at least 18 years of age at time of Screening.
2. If female, subject must be either postmenopausal, or permanently surgically sterile or for Women of Childbearing Potential practicing at least one protocol specified method of birth control (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 GT1-, 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 IFN or pegIFN with or without RBV or SOF plus RBV with or without pegIFN). GT3 subjects must be HCV

treatment-naïve. Previous HCV treatment must have been completed ≥ 2 months prior to Screening.

8. Body Mass Index (BMI) is ≥ 18.0 kg/m^2 at the time of Screening. BMI is calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m).

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

Non-Cirrhotics

- A liver biopsy within 24 months prior to or during Screening demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of ≤ 3, Ishak fibrosis score of ≤ 4; or
- A FibroScan® score of < 12.5 kPa within ≤ 6 months of Screening or during Screening period (FibroScan® must be approved by the local regulatory agency to qualify for entrance criteria); or
- A Screening FibroTest score of ≤ 0.48 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) < 1.

Cirrhotic

- Previous histologic diagnosis of cirrhosis on liver biopsy, e.g., METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of > 3, Ishak score of > 4 or on a liver biopsy conducted during Screening; or
- A FibroScan® score of ≥ 12.5 kPa within ≤ 6 months of Screening or during Screening period (FibroScan® must be approved by the local regulatory agency to qualify for entrance criteria); or
- A Screening FibroTest result that is ≥ 0.75 and an APRI > 2.

In the absence of a definitive diagnosis of presence or absence of cirrhosis by Fibrotest/APRI using the above criteria (indeterminate FibroTest [0.48 < result < 0.75], or conflicting FibroTest and APRI results [e.g., FibroTest ≤ 0.48, but APRI ≥ 1]), a liver biopsy or FibroScan® is required. 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 presence or absence of cirrhosis.

10. Cirrhotic Subjects Only: Compensated cirrhosis defined as Child-Pugh score of ≤ 6 at Screening and no current or past evidence of Child-Pugh B or C Classification or clinical history of liver decompensation including ascites noted on physical exam, hepatic encephalopathy or esophageal variceal bleeding.

11. Cirrhotic Subjects Only: Absence of hepatocellular carcinoma (HCC) as indicated by a negative ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or a negative ultrasound at Screening. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.

12. Positive test result for anti-Human Immunodeficiency Virus antibody at Screening.

13. Naïve to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study), or

    On a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to Screening.

    The HIV-1 ART regimen must include at least one of the following ARV agents:

    - For cirrhotic and non-cirrhotic subjects:
      - Raltegravir (RAL) PO BID
      - Dolutegravir (DTG) PO QD or PO BID
      - Rilpivirine (RPV) PO QD
      - Elvitegravir/cobicistat (EVG/COBI) PO QD
    - For non-cirrhotic subjects, the following regimens are also allowed:
      - Darunavir (DRV) co-administered with ritonavir (RTV) PO QD
      - Darunavir/cobicistat (DRV/COBI) PO QD
      - Lopinavir/ritonavir (LPV/r) PO BID

In addition to the above medications, subjects (both cirrhotic and non-cirrhotic) may take a nucleoside/nucleotide reverse transcriptase inhibitor (N(t)RTI) backbone containing any of the following:

- Tenofovir disoproxil fumarate (TDF) PO QD
- Tenofovir alafenamide (TAF) PO QD
- Abacavir (ABC) PO QD or BID
- Emtricitabine (FTC) PO QD
- Lamivudine (3TC) PO QD or BID

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

14. Subjects naïve to ART must have a CD4+ count ≥ 500 cells/mm^3 (or CD4+ % ≥ 29%) at Screening or

    Subjects on a stable ART regimen must have the following:

    - CD4+ count ≥ 200 cells/mm^3 (or CD4+ % ≥ 14%) at Screening; and
    - Plasma HIV-1 RNA below LLOQ at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once during the 12 months prior to Screening (by an approved plasma HIV-1 RNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTi*m*e HIV-1 assay).

15. Subject 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.

16. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.

Rationale for Inclusion Criteria

1, 4 – 7, 9 – 14	In order to select the appropriate subject population with appropriate disease characteristics for evaluation

8	For the safety of study subjects
2, 3	The impact of ABT-493 and ABT-530 on human pregnancies has not been established. However, assessment of the completed nonclinical reproductive toxicology studies indicates that there is no drug-related effect on teratogenicity/fetotoxicity. In addition, the compounds are non-genotoxic
15 – 16	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).
4. HCV genotype performed during Screening indicating HCV GT3 in a subject with prior HCV treatment experience.
5. HCV genotype performed during Screening indicating co-infection with more than one HCV genotype.
6. Positive Human Immunodeficiency virus, type 2 (HIV-2) Ab at Screening.
7. Requirement for and inability to safely discontinue the medications or supplements listed in Table 2 at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of any study drug.
8. Clinically significant abnormalities or co-morbidities, other than HCV/HIV-1 co-infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile, and a 12-lead electrocardiogram (ECG) that make

the subject an unsuitable candidate for this study in the opinion of the investigator, including, but not limited to:

- Uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% during Screening.
- Active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
- Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric, or other medical disease or disorder, which is unrelated to the existing HCV infection.

9. Any cause of liver disease other than chronic HCV-infection, including but not limited to the following:
   - Hemochromatosis.
   - Alpha-1 antitrypsin deficiency.
   - Wilson's disease.
   - Autoimmune hepatitis.
   - Alcoholic liver disease.
   - Steatohepatitis on liver biopsy considered to be the primary cause of the liver disease rather than concomitant/incidental with HCV infection.
10. Screening laboratory analyses showing any of the following abnormal laboratory results:
    - ALT > 10 × ULN
    - AST > 10 × ULN
    - Calculated creatinine clearance (using Cockcroft-Gault method) of < 50 mL/min
    - Direct bilirubin > ULN
    - Albumin < 3.0 g/dL
    - International normalized ratio (INR) > 1.5 × ULN, unless subject has known hemophilia or is on a stable anticoagulant regimen affecting INR
    - Hemoglobin < 10 g/dL for women; < 11 g/dL for men

- Platelets < 60,000 cells per mm^3 for subjects with cirrhosis; < 90,000 cells per mm^3 for subjects without cirrhosis

11. History of solid organ transplantation.
12. 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.
13. Receipt of any other investigational or commercially available direct acting anti-HCV agents other than sofosbuvir (e.g., telaprevir, boceprevir, simeprevir, paritaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir or dasabuvir).
14. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-493/ABT-530.
15. Requirement for chronic use of systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab).
16. History of severe, life-threatening or other significant sensitivity to any excipients of the study drug.
17. Treatment for an AIDS-associated opportunistic infection (OI) (Appendix E) within 6 months of Screening.
18. Subjects who cannot participate in the study per local law.

Rationale for Exclusion Criteria

1, 10, 11, 14 – 18	In order to ensure safety of the subjects throughout the study
2, 7, 12, 13	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications
3 – 6, 8, 9	To exclude subjects with liver diseases other than chronic HCV GT1 – 6 infection and subjects with HIV-2 co-infection

5.2.3 Prior and Concomitant Therapy

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

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

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

The AbbVie Primary Therapeutic Area Medical Director should be contacted if there are any questions regarding concomitant or prior therapies.

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. Subject will be considered treatment-experienced, if they have previously received HCV treatment with IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN.

Subjects will be categorized as:

- HCV Treatment-naïve: subject has never received any treatment for HCV infection.
- Subjects **with an allowed prior HCV treatment** will be categorized as:
  - **Non-responder:** HCV RNA detected at the end of a prior treatment course (except for breakthrough, which is captured separately). These subjects are further categorized as:
    - Null responder: failed to achieve a 1 $\log_{10}$ IU/mL reduction in HCV RNA by Week 4 or a 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior treatment course;
    - Partial responder: achieved at least a 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior treatment course but failed to achieve HCV RNA undetectable at the end of treatment;
    - Unknown or unable to specify: insufficient data to categorize as null or partial responder.
  - **Breakthrough:** confirmed $\geq$ 1 $\log_{10}$ IU/mL increase from nadir or achieved HCV RNA undetectable (or unquantifiable) during a prior treatment course but HCV RNA was quantifiable during or at the end of treatment.
  - **Relapse:** achieved HCV RNA undetectable at the end of a prior treatment course but HCV RNA was detectable following cessation of therapy.
  - **Other:** subject received a prior treatment course and reason for not achieving SVR is other than above.
  - **Unknown:** subject received a prior treatment course and reason for not achieving SVR is unknown.

Subjects must have discontinued prior HCV therapy $\geq$ 2 months prior to the Screening Visit in order to be eligible for the study. For subjects who had multiple HCV treatment courses, the categorization of previous response category will be based on the last prior treatment.

5.2.3.2 Prior and Concomitant HIV-1 Therapy

Subjects must be naïve to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study), or must be on a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to Screening.

If on an HIV-1 ART regimen, it must include at least one of the ARV agents as per Inclusion Criterion 13 (Section 5.2.1).

Subjects will maintain the same dose and dosing interval of their HIV-1 ART regimen upon initiating the study drugs regimen.

Subjects must remain on the same HIV-1 ART regimen for the entire Treatment Period. Any change in the HIV-1 ART regimen during the Treatment Period must be discussed with the AbbVie Primary Therapeutic Area Medical Director prior to the change, unless the change is being made to address an immediate safety concern.

Subjects receiving any other HIV-1 ART in addition to those listed in Inclusion Criterion 13 (Section 5.2.1) would not be eligible for enrollment in the study.

Cirrhotic subjects on a regimen containing DRV or LPV will not be eligible for the study as indicated in Inclusion Criterion 13 (Section 5.2.1).

5.2.3.3 Other 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.

Flu shots and all essential vaccinations in HCV/HIV-1 co-infected subjects are allowed during Screening through the Post-Treatment Period.

5.2.3.4 Prohibited Therapy

Subjects must be able to safely discontinue any prohibited medications or supplements listed in Table 2 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 2. 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
Tipranavir/r
Atazanavir
Efavirenz
Etravirine
Nevirapine

* 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) and hormonal replacement therapy 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 and hormonal

replacement therapy, such as those containing norethindrone, desogestrel, or levonorgestrel, without ethinyl estradiol, may be used with ABT-493/ABT-530. Post-menopausal hormone replacement therapy, such as with esterified or conjugated estrogens, i.e., not containing ethinyl estradiol, may be used with ABT-493/ABT-530 at the discretion of the Investigator.

The chronic use of systemic immunosuppressants 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), azathioprine, or monoclonal antibodies (e.g., infliximab).

The investigator must refer to the current package insert(s) or product label(s) of a subject's ART regimen for a complete list of prohibited medications.

5.2.4 Contraception Recommendations and Pregnancy Testing

If female, subject must be either postmenopausal defined as:

- Age ≥ 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).

OR

For women of childbearing potential (WOCBP):

- 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. Condoms without spermicide are 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 and Appendix D.

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 history of tobacco, alcohol and drug use, will be taken from each subject at Screening Visit. 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.

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. Waist circumference will be measured at Screening; however, if it is not measured at Screening, it can be measured on Day 1.

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. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes. The subject should wear lightweight clothing and no shoes during weighing. The vital signs performed on Day 1 of the Treatment Period will serve as the baseline for clinical assessment.

12-Lead Electrocardiogram

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

The ECG 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.

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 3 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 the clinical laboratory tests.

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

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

Table 3. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Other Tests
Hematocrit	Blood Urea Nitrogen (BUN)	HBsAg[d]
Hemoglobin	Creatinine	Anti-HCV Ab[d]
Red Blood Cell (RBC) count	Total bilirubin[a,g]	HIV Ab[d]
White Blood Cell (WBC) count	Direct and indirect bilirubin	Opiates[d]
Neutrophils	Alanine transaminase (SGPT/ALT)	Barbiturates[d]
Bands, if detected	Aspartate transaminase (SGOT/AST)	Amphetamines[d]
Lymphocytes	Alkaline phosphatase	Cocaine[d]
Monocytes	Sodium	Benzodiazepines[d]
Basophils	Potassium	Alcohol[d]
Eosinophils	Calcium	Phencyclidine[d]
Platelet count (estimate not acceptable)	Inorganic phosphorus	Propoxyphene[d]
Reticulocyte count	Cholesterol	Methadone[d]
Prothrombin Time/INR[a]	Total protein	Urine and Serum Human Chorionic Gonadotropin (hCG) for females[e]
Activated partial thromboplastin time (aPTT)	Glucose	HCV RNA
Urinalysis	Triglycerides	HIV-1 RNA
Specific gravity	Low Density Lipoproteins (LDL)[b,c]	Hepatitis B Panel[f]
Ketones	High Density Lipoprotein (HDL)[c]	Hemoglobin A1C[d]
pH	Albumin[a]	IL28B[c]
Protein	Chloride	HCV genotype and subtype[d]
Blood	Bicarbonate	Pharmacogenetic sample (optional)
Glucose	Magnesium	Alpha2-macroglobulin[g]
Urobilinogen	Total insulin[c]	Haptoglobin[g]
Bilirubin	Gamma-glutamyl transferase (GGT)	Apolipoprotein A1[g]
Leukocyte esterase	Creatinine clearance (Cockcroft-Gault calculation)	CD4, CD4%
Microscopic (reflex)		CD8, CD8%
		CD4:CD8

a. Also a component of Child-Pugh Assessment.

b. Directly measured.

c. Performed only at Baseline.

d. Performed only at Screening.

e. Pregnancy testing is not required for females of non-childbearing potential.

f. Performed for management of transaminase elevation (Section 6.1.7.1).

g. Component of FibroTest and collected only if needed during the Screening Period.

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 Testing

A serum pregnancy test will be performed for all female subjects of childbearing potential at Screening. Additional urine pregnancy tests will be performed every 4 weeks, starting at Day 1 (prior to enrollment) during the treatment period, including at the last Treatment Period visit and until 30 days of last study drug dose, as indicated in Appendix C and Appendix D. Determination of postmenopausal status will be made during the Screening period, based on the subject's history.

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

Concomitant Medication Assessment

Please refer to Section 5.2.3.

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.

Urine Screens for Drugs of Abuse and Alcohol

Urine specimens will be tested at the Screening Visit for the presence of drugs of abuse and alcohol. The panel for drugs of abuse will minimally include the drugs listed in Table 3. 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 24 months of Screening or who have not had a qualifying FibroScan® within the previous ≤ 6 months of Screening 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. Subjects that have a previous liver biopsy performed at any time in the past showing cirrhosis (Metavir F3/4 or F4, Ishak 5 or 6, or equivalent) will not require the additional liver diagnosis testing for the purposes of eligibility. Selection of liver biopsy or non-invasive testing performed should be based on local standard practice.

Subject will be considered to be non-cirrhotic or 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).

Child-Pugh Score and Category

Subjects with compensated cirrhosis will have Child-Pugh scores assessed. The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and

2 clinical assessments) as shown in Table 4. Child-Pugh score will be determined at the visits indicated in Appendix C and Appendix D.

Table 4. Child-Pugh Classification of Severity of Cirrhosis

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

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

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

Clinical Assessment of Hepatic Decompensation

A clinical assessment of hepatic encephalopathy and ascites will be performed at Study Day 1 prior to dosing to confirm the subject has not progressed to hepatic decompensation since Screening for all subjects who have compensated cirrhosis. Grading system guidelines for ascites are listed above in Table 4.

Hepatocellular Carcinoma Screening

Subjects with compensated cirrhosis who do not have a historical qualifying liver ultrasound, CT, or MRI will have an ultrasound performed during Screening. A positive

ultrasound result suspicious for HCC will be confirmed with CT scan or MRI during Screening. Suspicious ultrasound lesions confirmed by CT or MRI are exclusionary.

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 instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaire to them. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

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.

Short Form 36 – Version 2 Health Survey

The SF-36v2 is a general Health Related Quality of Life (HRQoL) instrument with extensive use 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.

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

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 100201 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. Subjects will be enrolled on Study Day 1 as described in Section 5.5.4.

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 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 Subgenotype

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 and subtype will be determined by a Sanger sequencing assay of a region of the NS5B gene by the central laboratory.

HCV RNA and HCV Resistance Testing Sample

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.

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

Flow Cytometry, HIV RNA and HIV Resistance Testing Samples

Samples for plasma HIV-1 RNA levels and flow cytometry (including but not limited to CD4+ T-cell and CD8+ T-cell counts [absolute and percent]) will be obtained at the times specified in Appendix C and Appendix D. Plasma HIV-1 RNA will be measured by the central laboratory using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, version 2.0 HIV-1 Assay. Results below the LLOD are reported as: "Not Detected." Subjects will also have blood samples drawn and archived at the study visits indicated in Appendix C and Appendix D. These samples may be used for other analyses including drug resistance testing. These samples may be tested at the discretion of AbbVie.

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

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

If the subject's repeat HIV-1 RNA is < 200 copies/mL, then the subject will resume routine plasma HIV-1 RNA assessments as shown in Appendix C and Appendix D, and described in Section 5.4.1.1.

Specific instructions for preparation and storage of flow cytometry, plasma HIV-1 RNA, archive and HIV 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, as determined by AbbVie.

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

HIV-1 ARV Regimen Dosing Card

A dosing card will be provided to subjects on stable ART treatment at each study visit in order to collect information for the last two doses of their HIV-1 ARV medications taken prior to each scheduled pharmacokinetic sample collection as specified in Appendix C.

The information recorded on the dosing cards may be used to guide HIV-1 ARV treatment compliance discussion and to assess pharmacokinetic (PK) collection time relative to HIV-1 ARV dose. If poor adherence is noted, the subject should be counseled and this should be documented in the subject's source.

Site personnel will provide training on its proper use and subjects will be instructed to complete the required information and ensure that entries are up-to-date prior to arrival at the study site on study visit days. In addition, the investigator or designee will contact the subject approximately 2 days prior to the scheduled pharmacokinetic sample collection date to review the importance of proper HIV-1 ARV administration and documentation of dosing times on the dosing card. The date and time of the phone contact will be entered into source documentation.

Subjects will be required to enter the exact date, time, and number of pills taken for each medication of the ART regimen separately. The information recorded will be reviewed by the site staff; then site staff will enter the information for the last 2 doses taken prior to the scheduled pharmacokinetic sampling into the eCRF. The completed dosing card will be collected by the site personnel on the day of the pharmacokinetic sampling and will be kept as a source record of dosage administration.

In the event that the dosing card is not available at the time of pharmacokinetic sample collection, the site may obtain dosing information via patient interview and record the information for the last 2 doses taken prior to the scheduled pharmacokinetic sampling in the source notes and the eCRF.

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.
- The Investigator or designee will contact the subject approximately 2 days before the scheduled visit date to review the importance of proper study drug administration relative to the pharmacokinetic blood collection and documentation of dosing times on the dosing card. The date and time of the contact will be entered into the subject's source documents.
- 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 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.

Optional Samples 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.

5.3.1.3 Meals and Dietary Requirements

Study drug (i.e., ABT-493/ABT-530) tablets should be dosed together and taken with food.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Pharmacokinetic Sparse Sampling of ABT-493, ABT-530 and HIV-1 ARVs:

Pharmacokinetic blood samples will be collected by venipuncture at each study visit indicated in Appendix C. One sample is for the pharmacokinetic assays of ABT-493, ABT-530 and their possible metabolites and a second sample for the assay of HIV-1 ARVs, if applicable (subject on stable ART regimen), as mentioned below.

- At all Treatment Period visits, except for Study Day 1 and Week 4, one or two blood samples, as applicable, 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 and HIV-1 ARVs, if applicable, will be recorded to the nearest minute in the source documents. Additionally, the dates and time of the two previous doses of the study drug and HIV-1 ARVs, if applicable, will be recorded to the nearest minute on the eCRF.

Pharmacokinetic Intensive Sampling of ABT-493, ABT-530 and HIV-1 ARVs:

Blood samples for pharmacokinetic assays of ABT-493, ABT-530 and their possible metabolites and for the assay of HIV-1 ARVs, if applicable, will be collected by venipuncture at the study visits indicated below and in Appendix C.

- On Study Day 1: Subjects will have their study drug dose administered by study site personnel with food. Pharmacokinetic intensive blood samples will be collected from each subject at 2, 4 and 6 hours post-dose. One or two samples will be collected at each of the 3 time points, as applicable, (one for ABT-493, ABT-530 and another for HIV-1 ARVs, if applicable).

- The date and time of site-administered dose of study drug and blood sample collection will be recorded to the nearest minute in the source documents. Additionally the date and time of site-administered dose of study drug will be recorded to the nearest minute on the eCRF. The two previous doses of HIV-1 ARVs, if applicable, will be recorded to the nearest minute in the dosing card or the source documents and on the eCRF.

- On Week 4 Visit: Pharmacokinetic intensive blood samples will be collected from each subject immediately prior to study drug dose (0 hour) and at 2 and 4 hours post-dose. One or two samples will be collected at each of the 3 time points, as applicable, (one for ABT-493, ABT-530 and another for HIV-1 ARVs, if applicable).
  - The date and time of site-administered dose of study drug and blood sample collection will be recorded to the nearest minute in the source documents. Additionally the date and time of site-administered dose of study drug will be recorded to the nearest minute on the eCRF. The two previous doses of study drug and HIV-1 ARVs, if applicable, will be recorded to the nearest minute in the dosing card or the source documents and on the eCRF.

One or two blood samples, of approximately 4 mL each, will be collected from each subject at each time point (as applicable) for PK analysis.

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, ABT-530 and HIV ARVs 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, HIV ARVs 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, ABT-530 and HIV ARVs 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 a validated assay method by 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.

The samples for HIV ARVs for individual subjects, a group of subjects or for the whole study may be analyzed based on safety, HCV RNA and plasma HIV-1 RNA results. The plasma concentrations of HIV ARVs will be determined at a separate laboratory (PPD) using validated assay methods under the supervision of the Drug Analysis Department at AbbVie.

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 SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study dose).

5.3.3.2 Secondary Variables

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

5.3.3.3 HCV Resistance Variables

The following resistance information will be analyzed for subjects receiving ABT-493/ABT-530 who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA ≥ 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.

5.3.3.4 HIV Resistance Variables

If any subject on stable ART develops a confirmed, plasma HIV-1 RNA level ≥ 500 copies/mL after starting the study, the HIV-1 protease (PR), reverse transcriptase (RT) and integrase (IN) sequences, as applicable, will be analyzed.

5.3.4 Safety Variables

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

5.3.5 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.

Plasma concentrations of HIV-1 ARVs for an individual subject, a group of subjects or for the whole study will be analyzed based on HCV RNA and/or plasma HIV-1 RNA results and summarized.

5.3.6 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 study drug or drugs of a similar class. The results may also be used for the development of diagnostic tests related to IL28B and study treatment, or drugs of a similar class. The results of additional pharmacogenetic IL28B 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, the emergence and persistence of resistant viral variants. Plasma HIV-1 RNA and emergence of HIV resistance will also be monitored during the Post-Treatment Period at the visits specified in Appendix D.

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.

5.4.1.1 HCV Virologic Failure Criteria

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

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurement 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 < 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 drug 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.

5.4.1.2 Failure to Maintain HIV Virologic Suppression

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

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

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

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

During the Treatment Period, subjects with confirmed failure to maintain HIV-1 RNA suppression should continue HCV study drug treatment unless there is a requirement for prohibited concomitant medications (Section 5.2.3.2) to construct a new HIV ART regimen.

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

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

5.4.1.3 Efficacy Treatment Adjustment Criteria

The Sponsor will evaluate efficacy by reviewing HCV RNA levels throughout the study. If the virologic relapse criterion below is met, the findings will be reviewed by the Sponsor. The characteristics of the subjects experiencing virologic failure will be reviewed to determine what changes are needed and whether the changes should be applied to the entire Arm A or to certain subgroups, such as those defined by baseline viral load, gender, or other potential predictors of response.

Virologic relapse: If ≥ 4 of the first 20 subjects who complete 8 weeks of therapy in Arm A experience virologic relapse after treatment, then the Sponsor will review the data to determine whether the treatment in Arm A should be extended from 8 to 12 weeks for subjects who have not yet completed treatment and if treatment should be extended for all subjects in Arm A or only for certain subgroups. Enrollment into the study will continue during the data review process. For any subgroup of subjects for whom treatment duration is extended to 12 weeks, the remaining subjects in that subgroup will be treated for 12 weeks (see Appendix C for 12-weeks Treatment Period Study Activities table). Subgroups of subjects whose treatment is not extended to 12 weeks will continue to be treated for 8 weeks.

This efficacy treatment adjustment assessment will be conducted starting when the first 4 subjects in Arm A complete Post-Treatment Week 2. Evaluations of virologic relapse will be performed on an ongoing basis until all subjects in Arm A reach the end of treatment. Subjects who drop out for reasons other than virologic failure will not be included in these evaluations.

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 film coated 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. On Study Day 1 and at the Week 4 visit, subjects will have their study drug dose administered by study site personnel with food. Please refer to Section 5.3.1.1 and Section 5.3.2.1 for more details.

ABT-493/ABT-530 will be provided by AbbVie as 100 mg/40 mg co-formulated tablets. ABT-493/ABT-530 will be taken orally as 3 tablets once daily with food, which corresponds to ABT-493 300 mg/ABT-530 120 mg QD.

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 (Section 5.5.7).

All subjects who receive at least one dose of study drug and meet the HCV 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 5.

Table 5. 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 Drugs

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 (or designee).

5.5.3 Method of Assigning Subjects to Treatment Groups

At the Screening Visit, all subjects will be assigned a unique subject number through the use of IRT. For subjects who do not meet the study selection criteria, 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 the treatment assignment. Enrolled subjects will be assigned to either the 8 or 12 week treatment arms based on cirrhotic status. 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.

Subjects meeting the eligibility criteria will be enrolled as described in Section 8.2.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.6.4. Study drug dosing will be initiated at the Study Day 1 Visit.

All tablets of ABT-493/ABT-530 will be dosed together QD (three tablets). All subjects should take all doses of study medications with food.

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 HCV 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 record the status of each one, as well as 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 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 and Choice of Control Groups

Based upon the results of ongoing, Phase 2b Studies M14-867 and M14-868, AbbVie plans to evaluate the safety and efficacy of the ABT-493/ABT-530 300/120 mg QD combination in treatment-naïve or prior treatment-experienced (i.e., IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN) HCV genotype 1 – 6 infected subjects with HIV-1 co-infection, with or without cirrhosis, evaluating for 8 weeks in non-cirrhotics or 12 weeks in cirrhotics (with the exception of GT3 HCV treatment-experienced non-cirrhotic and cirrhotic subjects) in this multicenter, open label, Phase 3 study. Since this study will enroll more than one genotype, there is no single standard of care for comparison. A randomized, double-blind, placebo-controlled study, Study M15-464, is currently being conducted study to evaluate the efficacy and safety of

ABT-493/ABT-530 in adults with chronic HCV GT2 infection; thus, a placebo-controlled investigational design was not implemented in this study. A placebo-controlled study is not considered to be appropriate in HCV subjects with compensated liver disease because they have greater risk of progression to decompensated liver disease with treatment delays for a placebo group.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study. HCV RNA and HIV 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 subjects infected with HCV GT1 – 6 with HIV-1 co-infection will allow for assessment of the safety, pharmacokinetics and efficacy of the combination ABT-493/ABT-530 regimen for the duration of 8 weeks in non-cirrhotics or 12 weeks in cirrhotics (excluding GT-3 HCV treatment-experienced both non-cirrhotics and cirrhotics).

Safety and pharmacokinetic results from drug-drug interaction studies (see Section 3.0) between various ARVs and the ABT-493/ABT-530 combination including abacavir, lamivudine, dolutegravir, tenofovir alafenamide, darunavir co-administered with ritonavir or cobicistat, lopinavir/ritonavir, elvitegravir/cobicistat, tenofovir disoproxil fumarate, emtricitabine, rilpivirine and raltegravir support the use in the current study with ABT-493/ABT-530. The ARV medications allowed for the co-infected subjects in this study are not anticipated to impact the efficacy and safety of HCV GT1 or HIV-1 treatments in co-infected subjects.

This study will enroll subjects who are either HCV treatment-naïve or prior treatment-experienced (i.e., IFN or pegIFN with or without RBV, or SOF plus RBV with

or without pegIFN). This will include "PR-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 when comparing treatment-naïve patients (49 of 50 with SVR_{12}) and PR null responders (28 of 28 with SVR_{12}). Similarly, preliminary data from Study M14-867 Part 2 Arm K shows no difference in efficacy when comparing treatment-naïve patients (28 of 28 with SVR_{12}) and treatment-experienced patients (5 of 5 with SVR_{12}) with available Post-Treatment Week 12 data.

This study will specifically exclude subjects with any prior exposure to DAA treatment other than treatment with SOF plus RBV with or without pegIFN as the effect of possible viral mutants on efficacy of ABT-493/ABT-530 is not fully understood.

This study will enroll HCV GT1 – 6 infected subjects with or without cirrhosis based on the efficacy and safety of ABT-493/ABT-530 demonstrated in non-cirrhotic and cirrhotic subjects in Phase 2b Studies as detailed in Section 3.0. These efficacy and safety results support the 8 week treatment duration for HCV GT1 – 6 subjects without cirrhosis and the 12 week treatment duration for GT1 – 6 subjects with cirrhosis. HCV GT3, treatment-experienced subjects with or without cirrhosis are excluded from this study, as this sub-population of HCV-monoinfected subjects is currently being evaluated to identify the optimal treatment duration in Part 3 of Study M14-868.

HCV-infected subjects with transaminase levels up to 10 times the ULN will be allowed to enroll, as many otherwise healthy patients with chronic HCV infection have moderate stable elevations of ALT and AST levels and are considered representative of the population who will receive ABT-493/ABT-530. The age range selected for this study, at least 18 years of age, is 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/m^2.

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 evaluating the pharmacokinetic, pharmacodynamic, safety and tolerability effects of the co-administration of buprenorphine/naloxone or methadone and the DAAs (ABT-493 + ABT-530) in adult subjects on stable opioid maintenance therapy showing acceptable safety and no relevant pharmacokinetic or pharmacodynamic interactions.

5.6.4 Selection of Doses in the Study

5.6.4.1 Rationale for Dose Selections

The doses of 300 mg ABT-493 and 120 mg ABT-530 were selected to optimize efficacy of the combination while maintaining an acceptable safety profile.

5.6.4.1.1 ABT-493 and ABT-530 Dose

Based on the results from the Phase 2b studies, Studies M14-867 and M14-868, the 300 mg dose of the ABT-493 and 120 mg dose of ABT-530 in combination has been selected for Phase 3 studies in HCV GT1 to 6 cirrhotic and non-cirrhotic populations. This dose has been demonstrated efficacious for the proposed Phase 3 study populations with the planned study duration and would reduce chances of virologic failures across genotypes and difficult-to-treat patient populations to maximize the chance for SVR. Importantly, 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.

Results from ABT-493 300 mg QD + ABT-530 120 mg QD for 8-week treatment duration in HCV GT1 (Study M14-867 Part 2) and HCV GT2 (Study M14-867 Part 2) showed 100% SVR_{12}. In Study M14-867 Part 2, ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks was evaluated in 34 DAA-naïve HCV GT4 (n = 22), GT5 (n = 1), and GT6 (n = 11)-infected non-cirrhotic subjects. All 34 subjects achieved SVR_{12}. Based on exposure-response analyses, simulations were conducted to predict SVR rates for ABT-493 and ABT-530 administered 8 weeks in HCV GT4-infected subjects and showed > 95% SVR in this population. As data suggested that HCV/HIV-co-infected patients treated with new, all-oral HCV DAA regimens have SVR

rates comparable to those of HCV mono-infected patients, ABT-493 300 mg QD + ABT-530 120 mg QD for 8 weeks will be used in this study for HCV genotype 1, 2, 4, 5, and 6 non-cirrhotic subjects.

For cirrhotic patients, efficacy data of 200 mg/120 mg dose in GT1-infected cirrhotic patients and safety and efficacy data of the 300 mg/120 mg dose in GT3 cirrhotic patients from Part 2 of Phase 2b studies would support efficacy and safety in cirrhotic subjects across GT1, GT2, and GT4 to GT6.

Efficacy results from Part 2 of Study M14-867 in GT1 cirrhotic patients showed 96% SVR_{12} for ABT-493 200 mg + ABT-530 120 mg QD administered for 12 weeks which is in line with the clinical exposure-response simulation predicted range. In addition, efficacy results from Part 2 of Study M14-868 in GT3 cirrhotic patients showed 100% SVR_4 for ABT-493 300 mg + ABT-530 120 mg QD administered for 12 weeks. Based on simulations conducted to predict SVR rates of 300 mg/120 mg ABT-493/ABT-530 for 12 and 16 weeks in HCV GT1 subjects with cirrhosis, this ABT-493/ABT-530 dose could provide improved SVR rates compared to lower doses and a duration of 12 weeks could achieve an SVR rate close to 100% in cirrhotic subjects with HCV GT1 infection. Longer duration (e.g., 16 weeks) of 300 mg/120 mg ABT-493/ABT-530 QD treatment is not expected to provide a significant improvement in the SVR rate (in GT1). Similar to GT1, the predicted SVR rates for GT2 subjects with cirrhosis following 300 mg/120 mg ABT-493/ABT-530 QD treatment for 12 weeks is 98%. This dose is also anticipated to yield high SVR rate following 12-week treatment duration in GT4 to GT6 infected cirrhotic population.

Antiretroviral DDI with ABT-493 and ABT-530

Multiple clinical studies have been conducted to evaluate the DDI potential for the ABT-493/ABT-530 combination with commonly used antiretroviral drugs, including raltegravir, rilpivirine, darunavir + ritonavir, atazanavir + ritonavir, lopinavir/ritonavir, elvitegravir/cobicistat, abacavir, lamivudine, dolutegravir, efavirenz, emtricitabine, tenofovir alfenamide and tenofovir disoproxil fumarate. Results showed ABT-493 and

ABT-530 combination had limited impact on the exposure of these ARTs and no dose adjustment is needed for these ARTs when co-administered with ABT-493 and ABT-530. Raltegravir rilpivirine, and dolutegravir, abacavir and lamivudine had no clinical meaningful effect on ABT-493 and ABT-530 exposures.

The projected ABT-493 and ABT-530 exposures when co-administered with raltegravir or rilpivirine in the current study compared to the estimated exposures in Phase 2b studies are presented in Table 6.

Table 6. Projected ABT-493 and ABT-530 Exposures When Co-Administered with Antiretroviral Regimens

[redacted]

Elvitegravir/cobicistat increased the exposure of ABT-493 by 3-fold and the exposure of ABT-530 by 57% with no toxicity associated. Darunavir + ritonavir and lopinavir/ritonavir increased the ABT-493 exposure by 3- to < 5-fold and the ABT-530 exposures by < 2-fold [redacted] in healthy volunteers. [redacted] For cirrhotic patients, [redacted] in this population, only the elvitegravir/cobicistat regimen is allowed in the current study.

Up to date, the 300 mg/120 mg ABT-493/ABT-530 dose is well-tolerated in healthy, HCV non-cirrhotic as well as cirrhotic subjects and provides sufficient safety margin from the exposure that causes ALT increase. Safety of the 300 mg/120 mg ABT-493/ABT-530 in cirrhotics is being evaluated in Part 2 of Study M14-868. The most frequently reported adverse events were headache, fatigue, nausea, diarrhea, insomnia, URTI, and vomiting (occurring in > 5% of Part 2 subjects) and were generally Grade 1 or Grade 2 in severity. The frequency and severity of adverse events appears to be similar between the non-cirrhotic and the cirrhotic cohorts in the non-RBV containing arms. In all subjects with baseline ALT elevations, the ALT levels have trended toward normal with DAA treatment, and there have been no on-treatment ALT elevations above baseline grade.

ABT-530 was shown to be safe and well-tolerated up to 600 mg QD without reaching the maximum tolerated dose.

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

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-530 and ABT-493 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 GT1-infected subjects without cirrhosis for a 12 week duration, 79 subjects have reached post-treatment Week 12 as of 22 May 2015. Among these 79 subjects, 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, (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 causality or deemed it not assessable, AbbVie will consider the event associated.

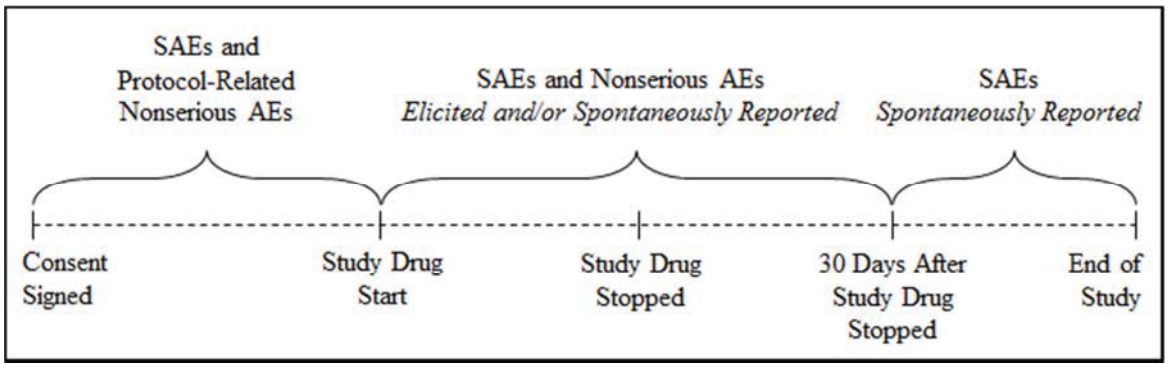
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

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

[redacted]

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

Primary Therapeutic Area Medical Director:

[redacted]

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

Phone:	[redacted]

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

6.1.6 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).

6.1.7.1 Management of Increases in ALT

If a subject experiences a post-baseline increase in ALT to > 5 × ULN which is also > 2 × baseline value, the subject should have a confirmatory ALT measurement performed.

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

- Evaluate for alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain additional testing as appropriate (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 ≥ 20 × ULN in the absence of an alternate etiology.
  - Increasing direct bilirubin or INR or onset of symptoms/signs of hepatitis.
  - At the discretion of the investigator.

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

6.1.8 Collection of Data Regarding Known AIDS-Associated Opportunistic Infections

HIV-1 infected subjects participating in clinical trials may develop infections typically associated with AIDS. A list of these known AIDS-associated opportunistic infections (OI) is presented in Appendix E. The events listed in Appendix E will be summarized as HIV-related events, not as adverse events. These OIs will be collected from the time of study drug administration until 30 days following discontinuation of study drug.

6.2 Product Complaint

6.2.1 Definition

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

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

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

6.2.2 Reporting

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

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

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

7.0 Protocol Deviations

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

Primary Contact: Alternate Contact:

[redacted]

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 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, when applicable, will be performed on the intention-to-treat 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 SVR_{12} 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., SVR_4, SVR_{12}, and SVR_{24}) 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 and baseline characteristics will be summarized for all treated subjects. Demographics 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 genotype/subtype, IL28B genotype, prior HCV treatment history, HIV-1 treatment status (ART-naïve, ART-treated), baseline HCV RNA level, fibrosis stage (F0-F1, F2, F3, F4), baseline CD4+ T-cell count, baseline CD4+ T cell %, HIV ART regimen, 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, 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, standard deviation, minimum, and maximum. The percentage of compliant subjects will be summarized for each treatment arm and overall.

8.1.2 Efficacy

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

Efficacy analyses will be performed overall, combining Arms A and B.

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 and HCV RNA not detected. HCV RNA ≥ LLOQ are all quantifiable values.

IL28B rs12979860 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 SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in the ITT population. The number and percentage of subjects achieving SVR_{12} will be summarized and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial. If the SVR_{12} rate is 100%, then the Wilson's score method will be used to calculate the confidence interval.

The percentage of the subjects treated with ABT-493/ABT-530 with SVR_{12} will be non-inferior to the 96% SVR_{12} rate of the current standard of care (i.e., sofosbuvir/ledipasvir for 12 weeks [96%; 321/335][37] or grazoprevir/elbasvir for 12 weeks [96%; 210/218][32]) if the lower confidence bound of the 2-sided 95% confidence interval of the percentage of subjects with SVR_{12} is > 90%.

A summary of reason for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse, other) will be provided.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The percentage of subjects with on-treatment HCV virologic failure (defined as confirmed increase of > 1 $\log_{10}$ 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),

- The percentage of subjects with post-treatment HCV relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment).

For the analysis of relapse, 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 52 days or greater for subjects who were assigned to the 8-week treatment regimen and with study drug duration of 77 days or greater for the subjects who were assigned to 12-week treatment regimen.

On-treatment virologic failure and relapse will be summarized for the ITT population.

For the secondary endpoints, the number and percentage of subjects will be summarized along with 95% Wilson score intervals.

8.1.2.3 Sensitivity Analysis

As sensitivity analyses, the percentage of subjects in the mITT-GT and mITT GT-VF populations achieving SVR_{12}, as applicable, will be summarized.

As a sensitivity analysis, a two-sided 95% confidence interval for the SVR_{12} rate in the ITT population will be calculated using a Wilson score interval.

8.1.2.4 Subgroup Analysis

The percentage (and two-sided Wilson score confidence intervals) of subjects with SVR_{12} in the ITT population will be presented for the following subgroups if data are available:

- 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).
- Presence of cirrhosis (Yes [Arm B] or No [Arm A]);
- 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/m^2);
- 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 mU × mmol/L2) and (< 3 or ≥ 3 mU × mmol/L2);
- Baseline fibrosis stage (F0 – F1, F2, F3, or F4);
- Baseline platelet count (< 100 or ≥ 100 × 10^9/L) and (< 120 or ≥ 120 × 10^9/L);
- Baseline albumin (< LLN or ≥ LLN);
- Baseline GGT (≤ ULN or > 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);
- 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);
- Compliant to study drug (yes/no);
- HIV ART Regimen (for those on stable ART);
- Baseline CD4+ Count (≤ 50, > 50 to < 200, 200 to < 350, 350 to < 500, or ≥ 500 cells/mm^3);
- Presence of baseline resistance-associated variants (yes/no).

For subjects with cirrhosis only:

- Baseline Child-Pugh Score (5, 6, or > 6);
- Baseline APRI (≤ 2 or > 2);
- Baseline platelets (< 90 or $\geq 90 \times 10^9$/L; <50 or $\geq 50 \times 10^9$/L; < 100 or $\geq 100 \times 10^9$/L; < 150 or $\geq 150 \times 10^9$/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Any of baseline platelets $< 90 \times 10^9$/L and baseline albumin < 35 g/L;

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 and analyzed for the ITT population:

- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of subjects with SVR_4;
- The percentage of subjects with SVR_{24};
- The percentage of subjects who relapsed after achieving SVR_{12}.

In the above analyses for SVR and relapse, the percentage of subjects with a two-sided 95% Wilson score confidence interval will be summarized.

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 Mental and Physical Component Summary measures will not be computed if any domain is 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 timepoint 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.

The following analyses of PROs also will be performed:

- Cumulative number and percentage of subjects who have ever experienced an increase from baseline up through each applicable timepoint of greater than or equal to 3 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 timepoint of greater than or equal to 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 timepoint 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 timepoint of greater than or equal to 0.7 in the FSS total score;
- Cumulative number and percentage of subjects who have ever experienced an increase from baseline up through each applicable timepoint of greater than or equal to 1 in the FSS total score.

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

8.1.4 Resistance Analyses

8.1.4.1 HCV Drug-Resistance Analyses

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 SVR_{12} 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 % ≥ 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 are 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 SVR_{12} 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 ≥ 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 EC_{50} values may not be obtainable for all samples, but for samples where phenotype data are obtained, the fold change in EC_{50} 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.

8.1.4.2 HIV Drug-Resistance Analyses

If a subject develops a confirmed, plasma HIV-1 RNA level ≥ 500 copies/mL after starting the study, the subject's HIV-1 PR, RT, and/or IN sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assays. The number of subjects who demonstrate HIV genotypic resistance and the genotypic resistant mutations detected in the samples obtained from these subjects will be tabulated and summarized. Resistance will be defined as described by the IAS-USA Panel.[36]

8.1.5 Safety

All subjects who receive at least one dose of study drug will be included in the safety analyses. Safety analyses will be performed overall and by treatment arm (i.e., by study drug duration/cirrhotic status).

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 overall and in each arm 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 overall and by arm 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.

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 overall and by arm.

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 overall and by arm.

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 overall and by arm. Frequencies and percentages of subjects with post-baseline values meeting pre-defined criteria for PCS vital signs values will be summarized.

8.1.5.4 HCV/HIV-1 Co-Infection

The following additional safety data will be summarized and analyzed for subjects with HCV/HIV-1 co-infection overall and in each treatment arm:

- The percentage of subjects with plasma HIV-1 RNA suppression at the end of treatment and at Post-Treatment Week 12 using the FDA Snapshot Algorithm;
- The number and percentage of subjects with plasma HIV-1 RNA < 20 copies/mL at each applicable time point;

- Change from baseline in CD4+ T-cell count (absolute and percent) to each applicable post-baseline time point;
- Change from baseline in lymphocytes (count and percentage) and CD8+ T-cell counts (absolute and percent) to each applicable post-baseline time point;
- The listing of subjects with a plasma HIV-1 RNA value ≥ 200 copies/mL at any baseline or post-baseline visit during the study.

The analysis of change from baseline in CD4+ T-cell count (absolute and percent), lymphocytes (count and percentage) and CD8+ T-cell counts (absolute and percent) will report the mean and median values at baseline and at each applicable post-baseline visit, as well as N, mean, median, standard deviation (SD), minimum and maximum values for the change from baseline overall and within each treatment arm.

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. Summary statistics will be computed for each time and visit. Summary of statistics may also be computed based on HIV-1 ART regimen. Plasma concentrations of HIV ARVs, if measured, will also be summarized at each study visit through the end of the Treatment Period.

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 analytes will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis.

The evaluation criteria described below will be used to examine the performance of different models.

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

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

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

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

Where TVCLi = Typical value of clearance for an individual1, Theta(1) is the intercept and Theta(2) – (4) are regression parameters relating the fixed effects (weight and age centered on the median value) to clearance.

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

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

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 a total of approximately 160 subjects to this study. A maximum of approximately 110 HCV GT-1 infected subjects will be enrolled. The primary efficacy endpoint of SVR_{12} will be assessed for the ITT population.

With 160 subjects and assuming that 97% of the subjects achieve SVR_{12}, this study has greater than 90% power to demonstrate non inferiority to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 90%) using a one-sample test for superiority using EAST 6.3. No adjustment for dropout is applicable because subjects who do not have data at Post-Treatment Week 12 (after imputing) are counted as failures for SVR_{12}.

8.2.1 Justification of Success Criterion and Non-Inferiority Margin for SVR_{12}

Efficacy of the ABT-493/ABT-530 regimen in this study will be established by demonstrating non-inferiority to a historical control regimen. The SVR_{12} rate of the

historical control regimen was calculated, and a threshold was determined by subtracting a non-inferiority margin from the historical SVR_{12} rate. Efficacy will be established if the lower 95% confidence bound of the SVR_{12} rate for the ABT-493/ABT-530 regimen is greater than the threshold.

To align with the Phase 3 studies of ABT-493/ABT-530 in the HCV mono-infected population, a non-inferiority margin of 6% was chosen for this study. In addition, consideration was given to the fact that limited efficacy data exists for non-GT1 HCV/HIV co-infected patients.

A historical SVR_{12} rate of 96% for the current standard of care will be used and is based on the SVR_{12} rates for sofosbuvir/ledipasvir for 12 weeks (96%; 321/335) and grazoprevir/elbasvir for 12 weeks (96%; 210/218).[32,37] To establish non-inferiority to the historical control, a margin of 6% is applied to the historical control rate of 96%, resulting in a threshold of 90%.

8.3 Randomization Methods

This study is not randomized. All enrolled subjects will be treated with ABT-493/ABT-530 300 mg/120 mg. Enrolled subjects will be assigned to either the 8 or 12 week treatment arms based on cirrhotic status. Subjects without cirrhosis will be treated for 8 weeks and subjects with compensated cirrhosis will be treated for 12 weeks.

9.0 Ethics

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

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

advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

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

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

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

documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

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

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

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 (EMEA) Guidance on Investigator's Signature for Study Reports.

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

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for ABT-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 Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection and Human Immunodeficiency Virus-1 (HIV-1) Co-Infection (EXPEDITION-2)
Protocol Date:	12 July 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
[redacted]		Pharmacokinetics
		Clinical
		Clinical
		Bioanalysis
		Statistics
		Clinical
		Global Drug Supply Management

Appendix C. Study Activities – Treatment Period

Activity	Screening	Day 1[a]	Wk 1	Wk 2	Wk 4	Wk 8*,[c]	Wk 8 EOT or Wk 12 EOT* or Premature D/C from Treatment[b,c]
Informed Consent[d]	X						
Dispense/Review HIV-1 ART Dosing Card, if applicable	X (Dispense only)	X	X	X	X	X	X (Review only)
Dispense/Review Study Drug Dosing Card		X (Dispense only)	X	X	X	X	X (Review only)
Medical History[e]	X	X					
Physical Exam	X	X					X
Vital Signs, Weight, Waist Circumference[f], Height[f]	X	X	X	X	X	X	X
ECG	X						
Hematology/Chemistry/Urinalysis/Coagulation Panel	X	X	X	X	X	X	X
Pregnancy Test (serum [s] urine [u])[g]	X (s)	X (u)			X (u)	X (u)	X (u)
HBsAg, Anti-HCV Ab, Anti-HIV Ab	X						
Drug/Alcohol Screen	X						
Hemoglobin A1C (HgbA1c)[h]	X						
HCV Genotype and Subgenotype	X						
FibroTest and APRI or FibroScan® or Liver Biopsy[i]	X						
IL28B Sample[j]		X					
Pharmacogenetic Sample (optional)[j]		X					
Total Insulin		X					
Concomitant Medication Assessment	X	X	X	X	X	X	X

Activity	Screening	Day 1[a]	Wk 1	Wk 2	Wk 4	Wk 8*,[c]	Wk 8 EOT or Wk 12 EOT* or Premature D/C from Treatment[b,c]
Adverse Event Assessment[k]	X	X	X	X	X	X	X
Patient Reported Outcomes Instruments (PROs)[l]		X					X
Study Drugs Dispensed		X			X	X[m]	
HCV RNA Samples	X	X	X	X	X	X	X
Study Drug Accountability and Review of Study Drug Adherence[n]					X	X	X
HCV Resistance Sample		X	X	X	X	X	X
Archive Plasma Sample	X	X	X	X	X	X	X
Pharmacokinetic Sparse Samples[o]			X	X		X	X
Pharmacokinetic Intensive Samples[o]		X[p]			X[p]		
Child-Pugh score[q]	X						X
Clinical Assessment of hepatic Decompensation[q]		X[q]					
HCC Screening Liver ultrasound[q]	X						
HIV-1 RNA[r]	X	X		X	X	X	X
Flow Cytometry Sample	X	X			X		X

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

* The EOT visit can be at Weeks 8 or 12 depending on the subject's allocated arm.

a. All procedures to be performed prior to first dose, with the exception of the post-dose pharmacokinetic intensive samples (Section 5.3.2.1).

b. Subjects who prematurely discontinue the Treatment Period should return to the site to complete the Premature D/C Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy).

c. For subjects whose treatment duration is extended to 12 weeks due to Efficacy Treatment Adjustment Criteria, all study procedures for Week 8 and Week 12 EOT will be completed.

d. Subjects need to sign an IRB/IEC approved informed consent for the study (prior to performing any Screening or study-specific procedures) and the optional pharmacogenetic, if applicable.

e. A complete medical history will be taken at Screening and will be updated at the Study Day 1 Visit.

f. Height will be measured at the Screening Visit only. Waist circumference will be measured at the Screening Visit, but if it is not measured at Screening, it may be measured on Day 1.

g. Pregnancy testing is not required for women not of childbearing potential as defined in Inclusion Criterion 3.

h. For those with history of Diabetes Mellitus.

i. For subjects who have not had a qualifying liver biopsy within the previous 24 months or a qualifying FibroScan within the previous 6 months.

j. If the IL28B or the optional Pharmacogenetic sample is not collected at Study Day 1, they may be collected at any other visit during the study.

k. See specific information regarding adverse event collection in Section 6.1.1.1.

l. PRO should be administered before any study procedure in the order listed in Section 5.3.1.1. EOT PRO is at Week 8 EOT or Week 12 EOT, as applicable.

m. Applicable only to those subjects enrolled into a 12-week Treatment Arm. For subjects whose treatment duration is extended to 12 weeks due to Efficacy Treatment Adjustment Criteria, study drug will also be dispensed at the Week 8 visit.

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, 12 or Premature D/C.

o. Detail regarding timing of samples is provided in Section 5.3.2.1.

p. 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.

q. Child-Pugh Score, Clinical Assessment of Hepatic Decompensation, and Liver Ultrasound are only performed on subjects with compensated cirrhosis as described in Section 5.3.1.1, Study Procedures.

r. As detailed in Section 5.4.1.2, a repeat HIV-1 RNA blood draw to confirm a HIV-1 RNA result of ≥ 200 copies/mL can be done as an unscheduled visit, but should be performed at least 2 weeks apart from the prior HIV-1 RNA result. At the time a confirmatory plasma HIV-1 RNA is drawn, a sample for HIV-1 genotypic resistance testing should also be obtained. If the confirmatory HIV-1 RNA lab draw falls on the date of a scheduled visit, only a single HIV-1 RNA and HIV-1 resistance blood draw is needed at the visit.

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

Activity	PT Wk 2	PT Wk 4	PT Wk 8	PT Wk 12	PT Wk 24 or PT D/C[a]
Vital Signs and Weight	X	X	X	X	X
Hematology/Chemistry/Urinalysis/Coagulation Panel		X		X[f]	X[b,f]
Pregnancy Test (urine)[c]		X (u)			X (u)[b]
PRO Instruments[d]				X	X
Concomitant Medication Assessment	X	X	X[e]	X[e]	X[e]
Child-Pugh Score[f]				X	X
Adverse Event Assessment	X[g]	X[g]	X[h]	X[h]	X[h]
HCV RNA Samples	X	X	X	X	X
HIV RNA Sample[i]		X		X	
HCV Resistance Sample	X	X	X	X	X
Flow Cytometry Sample		X		X	
Archive Plasma Sample	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. Hematology/Chemistry/Urinalysis/Coagulation Panel and Pregnancy Test are not required at PT Wk 24, but only at PT D/C if subject discontinued prior to PT Wk 4.

c. Urine pregnancy testing is not required in the PT period for women that are not of childbearing potential.

d. PROs should be administered before any study procedures in the order listed in Section 5.3.1.1.

e. Only medications associate with HCV and HIV treatment or taken for a serious adverse event (SAE) will be collected after 30 days post-dosing.

f. For the subject with cirrhosis at baseline. Chemistry and Coagulation Panel are required to calculate the Child Pugh Score.

g. Nonserious AEs and all SAEs will be collected until 30 days post dosing.

h. Only SAEs will be collected thereafter (Section 6.1.4).

i. As detailed in Section 5.4.1.2, a repeat HIV-1 RNA blood draw to confirm a HIV-1 RNA result of ≥ 200 copies/mL can be done as an unscheduled visit, but should be performed at least 2 weeks apart from the prior HIV-1 RNA result. At the time a confirmatory plasma HIV-1 RNA is drawn, a sample for HIV-1 genotypic resistance testing should also be obtained. If the confirmatory HIV-1 RNA lab draw falls on the date of a scheduled visit, only a single HIV-1 RNA and HIV-1 resistance blood draw is needed at the visit.

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

Appendix E. List of AIDS-Associated Opportunistic Infections

Collection of data regarding known AIDS-associated opportunistic infections is covered in Section 6.1.8.

- Aspergillosis
- Bartonellosis
- Candidiasis (*Bronchi; *Esophagus; *Lungs; Oropharyngeal [Thrush]; *Trachea; Vulvovaginal [Persistent, Frequent, or Poorly Responsive to Therapy])
- *Coccidioidomycosis
- *Cryptococcosis
- *Cryptosporidiosis
- Cytomegalovirus (*Retinitis; *Cytomegalovirus Disease [other than liver, spleen or nodes])
- Enteric infections, Recurrent (Bacterial)
- Herpes Simplex Virus (*Bronchitis; *Esophagitis; *Pneumonitis; *Chronic Ulcer(s) [> 1 month in duration])
- *Histoplasmosis
- Human Herpesvirus-8 Disease (Kaposi Sarcoma, Primary Effusion Lymphoma, Multicentric Castleman's Disease)
- Human Papilloma Virus Infections
- *Isosporiasis (Cystoisosporiasis)
- Microsporidiosis
- *Mycobacterium avium – Complex Disease (Disseminated)
- *Mycobacterium tuberculosis – Infection and Disease
- *Pneumonia
- *Pneumonia, recurrent bacterial (and/or other respiratory infections including sinusitis, bronchitis, otitis)
- *Progressive multifocal leukoencephalopathy (JC Virus Infection)
- Syphilis

- *Toxoplasma Gondii Encephalitis
- Varicella Zoster Virus Diseases

* AIDS-defining event as described by CDC Surveillance Case Definition of 1993.

Cross reference: Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Available from: http://aidsinfo nih.gov/guidelines.

Appendix F. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

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

Approximately 150 subjects

Has been changed to read:

Approximately 160 subjects

Section 1.2 Synopsis
Subsection Methodology:
Second paragraph previously read:

Subjects must be naïve to treatment with any HIV-1 antiretroviral therapy (ART) or on a stable, qualifying HIV-1 ART regimen that contains rilpivirine (RPV), raltegravir (RAL), or dolutegravir (DTG).

Has been changed to read:

Subjects must be naïve to treatment with any HIV-1 antiretroviral therapy (ART) or on a stable, qualifying HIV-1 ART regimen that contains rilpivirine (RPV), raltegravir (RAL), dolutegravir (DTG), or elvitegravir/cobicistat (EVG/COBI). Regimens that include darunavir coadministered with ritonavir (DRV+RTV) QD, darunavir/cobicistat (DRV/COBI) QD or lopinavir/ritonavir (LPV/r) BID will be allowed for non-cirrhotic subjects only.

Section 1.2 Synopsis
Subsection Methodology:
Last paragraph previously read:

A maximum of approximately 90 HCV GT1/HIV-1 co-infected subjects will be allowed to enroll in the study. A minimum of 10% (n = 15) of the overall study population will be subjects with compensated cirrhosis.

Has been changed to read:

A maximum of approximately 110 HCV GT1/HIV-1 co-infected subjects will be allowed to enroll in the study. A minimum of 10% (n = 16) of the overall study population will be subjects with compensated cirrhosis.

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Add: "COBI," "DRV," "EVG," "LPV," "LPV/r," and "RTV or r"

COBI	Cobicistat
DRV	Darunavir
EVG	Elvitegravir
LPV	Lopinavir
LPV/r	Lopinavir and ritonavir
RTV or r	Ritonavir

Section 3.0 Introduction
Subsection ABT-493 and ABT-530
Heading "HCV-Infected Patients"
Seventh paragraph previously read:

In Study M14-868 Part 2, among 29 treatment-naïve non-cirrhotic subjects with GT3 infection treated for 8 weeks with ABT-493 300 mg QD + ABT-530 120 mg QD, no subject has experienced on treatment virologic failure or post-treatment relapse to date. One subject prematurely discontinued from the study after Week 6 (undetectable HCV RNA at that visit) due to intolerance of blood draws, and thus is counted as a SVR_4 non-responder. The SVR_4 rate for this cohort is 28/29 (96.6%). Twenty-five (25) of these

subjects have achieved a SVR_{12} to date. Among 24 treatment-naïve cirrhotic subjects with GT3 infection treated for 12 weeks with ABT-493 300 mg QD + ABT-530 120 mg QD, no subject has experienced on treatment virologic failure or post-treatment relapse to date. The SVR_4 rate for this cohort is 24/24 (100%). Eleven (11) of these subjects have achieved a SVR_{12} to date.

Has been changed to read:

In Study M14-868 Part 2, among 29 treatment-naïve non-cirrhotic subjects with GT3 infection treated for 8 weeks with ABT-493 300 mg QD + ABT-530 120 mg QD, no subject experienced virologic failure. One subject prematurely discontinued from the study after Week 6 with an undetectable HCV RNA due to intolerance of blood draws, and did not return for follow up, thus is counted as a non-responder. The SVR_{12} rate for this cohort is 28/29 (96.6%). Among 24 treatment-naïve cirrhotic subjects with GT3 infection treated for 12 weeks with ABT-493 300 mg QD + ABT-530 120 mg QD, no subject experienced virologic failure. The SVR_{12} rate for this cohort is 24/24 (100%).

Section 3.0 Introduction
Subsection <u>ABT-493 and ABT-530</u>
Heading "ARV Drug-Drug Interaction Studies with ABT-493 and ABT-530"
Previously read:

Phase 1 DDI studies of the ABT-493 + ABT-530 combination with HIV antiretroviral (ARV) drugs have been conducted in healthy volunteers and/or HIV-1 infected subjects.

The ABT-493 + ABT-530 combination had no clinically meaningful impact on the exposures (≤ 80%) of evaluated ARV regimens: rilpivirine, raltegravir, emtricitabine and tenofovir disoproxil fumarate (TDF). ABT-493 and ABT-530 exposures were not affected by rilpivirine and raltegravir. Tenofovir alafenamide (TAF) is not anticipated to have impact on the exposures of ABT-493 and ABT-530 based on its in vitro profile.

Dolutegravir and abacavir (HIV-1 ARVs that are currently being evaluated in DDI studies) are substrates of P-gp and/or BCRP and exposure of these drugs may increase when coadministered with ABT-493 + ABT-530; however, the exposure changes are not

anticipated to require dose adjustment of these agents. Lamivudine is predominantly eliminated unchanged in the urine and is not expected to interact with ABT-493 + ABT-530.

Efavirenz induces P-gp and exposures of ABT-493 and ABT-530 in the presence of efavirenz were approximately 3- and 2-fold lower, respectively, and thus will not be allowed in this study.

When ABT-493 was administered with ritonavir, exposure of ABT-493 was 2-fold of ABT-493 exposure alone. Coadministration of ABT-493 + ABT-530 with ritonavir boosted protease inhibitors (atazanavir, darunavir, or lopinavir with ritonavir) resulted in further increases in ABT-493 exposure of 4.4- to ≥ 6.5-fold of DAAs alone. ABT-493 is a substrate of OATP and inhibition of OATP increases ABT-493 exposure. When ABT-493 + ABT-530 was administered with cyclosporine (400 mg), an OATP inhibitor, ABT-493 exposure was up to 5.1-fold of DAAs alone. Protease inhibitors as a class have potential to inhibit OATP, thus the larger exposure increases in ABT-493 with ritonavir boosted protease inhibitors than with ritonavir alone may result from interaction of ABT-493 with both the protease inhibitor and ritonavir components. Cobicistat has been shown in vitro and in vivo to have similar cytochrome P-450 enzyme and transporter inhibition potential as ritonavir. Thus, ritonavir- and cobicistat- boosted HIV-1 protease inhibitors (atazanavir, darunavir and lopinavir) will not be allowed in this study. A study evaluating the drug interaction profile when ABT-493/ABT-530 300 mg/120 mg is co-administered with Genvoya® (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, tenofovir alafenamide10 mg QD) is currently planned.

For a more detailed discussion of drug-drug interaction studies please refer to the ABT-493 and ABT-530 Fixed-Dose Combination Investigator's Brochures.[35]

Study M14-730 is an open-label, multicenter study to evaluate efficacy and safety of ABT-493/ABT-530 for an 8- or 12-week treatment duration in HCV treatment-naïve or prior treatment-experienced (i.e., IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN) adults with chronic HCV GT1-6 infection and HIV-1

co-infection, with and without cirrhosis. Additional discussion and justification of study design may be found in Section 5.6.

Has been changed to read:

Phase 1 DDI studies of the ABT-493 + ABT-530 combination with HIV antiretroviral (ARV) drugs have been conducted in healthy volunteers and/or HIV-1 infected subjects.

The ABT-493 + ABT-530 combination had no clinically meaningful impact on the exposures (≤ 80%) of evaluated ARV regimens: ritonavir-boosted protease inhibitors (darunavir, lopinavir), rilpivirine, raltegravir, emtricitabine and tenofovir disoproxil fumarate (TDF). ABT-493 and ABT-530 exposures were not affected by rilpivirine and raltegravir.

Dolutegravir, lamivudine and abacavir (Triumeq®) coadministered with ABT-493 + ABT-530 has recently been evaluated in a DDI study (Study M15-584 Arm 2). Coadministration was safe and well tolerated with mild adverse events reported. ABT-493 and ABT-530 had no impact on dolutegravir, lamivudine and abacavir exposures. There was a mild decrease in ABT-493 and ABT-530 exposures of no clinical significance.

Efavirenz induces P-gp and exposures of ABT-493 and ABT-530 in the presence of efavirenz were approximately 3- and 2-fold lower, respectively, and thus will not be allowed in this study.

ABT-493 is a substrate of OATP and inhibition of OATP increases ABT-493 exposure. When ABT-493 + ABT-530 was administered with cyclosporine (400 mg), an OATP inhibitor, ABT-493 exposure was up to 5.1-fold of DAAs alone. The observed increase in exposures, however, was not associated with clinically significant safety findings.

Protease inhibitors as a class have potential to inhibit OATP, thus the larger exposure increases in ABT-493 with ritonavir boosted protease inhibitors than with ritonavir alone may result from interaction of ABT-493 with both the protease inhibitor and ritonavir

components. Cobicistat has been shown in vitro and in vivo to have similar cytochrome P-450 enzyme and transporter inhibition potential as ritonavir.

When ABT-493 was administered with ritonavir, exposure of ABT-493 was 2-fold of ABT-493 exposure alone. Coadministration of ABT-493 + ABT-530 with ritonavir boosted protease inhibitors, darunavir QD or lopinavir BID resulted in increases in ABT-493 exposure of 3- to < 5-fold and < 2-fold exposure to ABT-530 without significant change in the LPV or DRV exposures. In spite of the increase in ABT-493 exposures while coadministered with DRV + RTV or LPV/r, co-administration of these agents were well tolerated with mild adverse events. Coadministration of ABT-493 + ABT-530 with ritonavir boosted atazanavir was studied in a DDI study that was terminated early due to an increase in ABT-493 exposure up to 16-fold and ABT-530 exposure up to 3-fold with Grade 1 and 2 increases in ALT and Grade 2 to 3 increase in total bilirubin (predominately indirect).

A recently completed study (Study M15-584) evaluated the drug interaction profile when ABT-493 + ABT-530 was co-administered with Genvoya® (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, tenofovir alafenamide 10 mg QD). Coadministration was safe and well tolerated, with mild adverse events reported and one grade 3 neutropenia deemed related to the combination of Genvoya®, ABT-493 and ABT-530 in a black male subject with a low baseline ANC, leading to premature study drug discontinuation. The ABT-493 exposure increased 3-fold and the ABT-530 exposure increased 57%, with non-clinically significant increases in elvitegravir, cobicistat, tenofovir and emtricitabine exposures. Thus, cobicistat boosted elvitegravir will be allowed in Study M14-730.

In addition, ritonavir and cobicistat-boosted HIV-1 protease inhibitors (darunavir and lopinavir) will be allowed in the non-cirrhotic treatment arm only. As detailed in Section 5.6.4.1.1, these HIV-1 protease inhibitors will not be allowed in cirrhotic subjects, as the ABT-493 predicted exposures in this population approach the ALT 5% Grade 2 threshold.

For a more detailed discussion of drug-drug interaction studies please refer to the ABT-493 and ABT-530 Fixed-Dose Combination Investigator's Brochures.[35]

Study M14-730 is an open-label, multicenter study to evaluate efficacy and safety of ABT-493/ABT-530 for an 8- or 12-week treatment duration in HCV treatment-naïve or prior treatment-experienced (i.e., IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN) adults with chronic HCV GT1-6 infection and HIV-1 co-infection, with and without cirrhosis. Additional discussion and justification of study design may be found in Section 5.6.

Section 3.2 Benefits and Risks
First paragraph
Add: new second, third and fourth sentence

Approved combination DAA regimens (sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir and dasabuvir, with or without RBV and grazoprevir/elbasvir) are not equally potent across all HCV genotypes and subtypes, and across subpopulations, including patients with HCV/HIV-1 co-infection, leaving important medical needs unaddressed. Currently available treatments in some subpopulations still require RBV, necessitate treatment durations longer than 12 weeks, and can potentially be associated with significant drug interactions. More convenient and tolerable regimens are also needed in order to improve patient compliance and, thereby, increase the chance of a sustained virologic response.

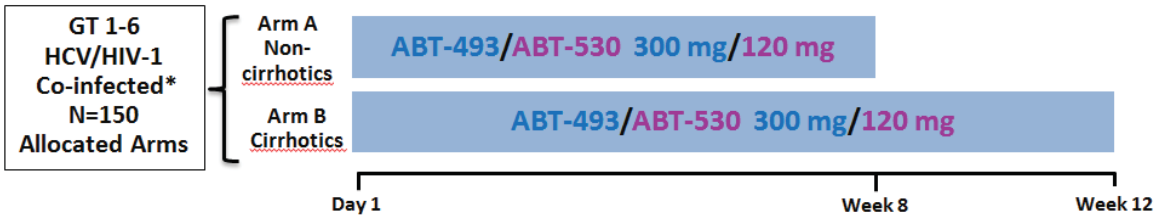
Section 5.1 Overall Study Design and Plan: Description
Second paragraph previously read:

Subjects must be naïve to treatment with any HIV-1 antiretroviral therapy (ART) or on a stable, qualifying HIV-1 ART regimen that contains rilpivirine (RPV), raltegravir (RAL), or dolutegravir (DTG).

Has been changed to read:

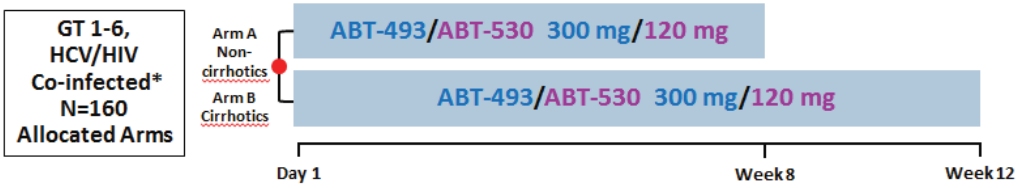
Subjects must be naïve to treatment with any HIV-1 antiretroviral therapy (ART) or on a stable, qualifying HIV-1 ART regimen that contains rilpivirine (RPV), raltegravir (RAL), dolutegravir (DTG), darunavir coadministered with ritonavir (DRV + RTV) QD, darunavir/cobicistat (DRV/COBI), lopinavir/ritonavir (LPV/r), BID or elvitegravir/cobicistat (EVG/COBI).

Figure 1. Study Design
Previously read:



* HCV GT3 treatment-experienced subjects are not eligible for this study.

Has been changed to read:



* HCV GT3 treatment-experienced subjects are not eligible for this study.

Section 5.1 Overall Study Design and Plan: Description
Fifth paragraph previously read:

Approximately 150 eligible subjects will be allocated to one of the following treatment arms:

Has been changed to read:

Approximately 160 eligible subjects will be allocated to one of the following treatment arms:

Section 5.1 Overall Study Design and Plan: Description
Sixth paragraph previously read:

A maximum of approximately 90 GT1 subjects will be enrolled in the study. A minimum of 10% (n = 15) of the overall study population will be subjects with compensated cirrhosis.

Has been changed to read:

A maximum of approximately 110 GT1 subjects will be enrolled in the study. A minimum of 10% (n = 16) of the overall study population will be subjects with compensated cirrhosis.

Section 5.1 Overall Study Design and Plan: Description
Seventh paragraph previously read:

The study was designed to enroll approximately 150 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Has been changed to read:

The study was designed to enroll approximately 160 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Section 5.2.1 Inclusion Criteria
Criterion 3, last paragraph 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 5.2.1 Inclusion Criteria
Criterion 13, first bullet list previously read:

- Raltegravir (RAL) PO BID
- Dolutegravir (DTG) PO QD or PO BID
- Rilpivirine (RPV) PO QD

Has been changed to read:

- For cirrhotic and non-cirrhotic subjects:
  - Raltegravir (RAL) PO BID
  - Dolutegravir (DTG) PO QD or PO BID
  - Rilpivirine (RPV) PO QD
  - Elvitegravir/cobicistat (EVG/COBI) PO QD
- For non-cirrhotic subjects, the following regimens are also allowed:
  - Darunavir (DRV) co-administered with ritonavir (RTV) PO QD
  - Darunavir/cobicistat (DRV/COBI) PO QD
  - Lopinavir/ritonavir (LPV/r) PO BID

Section 5.2.1 Inclusion Criteria
Criterion 13, fourth paragraph previously read:

In addition to the above medications, subjects may take a nucleoside/nucleotide reverse transcriptase inhibitor (N(t)RTI) backbone containing any of the following:

Has been changed to read:

In addition to the above medications, subjects (both cirrhotic and non-cirrhotic) may take a nucleoside/nucleotide reverse transcriptase inhibitor (N(t)RTI) backbone containing any of the following:

Section 5.2.1 Inclusion Criteria
Subsection Rationale for Inclusion Criteria
Previously read:

1, 4 – 7, 9 – 14	In order to select the appropriate subject population with appropriate disease characteristics for evaluation
8	For the safety of study subjects
2, 3	The impact of ABT-493 and ABT-530 on pregnancies is unknown
15 – 16	In accordance with harmonized Good Clinical Practice (GCP)

Has been changed to read:

1, 4 – 7, 9 – 14	In order to select the appropriate subject population with appropriate disease characteristics for evaluation
8	For the safety of study subjects
2, 3	The impact of ABT-493 and ABT-530 on human pregnancies has not been established. However, assessment of the completed nonclinical reproductive toxicology studies indicates that there is no drug-related effect on teratogenicity/fetotoxicity. In addition, the compounds are non-genotoxic
15 – 16	In accordance with harmonized Good Clinical Practice (GCP)

Section 5.2.3.2 Prior and Concomitant HIV-1 Therapy
Add: new last paragraph

Cirrhotic subjects on a regimen containing DRV or LPV will not be eligible for the study as indicated in Inclusion Criterion 13 (Section 5.2.1).

Section 5.3.2.4 Measurement Methods
First paragraph, first sentence previously read:

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.

Has been changed to read:

Plasma concentrations of ABT-493 and ABT-530 will be determined using a validated assay method by the Drug Analysis Department at AbbVie.

Section 5.6.3 Suitability of Subject Population
Second paragraph, first sentence previously read:

Safety and pharmacokinetic results from drug-drug interaction studies (see Section 3.0) between various ARVs and the ABT-493/ABT-530 combination including tenofovir disoproxil fumarate, emtricitabine, rilpivirine and raltegravir support the use in the current study with ABT-493/ABT-530.

Has been changed to read:

Safety and pharmacokinetic results from drug-drug interaction studies (see Section 3.0) between various ARVs and the ABT-493/ABT-530 combination including abacavir, lamivudine, dolutegravir, tenofovir alafenamide, darunavir co-administered with ritonavir or cobicistat, lopinavir/ritonavir, elvitegravir/cobicistat, tenofovir disoproxil fumarate, emtricitabine, rilpivirine and raltegravir support the use in the current study with ABT-493/ABT-530.

Section 5.6.4.1.1 ABT-493 and ABT-530 Dose
Subsection <u>Antiretroviral DDI with ABT-493 and ABT-530</u>
First paragraph previously read:

Multiple clinical studies have been conducted to evaluate the DDI potential for the ABT-493/ABT-530 combination with commonly used antiretroviral drugs, including raltegravir, rilpivirine, darunavir + ritonavir, atazanavir + ritonavir, lopinavir/ritonavir, and efavirenz/emtricitabine/tenofovir disoproxil fumarate. Results showed ABT-493 and

ABT-530 combination had limited impact on the exposure of these ARTs and no dose adjustment is needed for these ARTs when co-administered with ABT-493 and ABT-530. Raltegravir and rilpivirine had no effect on ABT-493 and ABT-530 exposures. The projected ABT-493 and ABT-530 exposures in the current study compared to the estimated exposures in Phase 2b studies are presented in Table 6.

Has been changed to read:

Multiple clinical studies have been conducted to evaluate the DDI potential for the ABT-493/ABT-530 combination with commonly used antiretroviral drugs, including raltegravir, rilpivirine, darunavir + ritonavir, atazanavir + ritonavir, lopinavir/ritonavir, elvitegravir/cobicistat, abacavir, lamivudine, dolutegravir, efavirenz, emtricitabine, tenofovir alfenamide and tenofovir disoproxil fumarate. Results showed ABT-493 and ABT-530 combination had limited impact on the exposure of these ARTs and no dose adjustment is needed for these ARTs when co-administered with ABT-493 and ABT-530. Raltegravir rilpivirine, and dolutegravir, abacavir and lamivudine had no clinical meaningful effect on ABT-493 and ABT-530 exposures.

The projected ABT-493 and ABT-530 exposures when co-administered with raltegravir or rilpivirine in the current study compared to the estimated exposures in Phase 2b studies are presented in Table 6.

Section 5.6.4.1.1 ABT-493 and ABT-530 Dose
Subsection <u>Antiretroviral DDI with ABT-493 and ABT-530</u>
Add: new second paragraph

Elvitegravir/cobicistat increased the exposure of ABT-493 by 3-fold and the exposure of ABT-530 by 57% with no toxicity associated. Darunavir + ritonavir and lopinavir/ritonavir increased the ABT-493 exposure by 3- to < 5-fold and the ABT-530 exposures by < 2-fold without added toxicity in healthy volunteers. Although these exposure increases are significant, the wide margin of ABT-493 therapeutic exposures to potential threshold of 5% incidence of Grade 2 bilirubin increase (8-fold) or Grade 2 ALT increase (> 30-fold) still allow the use of these ARV regimens in non-cirrhotic HCV

patients without major safety concern. For cirrhotic patients, due to the elevated ABT-493 exposures (approximately 2-fold) in this population, only the elvitegravir/cobicistat regimen is allowed in the current study.

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

It is planned to enroll a total of approximately 150 subjects to this study. A maximum of approximately 90 HCV GT-1 infected subjects will be enrolled.

Has been changed to read:

It is planned to enroll a total of approximately 160 subjects to this study. A maximum of approximately 110 HCV GT-1 infected subjects will be enrolled.

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

With 150 subjects and assuming that 97% of the subjects achieve SVR_{12}, this study has greater than 90% power to demonstrate non inferiority to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 90%) using a one-sample test for superiority using EAST 6.3.

Has been changed to read:

With 160 subjects and assuming that 97% of the subjects achieve SVR_{12}, this study has greater than 90% power to demonstrate non inferiority to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 90%) using a one-sample test for superiority using EAST 6.3.

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

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

Has been changed to read:

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

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Pharmacokinetics
		Clinical
		Clinical
		Bioanalysis
		Statistics
		Clinical
		Global Drug Supply Management

Has been changed to read:

Name	Title	Functional Area
[redacted]		Pharmacokinetics
		Clinical
		Clinical
		Bioanalysis
		Statistics
		Clinical
		Global Drug Supply Management

Document Approval

Study M14730 - A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection and Human Immunodeficiency Virus-1 (HIV-1) Co-Infection (EXPEDITION-2) - Amendment 3 - EudraCT 2015-005577-20 - 12Jul2016

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Signed by:	Date:	Meaning Of Signature:
[redacted]	12-Jul-2016 07:39:28 PM	Approver
	12-Jul-2016 08:19:38 PM	Author
	12-Jul-2016 09:05:40 PM	Approver
	13-Jul-2016 03:13:05 PM	Approver
	13-Jul-2016 08:31:06 PM	Approver
	15-Jul-2016 01:46:15 PM	Approver
	15-Jul-2016 03:22:14 PM	Author