Protocol for Investigator Initiated Study:

A Randomized Study to Evaluate the Safety and Efficacy of Adding Daclatasvir to the Combination of Sofosbuvir (SOF) and Ribavirin (RBV) for 16 Weeks Versus 24 Weeks in Cirrhotic Subjects with Chronic Hepatitis C Infection Genotype 3 (AI444284)

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1. ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APRI	aspartate aminotransferase platelet ratio index
AST	aspartate aminotransferase
ASV	Asunaprevir
HCG	human chorionic gonadotrophin
BID	bis in die, twice daily
BMI	body mass index
BMS	Bristol-Myers Squibb
BOC	boceprevir
BUN	blood urea nitrogen
C	Celsius
CFR	Code of Federal Regulations
CHC	chronic hepatitis C
CI	confidence interval
Cm	Centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CrCl	creatinine clearance
CRF	Case Report Form, paper
CVR	combined virologic response
CYP	cytochrome p-450
D/C	discontinue
DAA	direct acting antiviral
DCV	daclatasvir
DCV/ASV	daclatasvir and asunaprevir combination therapy
DCV/SOF	daclatasvir and sofosbuvir combination therapy
DILI	drug-induced liver injury

dL	Deciliter
DMC	Data Monitoring Committee
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
DUAL	daclatasvir/asunaprevir therapy
EAP	Expanded Access Program
ED50	50% effective concentration
ECG	electrocardiogram
E.g.	exempli gratia (for example)
EOT	End of Treatment
ERCP	endoscopic retrograde cholangiopancreatography
ESRD	end-stage renal disease
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
G	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GT	genotype
H	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	heptaocellular carcinoma
HCV	hepatitis C virus
HE	hepatic encephalopathy
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IUD	intrauterine device
Kg	kilogram

L	liter
LDV	ledipasvir
LLOQ	lower limit of quantification
LT	liver transplant
Mg	milligram
Min	minute
mITT	modified intent-to-treat
mL	milliliter
mg	microgram
N	number of subjects or observations
N/A	not applicable
NIMP	non-investigational medicinal products
NVCB	Next Value Carried Backwards
pegIFN	pegylated interferon
PI	protease-inhibitor
PK	pharmacokinetics
QD, qd	quaque die, once daily
QUAD	daclatasvir/asunaprevir/pegylated interferon/ribavirin therapy
RBV	ribavirin
RCI	replication complex inhibitor
SAE	serious adverse event
SAR	serious adverse reaction
SOC	standard of care
SOF	sofosbuvir
SOP	Standard Operating Procedures
SVR	sustained virologic response
TD	target detected
TND	target not detected
TVR	telaprevir
USPI	United States Package Insert
VBT	virologic breakthrough
WBC	white blood cell

WOCBP	women of childbearing potential

2. BACKGROUND

2.1 Chronic Hepatitis C

Approximately 170 million people worldwide are chronically infected with hepatitis C virus (HCV), including approximately 4 million in the United States. The majority of individuals infected progress to chronic hepatitis, which can lead to cirrhosis, liver failure and hepatocellular carcinoma (HCC). HCV is the leading indication for liver transplantation in most countries and a major cause of HCC.

There are 6 major HCV genotypes with many subtypes based on sequence heterogeneity of the genome [1]. Genotypes (GT) 1 - 3 have a worldwide distribution (with genotype 1 being the major genotype in the United States, Europe, Japan, and South America, genotypes 4 and 5 are found principally in Africa, and genotype 6 is distributed primarily in Asia. Although genotype does not predict the outcome of infection, different genotypes are associated with differential responses to treatment, and allow dosage of current pegylated interferon (pegIFN)-based treatment to be tailored to the genotype being treated [2-4].

Over 20-30 years of chronic HCV infection, 20% of the patients develop end stage liver disease and cirrhosis. Hepatocellular carcinoma occurs in patients with cirrhosis at a rate of 1% to 4% per year. Progression to cirrhosis is often silent, until patients present with complications of End Stage Liver Disease (ESLD) or HCC. HCV imposes burdens on both society and individuals. A major economic burden on the society is the hospital outpatient costs, which have reached $11 billion in the US in direct medical costs alone.

Two first generation direct acting antivirals (DAAs), the HCV protease inhibitors, telaprevir (TVR) and boceprevir (BOC), were approved in the US and EU in 2011 for the treatment of GT-1 chronic hepatitis C (CHC). These regimens are now considered the standard of care (SOC) for treating GT-1 CHC in countries where they are available.

The ability of daclatasvir (DCV) and sofosbuvir (SOF) combination is uniquely related to the limited and/or manageable drug-drug interaction potential with the concurrent medications in addition to its potent antiviral activity and safety in patients with hepatic impairment. The ability of DCV and SOF to be used in HIV/HCV coinfected population is uniquely related to the limited and/or manageable drug-drug interaction potential of these drugs in addition to this combination's potent antiviral activity and safety in patients with hepatic impairment.

Finally, the ability of DCV and SOF to treat GT-3 has the potential to improve on the currently limited all-oral options for this particular group of patients. This study will evaluate the safety and efficacy of DCV and SOF in subjects infected with HCV Genotype 3.

Epidemiological surveys have shown a geographical variation in the prevalence and distribution of hepatitis C genotypes throughout the world. HCV genotypes 1–3 (GT1–3) have a worldwide distribution. Although GT1a and GT1b account for 60% of global HCV infections, GT3 is endemic in Southeast Asia and is variably distributed in different countries.

2.2 Sofosbuvir

SOF is a potent and selective inhibitor of the HCV nonstructural protein 5B (NS5B) polymerase, an RNA-dependent RNA polymerase that is responsible for viral RNA synthesis and is essential for viral replication. In vitro, SOF demonstrates nanomolar potency against HCV GT-1 through-6.

In the SOF Phase 3 clinical program, the SOF + RBV treatment regimen for 12 or 16 weeks was evaluated in subjects with GT-2 or -3 HCV infection and the SOF + pegIFN/RBV treatment regimen for 12 weeks was evaluated in subjects with GT-1, -4,-5, or 6 HCV infection. Across all relevant HCV genotypes and multiple patient populations, SOF, in combination with RBV with or without pegIFN demonstrated similar or superior efficacy to currently available treatment. A 90% rate of SVR was reported in the single-arm NEUTRINO study that treated 327 GT-1, -4, -5 or-6 HCV-infected subjects (98% were either GT-1 or GT-4) following 12 weeks of SOF plus pegIFN/RBV [7] SOF and RBV combination regimen was investigated in GT-2 or GT-3 HCV infected patients in three phase 3 studies, FISSION, POSITRON and FUSION. The efficacy data from these studies are summarized below.

Efficacy Results for Phase 3 studies of SOF/RBV in patients with HCV GT-2, -3 Infection

Study	Population	Treatment Groups	Overall SVR12	SVR12 in Genotype 2	SVR12 in Genotype 3
FISSION	GT-2, -3 treatment-naive	SOF + RBV for 12 weeks or PegIFNα+ RBV for 24 weeks	67% 67%	97% 78%	56% 63%
POSITRON	GT-2, -3, IFN intolerant, ineligible or unwilling	SOF + RBV for 12 weeks or Placebo for 12 weeks	78% 0%	92% 0%	61% 0%
FUSION	GT-2, -3 treatment - experienced	SOF + RBV for 12 weeks or SOF + RBV for 16 weeks	50% 73%	86% 94%	30% 62%

Interim data from the Phase 3 VALENCE study demonstrate that extending the length of SOF+RBV combination therapy to 24 weeks vs. 12 weeks for GT3 subjects can provide much improved SVR rates (overall SVR12- 85%) with no additional safety signal [6, 9]. SVR for GT2 subjects in this study was 93% after 12 weeks of combination therapy. Collectively, the Phase 3 SOF program has demonstrated that high rates of efficacy are attainable with an all-oral regimen across HCV genotypes (1-6) without compromising the enhanced safety profile that has become the expectation of interferon-free alternatives. These data also provide great promise for the potential benefit associated with regimens that combine potent but well tolerated DAA agents, such as DCV+SOF.

2.3 Daclatasvir

DCV is a first-in-class, highly selective NS5A replication complex inhibitor (RCI) with picomolar potency and broad genotypic coverage in vitro. As a RCI, DCV inhibits HCV

replication with 50% effective concentration (EC50) values of 9 and 50 pM against genotypes GT-1b and GT-1a, respectively, in replicon assays and EC50 values ranging from pM to low nM for replicons with NS5A coding sequences derived from GT-2a, -3a, -4a, -5a and -6a.

Data from the DCV non-clinical studies can be found in the Investigator Brochure (IB) as included in IND 79,599.

A thorough review of clinical efficacy studies including DCV is available in the IB. Briefly, DCV has been studied as part of several IFN containing and IFN-free treatment combinations in treatment-naive and treatment experience patients infected with different HCV GTs. Selected results are presented below.

- DCV 60 mg once daily (QD) combined with pegIFNα/RBV has demonstrated high virologic response rates across all GTs tested (GT-1, -2/-3, and -4) in treatment-naive subjects. Sustained virologic response rates at follow-up Weeks 12 and 24 (SVR12/24) were 64% - 100%. Fifty GT-3 treatment naive subjects received DCV and pegIFNα/RBV combination therapy in BMS study AI444031. 83% (44/53) of them met the criteria of protocol defined response (PDR+, defined as HCV RNA at Week 4 < LLOQ, target detected or target not detected) and were eligible for shortening treatment duration to 12 weeks or 16 weeks. Among these PDR+ subjects, 80% (35/44) achieved SVR12 with shortened treatment duration. The SVRs for non-PDR subjects and subjects receiving placebo and pegIFNα/RBV combination are not available yet.
- Quad therapies including DCV (DCV + ASV + pegIFNα/RBV) have demonstrated efficacy in several hard-to-treat GT-1/-4 populations, including null responders to prior pegIFNα/RBV treatment. In the expansion of study AI447011, QUAD therapy including 60mg of DCV and ASV achieved SVR12 rates of 95%.
- DCV has been extensively studied as part of the IFN-free "DUAL" therapy in combination with ASV in patients infected with HCV GT-1b. In the expansion of BMS Study AI447011, GT-1b infected prior null responders were treated with DCV (60 mg QD) plus twice-daily ASV (200 mg) (N=18) and 89% (16/18) achieved SVR24 (based upon HCV RNA < LLOQ TD or TND). A larger group of GT-1b infected patients who were prior non-responders to IFN-based therapy were treated with DCV (60mg QD) plus twice daily ASV (200mg) in BMS Study AI447026. The SVR24 was 80.5% (70/87) and it was similarly effective among subgroups regardless of baseline characteristic including gender, age, HCV RNA and cirrhosis.
- In an ongoing study of the IFN-free regimen of DCV/ASV/BMS-791325 (75 mg twice daily [BID]) triple therapy in treatment-naive subjects infected with HCV GT-1a, -1b produced SVR12 rates of 94% after 12 weeks of treatment.
- As was seen in Study AI444040, 12 or 24 weeks of combination treatment of DCV and SOF with or without RBV led to an SVR12 of 98.4% in treatment-naïve HCV genotype 1 infected patients; an SVR12 of 97.6% (40/41) in GT-1 infected patients who had previously failed protease inhibitor; and an SVR12 of 90.9% (40/44, 2 missing patients and 2 with virologic failure) in treatment-naive patients infected with HCV GT-2 and -3.

2.4 Daclatasvir / Sofosbuvir Combination

Daclatasvir (DCV, BMS-790052) is an NS5A inhibitor, and sofosbuvir (SOF) is a nucleotide NS5B (polymerase) inhibitor. Together, this IFN and RBV free combination is an important

potential addition to the future anti-HCV armamentarium whose initial clinical data (study AI444040) demonstrates a well tolerated combination with potent in vivo anti-viral activity delivering > 90% sustained viral responses in HCV genotypes 1, 2, and 3.

DCV is an inhibitor of NS5A, a multifunctional protein necessary for HCV replication that is an essential component of the HCV replication complex. NS5A has three structural domains (I, II, and III). Domain I (N-terminus of the protein) contains a zinc binding motif and potential RNA binding pocket, and is required for NS5A dimer formation. Inhibitor-binding, resistance mapping and computer modeling indicate that DCV inhibits NS5A function(s) by interacting with the N terminus of the protein (domain I). In vitro 50% effective concentration (EC50) values of DCV ranged from pM to low nM in replicons with NS5A coding sequences derived from GT-1b, GT-1a, GT-2a, -3a, -4a, -5a and 6a. Among all tested genotypes, DCV demonstrates potent inhibitory activity towards GT-3 HCV with EC50 of 146pM [5].

Genotype Coverage by DCV	
HCV Replicon Genotype	**DCV (nM)**
1a (H77, wildtype)[a]	0.020 ± 0.009
1b (Con1, wildtype) [a]	0.004 ± 0.002
2a (JFH1) virus	0.020 ± 0.004
2a (JFH1) [a] replicon	0.034 ± 0.019
2a hybrid replicon (HC-J6 and 2 clinical isolates*)	8.8 - 19
3a hybrid replicon (4 clinical isolates)	0.14 -1.25
4a hybrid replicon (3 clinical isolates) [a]	0.007 - 0.013
5a hybrid replicon (3 clinical isolates) [a]	0.003 - 0.019
6a hybrid replicon	0.054 ± 0.008

[a] Cell lines used routinely in the lab; these are EC50 (SD values as of 6-Nov-2012, (n) > 20.
*Values for two GT-2a clinical isolates were derived from transient replication assay; others were derived from stable cell lines.

SOF is a potent inhibitor of NS5B (polymerase) and therefore inhibits RNA replication. It is a nucleotide analogue that is phosphorylated within the host hepatocyte to the active triphosphate and competes with natural nucleotides leading to chain termination of RNA replication of the viral genome. The active triphosphate of SOF has been shown to have activity in vitro against HCV genotypes 1-6. Potent activities were observed across all genotypes with EC50 values ranging from 14 nM to 181 nM. EC50 of SOF against GT-3 HCV replicon is only 81 nM. .In vitro and in vivo studies showed that the CYP450 system was not involved in the metabolism of SOF, that there was no significant inhibition or induction of CYP450 enzymes by these compounds, and that clinically significant drug interactions mediated by CYP450 were unlikely [6].

<u>Daclatasvir and sofosbuvir demonstrates activity as treating genotype 1-3 HCV infection (Study AI444040):</u>

The combination of DCV and SOF was first shown to be safe and highly effective in the Phase 2 Study AI444040. This is an open-label study that treated 211 GT-1, GT-2 and GT-3-infected subjects with this once-daily combination with or without RBV for either 12 or 24 weeks. The

overall SVR12 in GT-2/3 infected subjects (n = 44) following 24 weeks of treatment was 90.9% (40/44). The combination of DCV and SOF was well tolerated. Most adverse events were mild or moderate and did not lead to treatment discontinuation.

Therefore, this once-daily combination of DCV plus SOF was well tolerated and achieved high rates of SVR12 in both treatment-naïve HCV genotypes 1-3-infected subjects, as well as in subjects who failed PI-based therapy with no other treatment options [7-8].

Summary of Efficacy Results for Study AI444040				
Treatment group	**Patient population**	**Treatment regimen**	**Treatment duration**	**Efficacy results % (N achieving endpoint/N treated)**
B	GT-2,-3 naive	SOF 400 mg QD Lead in for 7 days then add DCV 60mg QD	24 weeks	SVR 12 88% (14/16)
D	GT-2, -3 naive	SOF 400 mg QD + DCV 60 mg QD	24 weeks	SVR 12 100% (14/14)
F	GT-2,-3 naive	SOF 400 mg QD + DCV 60 mg QD + RBV	24 weeks	SVR 24 86% (12/14)

In summary, treatment with the DCV and SOF combination regimen shows promise as a therapeutic option as demonstrated by very high SVR and favorable AE profile.

2.5 Rationale for Dose Selection

The choice of 60 mg DCV as the dose to be used in this study was based on the following data:

- AI444014 is a Phase 2a study that evaluated DCV (3 mg, 10 mg, and 60 mg once daily vs. placebo) plus pegIFNα/RBV for 48 weeks of triple therapy for subjects infected with HCV GT-1. The analysis on the clinical results demonstrated similar efficacy at the Week 12 analysis and remained similar through SVR12. However, exposures in the 10 mg group overlapped with those of the sub-therapeutic 3 mg group. This suggests that the 10 mg dose may provide subtherapeutic exposures in some subjects, an observation that could prove deleterious in the context of a direct-acting antiviral only regimen. No meaningful relationships between exposure and safety events were identified in AI444014, for any DCV dose, based on safety data from 48 weeks of triple therapy. The safety and tolerability of DCV plus pegIFNα/RBV was undistinguishable from control for any DCV treatment group. Specifically, there was no evidence of hepatic or hematologic safety signals observed.
- In study AI447011, DCV 60 mg QD was delivered for 24 weeks in combination with a protease inhibitor, ASV, and demonstrated a favorable safety profile. Although a clinically relevant trend in elevated hepatic transaminases was identified in this study it was attributed to the 600 mg BID ASV dose of the protease inhibitor administered in the study as indicated by similar findings in the ASV program without DCV in regimen. There were no serious adverse events, discontinuations due to adverse events, and no other clinically significant safety signals.

- As discussed previously, DCV 60 mg QD has been examined in combination with SOF in study AI444040 in subjects infected with HCV GT-1, -2, and -3 (N = 211) and has demonstrated high efficacy and favorable tolerability.

Therefore, based on the safety and efficacy of the 60 mg DCV observed in these studies, this dose will be used for this study.

2.6 Rationale for treatment duration

Available data suggests that 12 weeks of therapy with a potent treatment regimen is adequate to achieve SVR in many HCV patient types. This data includes the following observations.

Data from 3 Phase 3 studies, FISSION, POSITRON and FUSION also demonstrated GT-2 and GT-3 treatment naive subjects can be cured with 12 weeks of SOF and RBV combination therapy, achieving 86% - 97% SVR in GT-2 patients and 30%-56% SVR in GT-3 patients. Relatively lower SVR observed in GT-3 subjects treated with SOF is mainly due to the higher relapse rate compared to that of GT-2, which may be due to slower viral clearance. Thus, the higher rate of relapse in HCV GT3 infected subjects treated with SOF may reflect a reduced rate of virologic clearance possibly due to the underlying fibrosis or steatosis characteristic of HCV GT3. The addition of RBV with the potent antiviral DCV would be predicted to provide more rapid and intensive viral suppression and enhanced viral clearance.

In summary, we conclude that the combination of DCV and SOF/RBV is likely to have a high rate of SVR following 12 weeks of treatment in non-cirrhotic patients infected with GT-3 HCV. However, emerging data from clinical trials indicates that 24 weeks of treatment in cirrhotics is needed. Accordingly, a conservative approach will be taken and cirrhotic GT-3 subjects will be randomized to either 16 weeks or 24 weeks of DCV and SOF/RBV.

2.7 Rationale for study

Given the higher risk of disease progression compared to other genotypes, patients with chronic GT-3 HCV infection and cirrhosis represent a population with high unmet medical need. However, the efficacy and safety profile with the current standard of care (SOF/RBV), are still suboptimal with disappointing SVR rates at best comparable to pegIFNα/RBV. Therefore, new treatment options with better efficacy, safety, treatment duration and minimal drug-drug interaction potential are needed for treating HCV GT-3 infection in patients with cirrhosis.

The regimen of SOF plus RBV has been investigated in GT-2 or GT-3 HCV infected patients in three Phase 3 studies, FISSION, POSITRON and FUSION. The data demonstrated the patients with chronic GT-2 or GT-3 HCV infections can be cured with 12 weeks of SOF in combination with the weak antiviral RBV. Consistently high SVRs were observed in GT-2 subjects, including HCV treatment naive (SVR12 86% - 97%). Relatively lower SVRs were observed in GT-3 patients (SVR12 30% - 56%). The reason for the lower rates of sustained virologic response among patients with HCV GT-3 infection, as compared with those who had HCV GT-2 infection, a difference that has also been observed among patients treated with pegIFN/RBV, remains unclear. Although virologic declines during treatment are similar with the two genotypes, the higher rates of relapse among patients with HCV GT-3 infection indicate that virologic clearance is likely to be slower in some patients with HCV GT-3

infection, which may due to the underlying fibrosis and steatosis, adding a potent DAA is anticipated to eliminate the impact of these negative factors.

Treatment-experienced GT-3 infected patients also represent a population of high unmet medical need, especially patients with cirrhosis. These patients face further disease progression and limited treatment options. Results from the VALENCE study demonstrated an SVR12 rate of 85% in non-cirrhotic treatment-experienced GT-3 subjects following 24 weeks of SOF+RBV. Unfortunately, the response was considerably lower in cirrhotic treatment-experienced GT3 subjects (60%) despite the 24-week treatment duration [6, 9]. These results suggest that the optimal treatment duration with a SOF/RBV regimen is 24 weeks for GT-3 infected patients, similar to the currently approved pegIFNα-based regimen. Thus, there remains a need to improve treatment response in GT-3 cirrhotic patients who have advanced disease.

DCV demonstrates consistent SVR in non-cirrhotic and compensated cirrhotic subjects
Responses of cirrhotic subjects treated with DCV are similar to subjects without cirrhosis. DCV has been investigated within different combination regimens as an add-on antiviral to PegIFNα/RBV and as part of dual combination of DCV and asunaprevir (ASV).

Therefore, available efficacy data across DCV programs, including data from IFN-free combinations suggests consistent SVR in non-cirrhotic subjects and compensated cirrhotic subjects treated with DCV based regimens.

DCV has been approved by the U.S. FDA on July 24, 2015.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objectives of this study are:

1. To demonstrate the safety and tolerability of 16 weeks versus 24 weeks of DCV plus standard therapy SOF/RBV, in cirrhotic HCV genotype 3 subjects.
2. To explore the efficacy of 16 weeks versus 24 weeks of DCV plus standard therapy SOF/RBV in improving SVR12, defined as HCV RNA < LLOQ target detected at follow up Week 12, in cirrhotic HCV genotype 3 subjects.

3.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate SVR24 of 16 weeks versus 24 weeks of DCV/SOF/RBV in HCV genotype 3 subjects with cirrhosis.
- To evaluate the proportion of cirrhotic subjects who receive DCV/SOF/RBV for 16 weeks and achieve HCV RNA < LOQ TND at various time points (actual time points will depend on the availability of data) during and post treatment compared to a historical population that took 24 weeks of SOF/RBV.
- To evaluate the proportion of cirrhotic subjects who receive DCV/SOF/RBV for 24 weeks and achieve HCV RNA < LOQ TND at various time points (actual time points will depend

on the availability of data) during and post treatment compared to a historical population that took 24 weeks of SOF/RBV.

4. INVESTIGATIONAL PLAN

4.1 Study Design Overview

This is a randomized, open label, single center safety and efficacy study. At least 40 cirrhotic subjects with HCV genotype 3 will receive standard of care treatment of SOF/RBV as well as 60 mg daily of Daclatasvir (investigational product). Subjects will be randomized in a 1:1 to receive either:

- Group A: 16 weeks of DCV/SOF/RBV
- Group B: 24 weeks of DCV/SOF/RBV

Subjects will return to the study center at various time points throughout the 16 or 24 weeks of treatment in addition to 12 weeks post taking last dose of study drug to monitor safety and efficacy. These visits will be according to standard of care.

The total planned duration of subject participation in Group A is up to 36 weeks (a maximum of 8 weeks of screening, 16 weeks of treatment and 12 weeks of post last dose of study drugs follow-up). The total planned duration of subject participation in Group B is up to 44 weeks (a maximum of 8 weeks of screening, 24 weeks of treatment and 12 weeks of post last dose of study drugs follow-up).

4.2 Study Population

Approximately 40 subjects aged 18-75 years (all sexes, races and ethnic backgrounds) with chronic hepatitis C infection based on history of positive anti-HCV antibody and/or HCV RNA in serum will complete the study. Only genotype 3 subjects with cirrhosis will be considered for enrollment. Of note, treatment-naïve subjects with no previous exposure to an interferon formulation (i.e., IFNa, pegIFNa), RBV, or HCV DAA (protease, polymerase inhibitor, etc.) as well as treatment-experienced subjects who failed previous treatment with interferon formulation (i.e., IFNa, pegIFNa), RBV, or HCV DAA (excluding NS5A inhibitors) will be considered.

All subjects must meet the following eligibility criteria:

4.2.1 Inclusion Criteria

1. Signed, written, informed consent must be available from the subject before any study-specific procedures are performed;
2. Male or female 18-75 years of age;
3. All of the following at least 6 months prior to screening visit:
   - Documented HCV infection based on history of a positive serum anti-HCV antibody test and/or detectable levels of HCV RNA >= 10,000 IU/mL, and
   - Documented HCV genotype 3.
4. Subjects with evidence of cirrhosis defined by either a liver biopsy <= 3 years from screening demonstrating a Metavir Fibrosis Score of F4 (or equivalent); OR

Fibroscan® <= 1 year from screening > 12.5 kPa. If a subject is evaluated by more than one testing method, then the liver biopsy results take precedence;

5. Women of childbearing potential (WOCBP) must:
   - have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
   - WOCBP must agree to follow instructions for method(s) of contraception for 7 months post-treatment completion.
   - Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the following duration for 7 months post-treatment completion.
   - Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.
6. At minimum the subject agrees to the use of two methods of contraception, with at least one method being highly effective as listed below:

   Highly Effective Methods of Contraception
   - Male condoms with spermicide
   - Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® **by male subject's WOCBP partner**. Female partners of male subjects participating in the study may use hormone-based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug. **WOCBP cannot use hormonal contraception as one of the two methods of contraception** because there are no data on the effectiveness of systemic hormonal contraceptives in women taking SOF. However, WOCBP can continue to use hormonal contraceptives, if necessary, in addition to 2 other non-hormonal methods of contraception
   - Nonhormonal IUDs, such as ParaGard®
   - Tubal Ligation
   - Vasectomy
   - Complete Abstinence – defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

   Less Effective Methods of Contraception
   - Diaphragm with spermicide
   - Cervical cap with spermicide
   - Vaginal sponge
   - Male condom without spermicide
   - Progestin only pills

- Female condom; A male and female condom must not be used together

Azoospermic males, women who are not of childbearing potential and WOCBP who abstain from heterosexual activity on a continuous basis, are exempt from contraceptive requirements. However, WOCBP who abstain from heterosexual activity on a continuous basis must still undergo pregnancy testing.

4.2.2 Exclusion Criteria

1. Subjects who lack capacity to consent for themselves;
2. HCV Genotypes other than GT-3 infection; mixed genotype infections are not permitted;
3. Liver histology consistent with any other co-existing cause of chronic liver disease (apart from fatty liver and/or Chronic Hepatitis B Virus);
4. Body Mass Index > 40 at the Screening visit;
5. Any of the following within one month of screening:
   - Uncontrolled diabetes;
   - Unstable or uncontrolled thyroid disease (subjects requiring medication to control their thyroid disease are eligible if all other inclusion/exclusion criteria are met).
6. Any of the following within 6 months of screening visit, any of the following:
   - Decompensated liver disease, esophageal variceal bleeding, or a hepatic mass lesion suspicious for hepatocellular carcinoma (HCC);
   - Subjects who have been treated for HCV infection;
   - History of unstable or deteriorating cardiovascular or cerebrovascular disease;
   - Alcohol and/or drug.
7. QTcF ≥ 500 ms at the baseline visit.
8. Any of the following laboratory abnormalities within 8 weeks of the baseline visit:
   - Hemoglobin <8 g/dL;
   - Absolute neutrophil count <0.50 x 10^3 cells/μL;
   - Platelet count <25 x 10^3 cells/μL;
   - Total bilirubin >=3 mg/dL or >=34 mol/L (with the exception of subjects with Gilbert's syndrome);
   - Albumin <2.5g/dL;
   - Creatinine Clearance (CrCl) <=50 mL/min (as estimated by Cockcroft and Gault).
   - Serum ALT >=10 × ULN;
   - Alpha-fetoprotein >200ng/mL.
9. Prior exposure to NS5A inhibitors is prohibited but other classes and pegIFN/RBV are acceptable for treatment-experienced subjects;
10. Use of any prohibited or restricted treatment at least is five half-lives or 14 days (whichever is longer) of the first dose of study drug (refer to section 4.5);
11. History of cancer within 1 year of the screening visit with the exception of localized basal or squamous cell carcinoma;
12. Any gastrointestinal disease or surgical procedure that may impact the absorption of study drug. (Subjects who have had cholecystectomy are permitted to enter the study);
13. Known HIV infection;
14. Confirmed, uncontrolled hypertension (any screening systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg should be excluded);

15. Presence or history of non-HCV chronic liver disease, including autoimmune hepatitis, alpha-1-antitrypsin deficiency, hemochromatosis, Wilson's disease, drug- or toxin-induced liver disease, alcohol-related liver disease, primary biliary cirrhosis and sclerosing cholangitis. Subjects with fatty liver and/or chronic hepatitis B virus in addition to HCV may be considered in the study;
16. Uncontrolled seizures disorder;
17. History of hemoglobinopathies, (e.g., thalassemia, sickle cell anemia, spherocytosis) or other cause of hemolytic anemia, including autoimmune causes;
18. Active disease at screening visit known to cause significant alteration in immunologic function including hematologic malignancy, sarcoidosis or autoimmune disorder (e.g., rheumatoid arthritis, systemic lupus erythematosis, leukemia, lymphoma, autoimmune thyroid disease, scleroderma, unstable psoriasis, and multiple sclerosis);
19. Pregnant or lactating women or women who plan to become pregnant during the study;
20. History of hypersensitivity to drugs with a similar biochemical structure to DCV or SOF or RBV;
21. Any other criteria or known contraindication that would exclude the subject from receiving SOF or RBV (per the local label) or DCV;
22. Inability to tolerate oral medication;
23. Subjects, who in the opinion of the Investigator, are not suitable candidates for enrollment or who would not comply with the requirements of the study.

4.2.3 Discontinuation of IMP

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Virologic breakthrough defined as any confirmed >1 log10 increase in HCV RNA over nadir OR confirmed increase in HCV RNA ≥ LLOQ if HCV RNA previously declined to <LLOQ TD/TND
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Laboratory or Clinical Criteria: If any of the following laboratory or clinical criteria is obtained for any patient, the result must be repeated /confirmed within 72 hours. If the results are confirmed, the patient must discontinue treatment. Clinical criteria must have Principal Investigator or Sub-Investigator assessment prior to proceeding to permanent discontinuation:
  - Evidence of confirmed hepatic decompensation (Child-Pugh Class B or C, Score > 6);
  - ALT > 2 ´ baseline and 5 ´ ULN, and either total bilirubin > 4 ´ ULN or INR > 2.5;
  - Any Grade 4 AE or clinically significant laboratory abnormality considered study drug-related.

- Virologic Breakthrough:

If discontinuation of therapy is required, this must occur no later than the next study visit.

It is expected that all subjects who are on study will complete the protocol-defined durations for treatment and follow-up. Subjects who discontinue all study drugs prior to completing the assigned dosing regimen should complete 12 weeks of follow-up. However, if alternative HCV therapy is initiated in the post-treatment period for any reason, subject must withdraw from the study once the post-treatment Week 4 visit has occurred.

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

4.2.4 Subject Withdrawal

In accordance with the regulations governing human subject protection, a subject has the right to withdraw from the study at any time for any reason without jeopardy to his/her future of their medical care at the institution. Furthermore, reasons for terminating subjects from the study include but are not limited to the following:

- Any of the stopping rules included under "Expected Adverse Events and Management".
- Subject non-compliance.
- Pregnancy occurring on study.
- Intolerable adverse event (decision to be removed from study made by either the investigator or subject).
- Unrelated medical illness or complication.
- Evidence of hepatic decompensation.
- Decision by the investigator that it is in the subject's best medical interest.
- Lost to follow-up.
- Death
- Termination of the study by Bristol-Myers Squibb (BMS)

If the subject is going to be withdrawn from the study, all efforts will be made to complete the early termination/discontinuation visit.

4.2.5 Subject Replacement

Subjects who receive at least 1 dose of the study drug and discontinue prematurely will not be replaced.

4.3 Study Drug

4.3.1 Standard of care treatment – non investigational medicinal product (NIMP)

The recommended daily sofosbuvir dose (single pill) for patients with HCV genotype 3 (U.S. prescribing information) is 400 mg with or without food. The recommended daily ribavirin dose (divided into two doses) for patients with HCV genotype 3 (U.S. prescribing

information) is 1000 mg (<75 mg) or 1200 mg (>= 75 mg) with food. Standard of care treatment of Sofosbuvir (SOF) and Ribavirin will be prescribed and supplied directly to participant per standard of care protocol. This combination is not considered investigational.

4.3.2 Daclatasvir – investigational medicinal product (IMP)

In addition to the standard of care treatment mentioned above, subjects will take one tablet in the morning daily of Daclatasvir (BMS-790052-05), which will be supplied by Bristol-Myers Squibb. Each film coated tabled is 60 mg (as the free base) in potency. Each tablet is plain, green, biconvex, pentagonal and film-coated. There will be 33 tablets/bottle as open label. The dose can be taken with or without food.

Only subjects enrolled in the study may receive investigational product in accordance with all applicable regulatory requirements. Study drugs will be dispensed to subjects at scheduled study visits (refer to appendix **Error! Reference source not found.** for schedule of assessment). Subjects will be instructed on administration and storage. Study staff assigned by the site's investigator will dispense study drugs, perform and maintain accountability logs.

Study drug will be stored in a secure area with access limited to the investigator and authorized site staff and under physical conditions that are consistent with specific requirements. Storage will be at 15°C-25°C (59°F-77°F). Store in a tightly closed container.

4.4 Randomization

A randomized schedule will be generated prior to the initiation of the study. Following acquisition of the signed informed consent, successful completion of screening evaluations, and satisfaction of all eligibility criteria, subjects will be randomized in a 1:1 ratio in blocks of 2 to either Group A or Group B. Randomization will be centralized.

4.5 Concomitant and Excluded Therapy

All concomitant medications, including over the counter medications, vitamins, nutritional supplements and other herbal preparations, taken during the study as well as the reason for use will be recorded. The use of concomitant medication will be recorded at each visit.

The following treatments are prohibited during dosing with DCV and SOF and should be discontinued at least is five half-lives or 14 days (whichever is longer) of the first dose of study drug.

- Strong inhibitors of CYP3A4 are prohibited, including, but not limited to: ketoconazole, troleandomycin, itraconazole, voriconazole, mibefradil, clarithromycin, telithromycin, grapefruit juice and grapefruit-containing products, Seville oranges, juices and products that contain Seville oranges, conivaptan, nefazodone, etc.;
- Strong CYP3A4 inducers are prohibited, including but not limited to: rifampin, rifabutin, rifapentin, dexamethasone, phenytoin, carbamazepine, phenobarbital, St John's wort, etc.;

- Strong P-gp inhibitors are prohibited (e.g., ketoconazole, indinavir, lapatinib, quinidine, amiodarone, ranolazine, erythromycin, clarithromycin, and azithromycin (azithromycin will be allowed for a duration of 7 days or less or once weekly);
- CYP3A substrates with narrow therapeutic index are prohibited, including but not limited to alfentanil, cisapride, dihydroergotamine, ergotamine, fentanyl, pimozide, and quinidine;
- P-gp inducers are prohibited, including but not limited to, avasimibe, carbamazepine, oxcarbazepine, phenytoin, rifampin, rifabutin, rifapentine, St John's wort, and boosted tipranavir;
- Amiodarone or any of its trade/brand names/formulas.

The following treatments should be used with caution during dosing with DCV and SOF.

- Substrates of OATP1B1 and OATP1B3 should be used with caution (e.g., glyburide, bosentan, rosuvastatin, pravastatin, and pitavastatin);
- Substrates of BCRP should be used with caution (e.g., rosuvastatin);
- P-gp substrates with a narrow therapeutic index (e.g., digoxin) should be used with caution and at the lowest efficacious dose with appropriate monitoring (e.g., therapeutic drug monitoring).

In addition, the following will apply:

- Medications with known or potential anti-HCV activity other than the assigned study treatment are prohibited during the on treatment period. If alternative HCV therapy is initiated in the post-treatment period for any reason, subject must withdraw from the study once the post-treatment Week 4 visit has occurred. If the subject receives HCV therapy after post treatment Week 4, the subject should be discontinued from the study and a post Week 24 visit should be completed;
- Any prescription or herbal product which is not prescribed by the investigator or licensed physician for treatment of a specific clinical condition is prohibited;
- Methadone and buprenorphine should be used with caution. These drug levels may change with concomitant use of DCV and SOF;

4.6 Lost to follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

4.7 Study Termination

Reasons for terminating the study may include but are not limited to the following:

- Subject enrollment is unsatisfactory.
- Good clinical practice is not being maintained and/or followed adequately.
- Administrative reasons.

5. SAFETY AND EFFICACY ASSESSMENTS

5.1 Safety Variables and Assessments

Safety will be assessed through vital signs, physical examinations, adverse events, concomitant medication assessments as well as laboratory test. Subjects will return to clinic visits per the standard of care schedule at weeks 2, 4, 6, 8, 10, 12, and16 for all subjects as well as weeks 20 and 24 for subjects in Group B. All subjects will return for treatment-free follow-up 4, 12 and 24 weeks post discontinuation of study drug or early termination visit (if applicable). Also, an ECG will be conducted at screening, end of treatment (week 16 or week 24) and follow-up weeks 12 and 24 for safety. For women of child-bearing potential, serum or urine pregnancy tests will be performed at every visit. Refer to appendix **Error! Reference source not found.** for schedule of assessments.

The safety data will be tabulated and, the proportion of subjects with the following will be summarized for each arm of the study and cumulatively:

- Adverse events using the grading system outlined in section 6.
- Abnormal laboratory safety tests (liver injury tests as measured by AST, ALT, GGT, Total Bilirubin and Albumin as well as blood picture tests as measured by WBC, RBC, Hgb, Hct, Plts) and those requiring dose reduction, interruptions or discontinuations.

All blood sample collection will be part of the standard of care schedule, with the exception of any additional blood collection, outside standard of care, that are required to monitor the subject's safety.

5.2 Efficacy Variables and Assessments

Efficacy will be assessed through HCV RNA assessments that will be conducted at various time points during study drug period and follow-up. Refer to appendix **Error! Reference source not found.** for a detailed schedule of assessments.

Primary Efficacy Assessment: The HCV RNA collected at post-treatment follow-up Week 12, for subjects treated with DCV/ SOF/RBV for 16 or 24 weeks (depending on the group) will be used for the primary antiviral assessment in this study.

Secondary Efficacy Assessments: HCV RNA collected at each of the following Weeks: 2, 4, 6, 8, 10, 12, 16 as well as weeks 20 and 24 for subjects in Group B; post-treatment Weeks 4, 12 and 24 will be used for the secondary antiviral assessment in this study.

5.3 Study Assessments

The results of all procedures listed below will be documented in the subject's source documents. Refer to appendix **Error! Reference source not found.** for an overview of the schedule of assessments.

5.3.1 Informed Consent

Written informed consent will be obtained using the site's Institutional Review Board (IRB) or the Independent Ethics Committee (IEC) approved informed consent form prior to the initiation of screening procedures. Site staff will obtain informed consent by following the institution's procedures and regulations for the informed consent process.

5.3.2 Screening Visit

The results of the following procedures and evaluations will be used to determine subject eligibility for enrollment into this study. The assessments must be completed and results obtained within 8 weeks prior to the Baseline (Day 1) visit:

- Informed consent.
- Obtain medical history, list of concomitant medications used and ensure it meets inclusion/exclusion criteria.
- Vitals: height, weight, blood pressure, pulse, temperature, respiration rate and BMI.
- Physical examination.
- Obtain documentation of the laboratory and procedures results per the inclusion/exclusion criteria.
- Serum or urine HCG, if female of childbearing potential.
- ECG.

Any subject who signs an informed consent but does not meet inclusion/exclusion criteria will be considered a screen failure. The reason for screen fail will be included in the study chart.

5.3.3 Baseline (Day 1) Visit

All assessments will be performed before administration of first dose. The following assessments will be performed:

- Confirm that all the results of the screening procedures have been obtained, documented and that the subject meets eligibility criteria.
- Vitals: weight, blood pressure, pulse, temperature and respiration rate.
- Adverse events collection and symptoms directed physical exam.
- Concomitant medications review.
- Laboratory testing as per standard of care and appendix A.
- Serum or urine HCG, if female of childbearing potential.
- Administration of first dose of study drug in clinic.

5.3.4 Study Drug Period

All subjects will return for visits at weeks 2, 4, 6, 8, 10, 12, and 16. Subjects in Group B will additionally return at weeks 20 and 24. The following assessments will be performed:

- Vitals: weight, blood pressure, pulse, temperature and respiration rate.
- Laboratory testing as per standard of care and appendix A.
- Serum or urine HCG, if female of childbearing potential.
- Adverse events collection and symptoms directed physical exam.
- Concomitant medications review.
- Compliance assessment at every visit. The necessity for study drug compliance will be reinforced with the study participant at each study visit.
- IMP study drug dispensing will occur at weeks 4, 8, and 12 for Groups A and B subjects as well as weeks 16 and 20 for Group B subjects.
- IMP study drug return and accountability at each visit.
- ECG at end of treatment (week 16 or 24, depending on group subject randomized to).

5.3.5 Post-Study Drug Follow-up Period

Subjects will return for follow-up at 4, 12 and 24 weeks post last dose of study drug. The following assessments will be performed:

- Vitals: weight, blood pressure, pulse, temperature and respiration rate.
- Laboratory testing as per standard of care.
- Serum or urine HCG, if female of childbearing potential.
- Adverse events collection and symptom directed physical exam.
- Concomitant medications review.
- Any remaining study drug return and accountability.
- ECG at week 24.

5.3.6 Study Visits Window

Treatment weeks 2, 4, 6, 8, 10, 12, 16, 20, 24: ± 3 days.
Post treatment follow-up weeks 4, 12 and 24: ± 1 week.

5.3.7 Unscheduled Visit

Unscheduled visits will be conducted if necessary for the purposes of evaluating or following adverse events or to improve subject compliance and retention. Results from any evaluations including physical examination, or additional testing that are performed will be recorded.

5.3.8 Early Termination Visit

The following assessments will be conducted in case of an early withdrawal of a subject. Every effort should be made to collect the following information within 2-4 weeks of the last dose of study drug, if possible. The following will be performed:

- Physical examination.
- Vitals: weight, blood pressure, pulse, temperature and respiration rate.
- Laboratory testing as per standard of care and appendix A.
- Serum or urine HCG, if female of childbearing potential.
- Adverse events collection.
- Concomitant medications review.
- Compliance assessment, if applicable.
- Any remaining study drug return and accountability.
- ECG.

6. ADVERSE EVENTS

The investigator is responsible for monitoring subject's safety, as well as detection and documentation of events meeting the criteria and definition of an AE or SAE, according to the following guidelines. In addition, the investigator is responsible for providing appropriate medical care. Frequency of follow-up of any particular adverse event is left to the discretion of the investigator.

6.1 Adverse Event (AE)

6.1.1 Definition

An AE is any unfavorable, harmful or pathologic change or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) that occurs in a

subject throughout the duration of the study regardless of relationship to study drug. This definition includes surgery for a condition that was present prior to informed consent signature and unexpectedly worsens during the study. Lack of drug effect is not considered an AE.

6.1.2 Reporting Requirement

AEs will be collected and reported after the subject signs the informed consent until the subject's last visit for the study.

Study staff will instruct subjects to report any physical changes or new symptoms they may notice during the course of the study. In addition, AEs should be elicited with minimal connotations. Whenever possible, a diagnosis should be given for AE signs and symptoms of a common pathology.

As for laboratory assessments, all Grade 3 and 4 laboratory toxicities will be reported as adverse events. If a subject's dose is reduced or discontinued as a result of an AE, study site will clearly document this into the reason leading to any such dose reduction or discontinuation of study drug. AEs and SAEs will be reported according the guidelines outlined in this document regardless of less stringent regulatory requirements that might apply.

6.2 Serious Adverse Event (SAE)

6.2.1 Definition

An expected or unexpected adverse event is considered a serious adverse event (SAE) if it meets any of the following:

- Results in death.
- Is life-threatening: at the occurrence of the event, the subject was at immediate risk of death. It does not refer to an event that hypothetically might have caused death had the event been more severe nor is likely to cause death in the distant future if left untreated.
- Requires hospitalization or prolongs existing hospitalization: when in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability or incapacity that does not allow the subject to perform activities of daily living.
- Requires medical intervention to prevent one of the outcomes listed above.
- Is a congenital anomaly or birth defect.
- Is medically significant.
- A grade 4 laboratory toxicity requiring medical or surgical intervention, hospitalization, dose reduction or interruption, as well as toxicities that are symptomatic and considered clinically significant by the investigator.

6.2.2 Reporting Requirement

AEs will be collected and reported after the subject signs the informed consent until the subject's last visit for the study.

Regardless of the SAEs relationship to the study drug, the event must be described in the source documentation.

All SAE's will be reported to the U.S. Food and Drug Administration (FDA) and the respective governing regulatory agencies as required by local regulations and guidelines. In addition, SAEs will be reported to the site's IRB/IEC as required by local regulations and guidelines.

In addition, SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form. When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:
SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 609-818-3804.

The paper forms should be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

6.3 Severity

Severity of adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). If the AEs are not covered by these criteria, then severity of AEs are to be graded as follows:

- Grade 1: Mild; Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- Grade 2: Moderate; Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/ therapy required.
- Grade 3: Severe; Marked limitation in activity; some assistance usually required; medical intervention/ therapy required, hospitalization possible.
- Grade 4: Life threatening or disabling; Extreme limitation in activity; significant assistance required; significant medical intervention/ therapy required, hospitalization or hospice care probable.
- Grade 5: Death.

6.4 Relationship

The relationship of study drug to the AE will be determined by the investigator based on the following definitions:

- Not Related: Another cause of the event is most plausible; or clinically plausible temporal sequence is inconsistent with the onset of the event and the study drug administration; or a causal relationship is considered biologically implausible.
- Possibly Related: An event that follows a reasonable temporal sequence from administration of the study drug or a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors.
- Probably Related: An event that follows a reasonable temporal sequence from administration of the study drug, and there is a biologically plausible mechanism for study drug causing or contributing to the AE and the event could not be reasonably explained by the known characteristics of the subject's clinical state. In addition, the relationship may be confirmed by improvement on stopping and reappearance of the event on repeated exposure.

6.5 Recording Adverse Events or Serious Adverse Events

If possible, AEs and SAEs medical terminology will be recorded according to the CTCAE. Moreover, if known, the diagnosis rather than individual signs and symptoms will be recorded. AEs/SAEs occurring as secondary to other events (sequelae) should be identified by primary cause. The action taken, relationship to study drug and outcome of AE/SAE will also be recorded.

6.6 Follow-up of Adverse Event or Serious Adverse Event and Outcome

Non-serious adverse events will be followed until the event resolves or stabilizes or until the last study visit, whichever comes first, and must be recorded. If the adverse event is serious and is assessed as possibly or probably related to study drug, it must be followed until either the event is considered stable or resolved. Any SAE assessed as not related to study drug will be followed as clinically indicated until its resolution or, if non-resolving, until considered stable or until the final study visit, whichever comes first.

By the last study visit, each reported AE/SAE must have one of the following outcomes:

- Resolved without sequelae.
- Resolved with sequelae.
- Unresolved.
- Death.

6.7 Pregnancy

Pregnancies should be reported from the time of informed consent until 24 weeks after the last dose of study drug, depending on which occurs first. Pregnancies must be followed until termination of the pregnancy or for a minimum of six months following the birth of the child. If a female subject becomes pregnant while participating in this study, study drug will be immediately discontinued. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

Serum or urine pregnancy tests will be performed throughout the study. Refer to appendix **Error! Reference source not found.** for the schedule of assessments.

In addition, if, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study drug exposure,

including during at least 5 half lives after product administration, the investigator must immediately notify the BMS of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with the SAE reporting procedures. In most cases, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug, after a thorough discussion of benefits and risk with the subject. Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.8 Overdose

An overdose is defined as the consumption of a single dose that is greater than the scheduled dose of study drug. For the purposes of this study, an overdose is considered a total daily dose of >200 mg of DCV.

7. EXPECTED ADVERSE EVENTS AND MANAGEMENT

All complications, which occur or are exacerbated during the course of the subject's involvement in the study, will be recorded. All subjects will be given a 24-hour number where the principal investigator or a qualified member of the research team can be reached. Management of adverse events will be in accordance with standard of care guidelines as well as the following; however in the case of life-threatening adverse events, the drug may be discontinued permanently.

7.1 DCV

Thus far, more than 6000 subjects have exposed to DCV in clinical trial setting. In general, DCV has a favorable safety profile. No DCV specific safety signal has been identified.

The safety profile of DCV (60 mg QD)/pegIFNα/RBV therapy in the Phase 2 studies was consistent with the established safety profile of pegIFNα/RBV when these drugs were part of the background therapy. Few subjects treated with DCV/ASV DUAL, DCV/ASV/pegIFNα/RBV QUAD or DCV/ASV/BMS-791325 Triple therapy reported serious adverse events (SAEs) or adverse events (AEs) leading to discontinuation of study drugs. As expected, Grade 3/4 hematologic abnormalities (decreased neutrophils and lymphocytes) were more common with DCV/ASV/pegIFNα/RBV QUAD therapy (up to 16%) compared with DCV/ASV DUAL therapy (up to 4%) and DCV/ASV/BMS-791325 Triple therapy (up to 3%). No cases of potential drug induced liver injury (DILI) were reported with DCV/pegIFNαRBV, DCV/ASV Dual, DCV/ASV/pegIFNαRBV Quad, or DCV/ASV/BMS-791325 Triple therapy (with ASV 200 mg BID, tablet).

In Study AI444040, 167 GT-1 HCV infected subjects and 44 GT-2, -3 HCV infected non-cirrhotic subjects received either 12 weeks or 24 weeks combination treatment of DCV and SOF. An interim analysis was performed when all subjects had reached at least SVR12. The data showed the combination of DCV plus SOF was well tolerated. Overdose was the only SAE "related" to treatment. No other SAEs or discontinuations of study treatment were reported by investigators to be related to therapy. Most AEs were mild or moderate and did not

lead to treatment discontinuation. No Grade 3/4 events of elevated ALT, AST or total or direct bilirubin were observed.

Overall, 4 subjects have died while participating in DCV studies. This includes 3 subjects treated with DCV 20 mg QD/pegIFNαRBV [sudden death due to unknown causes, death due to an intraventricular hemorrhage (in the post-treatment period), death due to cardiopulmonary failure exacerbated by asthma [in the post-treatment period]; all 3 deaths were considered not to be related to study drugs by the investigator]. One subject treated with 60 mg QD + BMS-986094 200 mg QD died due to cardiogenic shock with multisystem organ failure, including biventricular heart failure and renal failure; the investigator considered the death to be possibly related to BMS-986094, a nucleotide polymerase (NS5B) inhibitor no longer in clinical development.

In Japanese subjects treated with the DUAL combination of DCV and ASV, a constellation of clinical symptoms (pyrexia, eosinophilia, and liver test abnormalities) was identified in 1 Japanese subject (sentinel case) treated with DCV/ASV Dual therapy in the Phase 3 AI447026 study. A total of 6 serious adverse reactions (SAR) of pyrexia were identified including the sentinel case; 4 of the 6 subjects experienced eosinophilia ($> 0.6 \times 10^3$ cells/μL) and 2/6 subjects had elevated ALT/AST > 5 x upper limit of normal (ULN). All cases were reported from studies conducted in the Japanese population with DCV/ASV Dual therapy. No SAR of pyrexia was identified in the non-Japanese population. At this time, it is not known conclusively if these findings are directly related to study medication or other factors but the constellation appears limited to Japanese subjects treated with ASV.

The lack of similar liver toxicity or concurrent pyrexia/eosinophilia in DCV studies not including ASV indicates that these events are less likely to be related to DCV. Otherwise, DCV was well tolerated at durations up to 12, 24, or 48 weeks, depending on the study.

Bristol-Myers Squibb has received 5 adverse event (AE) reports describing clinical significant arrhythmias, most involving severe bradycardia, when patients receiving amiodarone were administered daclatasvir (DCV) in combination with sofosbuvir (SOF) for treatment of hepatitis C virus (HCV) infection. These reports were received from the DCV Expanded Access Program (EAP) or from spontaneous post-marketing reports initiated by a local provider, in subjects with pre-existing cardiovascular comorbidity. None of these events occurred in the context of BMS sponsored clinical trials, where amiodarone was seldom, if ever, used by subjects in the trials. At this time, BMS is unable to determine if this potential drug-drug interaction with amiodarone results from interaction of amiodarone with DCV, SOF or both. However, to remain conservative regarding patient safety while this potential interaction is further investigated, BMS has decided to exclude amiodarone from use in clinical studies at this time.

Overall exposure to DCV includes approximately 7900 patients in clinical trials, 5500 patients in the EAP, and reportedly >10,000 patients in Japan; exposure to DCV/SOF has been approximately 707 patients in BMS clinical trials and 4111 patients in EAP programs.

Amiodarone was excluded from use in most DCV clinical trials (amiodarone was permitted to be “used with caution” in UNITY trials of DCV/ASV/beclabuvir [BCV]). Approximately 30 of

4111 patients enrolled in the French cohort Autorisation Temporaire d'Utilisation (ATU; compassionate use program) were receiving amiodarone upon initiation of hepatitis antiviral therapy. To date, no reports of potential amiodarone Drug-Drug Interactions (DDIs) have been received for the Dual regimen (DCV/ASV) in either clinical trials or the post-marketing setting; all reports have involved DCV/SOF.

In DCV-TRIO protocols with active dosing, including AI443123 and AI443131, amiodarone was categorized as "use with caution" due to its strong inhibition of P-glycoprotein. These protocols will be amended to prohibit amiodarone use during treatment with DCV-TRIO, with or without SOF.

Potential Drug Induced Liver Injury (DILI):
Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs. Potential drug induced liver injury is defined as:

- ALT ≥ 5 times baseline or nadir value, whichever is lower, AND ≥ 10 x ULN (upper limit of normal, AND
- Total bilirubin ≥ 2.5 x ULN, AND
- No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, acute viral hepatitis, cholestasis, pre-existing hepatic disease excluding HCV or the administration of other drug(s), herbal medications or substances known to be hepatotoxic.

Most common AEs with DCV:
No AEs or clinical laboratory abnormalities directly attributable to DCV are identified. The most common AEs reported with DCV treatment include headache, dizziness, nausea, diarrhea, fatigue, back pain, insomnia, abdominal pain and flatulence. The AE profiles of combined therapy are consistent with placebo or backbone of therapy when DCV was administrated in combination with other DAAs or pegIFNαRBV.

Dose reductions:
Dose modifications of DCV are not permitted.

Dose interruptions:
If an AE including a laboratory abnormality leads to dose interruption then close monitoring of the laboratory abnormality or AE that led to interruption of study drug(s) should occur at least until the interrupted drug can be restarted or until AE is resolved. When AEs occur that are considered by investigators to be unsafe, the necessity of dose interruption of DCV should be discussed with the principal investigator. If interruption is required for more than 7 days, treatment with DCV must be permanently discontinued.

Missed doses

- If the missed dose is remembered within 12 hours of the scheduled dose time, the dose should be taken as soon as possible.
- If the missed dose is remembered later than 12 hours after the scheduled dose time, the dose should be skipped and the next dose taken at the appropriate time.

7.2 Standard of care treatment and DCV

Dose adjustments and interruptions of SOF/RBV (NIMP – standard of care treatment) will be according to standard of care.

Data demonstrates no clinically meaningful PK interaction between DCV and SOF.

In Study AI444040, Population PK sampling occurred in all subjects while serial PK sampling occurred on Days 7 and 14 in a subgroup of subjects (N = 31). Plasma concentrations of DCV, SOF, and the SOF predominant circulating metabolite GS-331007 were determined by validated LC/MS/MS methods. Noncompartmental PK parameters were derived. Pooled data of DCV exposures across all arms (N = 87) were compared to historical data from study AI447011 (DCV 60 mg once-daily in combination with the NS3 protease inhibitor asunaprevir). The results showed the PK of GS-331007 was unchanged by the presence of DCV. No apparent effect of SOF on DCV PK was observed.
SOF is a substrate of Pgp. As such, SOF may be susceptible to Pgp transporter-based drug interactions. Potent intestinal inducers (rifampin and St John's wort) of Pgp may decrease SOF plasma concentration and reduce the therapeutic effect of SOF; as such, rifampin or St John's wort should not be used with SOF. Coadministration of SOF with drugs that inhibit Pgp may increase SOF plasma concentration. Based on these results, SOF may be administered with inhibitors of Pgp. SOF is not an inhibitor of Pgp and thus is not expected to increase exposures of drugs that are substrates of these transporters.

<u>Development of Resistance:</u>
Development of drug resistance has been observed with HCV replication inhibitors. Early emergence of resistant variants occurred in HCV-infected subjects dosed with DCV monotherapy (Study AI444004). However, such DCV resistant variants can be partially or fully suppressed when DCV is administrated as part of a potent DAA combination, in particular SOF. Viral breakthrough (VBT), in particular, is rare in subjects taking SOF and not expected in this study. In the SOF Phase 2 and 3 program results reported to date, only a single case of viral breakthrough occurred in a subject taking SOF. This particular subject was found to have undetectable SOF levels in PK analysis and clearly non-adherent to therapy.

In study AI444040, only one GT-3 subject receiving the combination DCV and SOF met a protocol definition of VBT. This subject demonstrated undetectable levels prior to administration of rescue therapy (addition of pegIFNαRBV) and thus does not appear to represent a true virologic failure. One additional GT-3 subject experienced virologic relapse at post treatment week 4. This subject demonstrated an A30K polymorphism at baseline and relapse. No emergent resistance variants were identified in the relapse virus.

Relapse has occurred in many patients who have been treated with SOF; however, the precise reason for relapse remains unclear. SOF resistant variants have been rare. There was a single case of the signature S282T mutation conferring resistance to SOF, which was reported in a GT-2 patient who relapsed post-treatment. The detection was transient and viral sequences reverted to wild-type during follow-up. An additional GT1 infected patient experienced viral relapse following 12 weeks of treatment with SOF and the NS5A inhibitor ledipasvir. The

S282T variant was detectable at low levels using next generation sequencing methods in the relapse virus in addition to NS5A resistance substitutions. Both of these patients were successfully retreated with longer durations of SOF containing therapy.

In summary, the risk of viral resistance is low and mitigated by the following:

- The high clinical efficacy rates cited previously suggest that the risk of developing two drug resistance as result of study participation is low during or after treatment.
- Subjects participating in this study will be closely monitored for viral breakthrough or relapse.
- In addition, as there is no cross resistance between DCV/SOF and other classes of DAAs, in particular telaprevir or boceprevir.
- Finally, since the SOF S282T mutation appears rare with rapid reversion to wild-type when detected, successful retreatment with a SOF-based regimen may be possible.

Resistance analysis is planned to take place after all subjects have completed the study drug period. The following will be analyzed (refer to appendix A):

- Nucleotide sequencing of the NS5A gene at baseline for all subjects and at the end of treatment for all subjects with evaluable viral loads;
- NS5B gene in the resistance analysis for subjects with previous sofosbuvir experience at baseline and at the end of treatment.

Potential Benefits of Treatment with DCV in Combination with SOF:

Based on data from the AI444040 study, the key potential benefits of a treatment regimen consisting of DCV/SOF in HCV GT-3 infected patients include:

- Improved rates of SVR compared to currently available therapies
- Better tolerability without interferon/RBV associated AEs
- The potential for shortened duration of treatment compared to pegIFNαRBV
- Convenient once daily dosing schedule and low pill burden

In summary, the overall Risk/Benefit for patients who may participate in this study is highly favorable. The currently available treatments for GT-3 patients are unsatisfactory due to suboptimal efficacy and tolerability issues related to pegIFNαRBV side effects. Thus, this pegIFNαRBV sparing combination regimen, shown to be well tolerated and highly potent in a study of > 200 patients is expected to provide significant benefit to participating subjects.

7.3 Other expected adverse events

- Drawing Blood: This is will be according to standard of care. Taking blood samples for tests can create certain discomfort and occasionally cause a small hemorrhage (bleeding), swelling, or bruising at the point of insertion of the needle, and in rare occasions, fainting or infection. The risk of blood draws will be managed according to standard of care and local regulations.
- Giving urine samples can cause discomfort.
- There are generally no risks associated with ECG. Because this procedure merely monitors the electrical impulses and does not give or send out electricity, there is no risk of shock. ECG will be performed according to the center's standard operating procedures.

- Another possible risk is loss of confidentiality. Every effort will be made to keep the study participant's identity confidential. The risk of loss of confidentiality will be minimized by keeping records in a secure location and on password-protected computers. Data collection forms and blood samples will be marked only with the initials of the subject and a code number.

7.4 Pregnancy

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, women under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Women treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

It is unknown if the study drug may cause harm to an unborn child. A serum or urine pregnancy test will be performed for women of childbearing potential before study drug is initiated and throughout the study. Refer to appendix **Error! Reference source not found.** for the schedule of assessments. It is essential for both fertile women and men to use two reliable forms of effective birth control to prevent pregnancy while participating in this study.

If a pregnancy occurs at any time during the study, demonstrated by a positive serum or urine pregnancy test, study drug will be discontinued immediately..

8. STATISTICAL ANALYSIS

The purpose of this study is to evaluate the safety, tolerability and efficacy of DCV and standard of care therapy of SOF/RBV for 16 weeks versus 24 weeks in HCV-infected genotype 3 subjects.

8.1 Sample Size

This is a randomized, open label, single center safety and efficacy study. This is a small study of at least 40 cirrhotic subjects with HCV genotype 3 will receive standard of care treatment of SOF/RBV as well as 60 mg daily of Daclatasvir (investigational product). Subjects will be randomized in a 1:1 to one of the following groups:

- Group A: 20 subjects will receive 16 weeks of DCV/SOF/RBV
- Group B: 20 subjects will receive 24 weeks of DCV/SOF/RBV

8.2 Statistical Methods and Analysis Populations

Analyses of safety and efficacy data will use the intent-to-treat (ITT) subject population. The ITT subject population will include all subjects who are randomized.

In all hypotheses tests for treatment effects, the null hypothesis is that there is no difference between triple therapy with DCV/SOF/RBV versus standard of care therapy of SOF/RBV (based on historical). The alternative hypothesis is that there is a difference between the two groups, regardless of direction (two-sided alternative).

Missing values will not be imputed for any variables, meaning all missing values will be treated as missing data. Descriptive statistics will be used to describe the sample. Correlational analyses will be used to explore relationships. The distribution of the variables will be conducted first to determine whether parametric or non-parametric measures should be used. In case parametric measures are used, paired t-tests will be employed for interval variables and chi-square for ordinal/nominal variables. In case the data is non-parametric, Wilcoxon Mann-Whitney tests will be used. Univariate and multivariate logistic regression may be used to evaluate factors associated with improvement.

8.3 Interim Analysis

Interim analysis will not be conducted.

9. STUDY ADMINISTRATION: ETHICAL AND LEGAL ASPECTS

This study will be conducted in compliance with GCP as described in FDA regulations and ICH. These practices are consistent with the principles stated in the Declaration of Helsinki. The study will be conducted in accordance with all applicable regulatory requirements for a US IND application and in keeping with local legal and regulatory requirements.

9.1 Human Subjects and Informed Consent

It is the responsibility of the investigator to obtain written informed consent from each individual participating in this study after adequate explanation. The investigator must utilize an IRB or IEC approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative, the person obtaining consent and the investigator.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

9.2 Institutional Review Board/Independent Ethics Committee

This protocol, any amendments and any accompanying material to be provided to the subject (such as a consent form, diary, advertisements) will be submitted to a properly constituted IRB or IEC, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/IEC concerning the conduct of the study will be made in writing to the

investigator and a copy of this decision must be on file before starting the study or use of the material.

9.3 Obligations of the Investigator

The investigator will also ensure that the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to.

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. The investigator should ensure that all persons involved in the conduct of the study are qualified by education and training, informed about the protocol, protocol amendments, study procedures, and any study-related duties.

The investigator is also responsible for obtaining informed consent from each subject participating in the study in accordance with the regulations. Informed consent must be obtained from the subject before any screening procedure is undertaken that is not part of routine care. The investigator will also ensure that all subjects enrolled meet the eligibility as defined in the protocol. The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

All appendices attached hereto and referred to herein are made part of this study protocol. Any amendment to the study protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, except where necessary to eliminate an immediate hazard(s) to study subject. In some instances, an amendment may require a change to the consent form. The investigator must receive an IRB/IEC approval/favorable opinion concerning the revised consent form prior to implementation of the change. Any necessary amendments to the study protocol and/or consent form will be prepared by the sponsor and provided to the investigator for submission to the IRB. Refer to appendix B for a history of all the changes made to the study protocol.

9.4 Quality Assurance

The principal investigator(s) will ensure that the study will be appropriately monitored by ensuring that all the rights of the subjects are adequately protected, that the trial data are accurate, complete and verifiable from source documents and that the conduct of the trial is in compliance with the protocol and its subsequent amendments, with GCP and with applicable regulatory requirements. Accurate, consistent, and reliable data will be ensured through the use of standard GCP.

9.5 Study Documentation and Records Retention

Source data is all information, original records of clinical findings, observations, or other activities conducted as part of the study and are necessary for the reconstruction and evaluation of the study. Source data are contained in source documents such as hospital records, clinical and office charts, laboratory notes, subjects' diaries, pharmacy dispensing records. The minimum retention time will meet the strictest standard applicable to that site for the study, as

dictated by any institutional requirements or local laws or regulations, otherwise, the retention period will default to 15 years.

10. REFERENCES

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3. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347(13): 975-982.
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9. Zeuzem S, Dusheiko GM, Salupere R et al. Sofosbuvir + ribavirin for 12 or 24 weeks for patients with HCV genotype 2 or 3: the VALENCE trial. AASLD 2013 (abstract 1085).

11. APPENDICES

A. Schedule of Assessments

Procedure		Screening	BL	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 16	[1]Wk 20	[1]Wk 24	Post Wk 4	Post Wk 12	Post Wk 24	Early Term
Consent and HIPPA		X														
Medical History Review		X														
Inclusion/Exclusion Review		X	X													
Liver fibrosis assessment		X[2]														
Vitals[3]		X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X														X
Symptom Directed Physical Exam			X	X	X	X	X	X	X	X	X	X	X	X	X	
AE Collection			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP Study Drug Dispensing			X		X		X		X	X[5]	X					
IMP Study Drug Return and Accountability				X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance Assessment				X	X	X	X	X	X	X	X	X				
ECG		X								X[6]		X			X	X
Laboratory Assessments[7]	Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	CBC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	HCV Genotype, and HIV Testing	X														
	NS5A and NS5B	X								X[6]		X[5]				X

[1] Weeks 20 and 24 visits are for Group B subjects only.

[2] This entails obtaining documentation of results. See inclusion criteria.

[3] Vitals include weight, blood pressure, pulse, temperature and respiration rate.

[4] Height and BMI must also be performed.

[5] For Group B subjects only.

[6] For Group A subjects only.

[7] Screening laboratory results will be based on previously documented results as per inclusion/exclusion criteria. All subsequent labs will be done per standard of care.

Procedure		Screening	BL	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 16	[1]Wk 20	[1]Wk 24	Post Wk 4	Post Wk 12	Post Wk 24	Early Term
	gene resistance analysis[8]															
Serum or Urine HCG		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[8] Refer to section 7.2 on which analyses will be performed and on which subjects.

B. History of Protocol Changes

The following is a list of changes made to the study protocol from version 0 dated September 29, 2014 to version 1 dated October 29, 2014:

Protocol Section	Rationale for Change
Page 1	Updated the project title to reflect the revision in the study design (variation in the treatment duration). Subjects without cirrhosis will receive 12 weeks of DCV/SOF/RBV, while subjects with cirrhosis will receive 24 weeks of DCV/SOF/RBV.
Page 1	Updated the Central Study Site name for accuracy.
Page 1 and footer	Updated the version number.
Protocol Table of Contents	Updated to reflect new page numbers.
Section 2.6	Added the rationale for varying the duration of treatment depending on the presence of cirrhosis. Subjects without cirrhosis will receive 12 weeks of DCV/SOF/RBV, while subjects with cirrhosis will receive 24 weeks of DCV/SOF/RBV.
Sections 3.1 and 3.2	Updated the study's primary and secondary objectives in light of the variation of treatment duration, which will be dependent on the subject's cirrhosis status.
Section 4.1	Updated the study design overview to clarify that the subjects will be classified according to one of two groups: group A will include those without cirrhosis ("Non-cirrhotics") and group B will include those with cirrhosis ("Cirrhotics"). Since subjects with F3 will be classified under group A, the number of subjects anticipated in each group has been revised.
Section 4.2.1	Revised inclusion criterion 4 to indicate the amended cut-point for a subject to be classified as cirrhotic on Fibroscan.
Section 4.2.2	Added exclusion criterion 8. Subjects with prior exposure to NS5A will be excluded. The subsequent exclusion criteria numbering has been revised accordingly.
Section 4.2.3	Added the virologic breakthrough and its definition as a reason for discontinuing IMP.
Sections 5.1 and 5.2, 5.3.4 and 5.3.6	Updated and added the visit weeks/assessments/window for Group B subjects.
Section 8.1	Updated the groups to reflect the update in study design.
Appendix A	Revised to include the additions of study visits/assessment for subjects in Group who will be receiving treatment for 24 weeks instead of 12 weeks.
Appendix B	Added the list of changes made to the study protocol from version 0 dated September 29, 2014 to version 1 dated October 29, 2014

The following is a list of changes made to the study protocol from version 1 dated October 29, 2014 to version 2 dated October 31, 2014:

Protocol Section	Rationale for Change
Page 1	Updated the project title to reflect the revision in the study design. Only subjects with HCV genotype 3 and cirrhosis will be considered for the study. They will be randomized to two groups: Group A will receive 16 weeks of DCV/SOF/RBV, while subjects in Group B will receive 24 weeks of DCV/SOF/RBV.
Page 1 and footer	Updated the version number.
Protocol Table of Contents	Updated to reflect new page numbers.
Section 2.1, 2.6 and 2.7	Minor revisions to clarify that only cirrhotic subjects will be considered and that subjects will be randomized to receive either 16 weeks or 24 weeks of DCV/SOF/RBV.
Sections 3.1 and 3.2	Updated the study's primary and secondary objectives in light of the amended study design.
Section 4.1	Updated the study design overview to state that this is a randomized study. Only subjects with HCV genotype 3 who have cirrhosis will be considered. Randomization will be in a 1:1 ratio to either group A or group B. Group A subjects will receive 16 weeks of DCV/SOF/RBV, while Group B subjects will receive 24 weeks of DCV/SOF/RBV.
Section 4.2	Updated study population overview in light of the amended study design.
Section 4.2.1	Revised inclusion criterion 4 to indicate that only subjects with evidence of cirrhosis will be included.
Section 4.4	Added this section on randomization in light of the amended study design. All subsequent numbering has been updated accordingly.
Sections 5.1 and 5.2, 5.3.4 and 5.3.6	Updated the timing of various assessments in light of the treatment duration for groups A and B. Also, corrected a discrepancy between section 5.1 and the Appendix A on the schedule of pregnancy assessments.
Section 8 and 8.1	Revised to reflect the update in study design.
Appendix A	Updated assessment for subjects to correspond to section 5 of the protocol in light of the amended study design.
Appendix B	Added the list of changes made to the study protocol from version 1 dated October 29, 2014 to version 2 dated October 31, 2014

The following is a list of changes made to the study protocol from version 2 dated October 31, 2014 to version 3 dated November 17, 2014:

Protocol Section	Rationale for Change
Page 1 and footer	Updated the version number.

Page 1	Updated the Central Study Site name for accuracy.
Protocol Table of Contents	Updated to reflect new page numbers.
Section 4.2.2	Revised criterion 9 to indicate last use of a prohibited or restricted treatment.
Section 4.3.1	Added dosing information for standard of care Sofosbuvir and Ribavirin.
Section 4.3.2	Specified that IMP can be taken with or without food.
Section 4.5	Added information on the last use of a prohibited or restricted treatment and corrected a typographical error.
Sections 5.3.3, 5.3.4 and 5.3.8	Updated to accurately specify that laboratory testing will be done according to standard of care and appendix A.
Section 7.2	Added a sentence that dose adjustments and interruptions for NIMP (SOF/RBV) will be per standard of care. Also, added the resistance analysis plan.
Appendix A	Amended to include the planned resistance analysis plan.
Appendix B	Updated changes made to the protocol from version 0 to 1 and version 1 to 2 to specify that the footers were also revised from one version to the other. This was inadvertently previously not included in the tables. In addition, added the list of changes made to the study protocol from version 2 dated October 31, 2014 to version 3 dated November 17, 2014.

The following is a list of changes made to the study protocol from version 3 dated November 17, 2014 to version 4 dated December 16, 2014:

Protocol Section	**Rationale for Change**
Page 1 and footer	Updated the version number.
Protocol Table of Contents	Updated to reflect new page numbers.
Section 4.1	Updated to clearly state the total duration of subject participation for each study group.
Section 4.2.1	Amended inclusion criterion 1 to exclude legal representatives.
Section 4.2.2	Added exclusion criterion 1 (all others have been re-numbered accordingly) to state that subjects who lack capacity to consent for themselves will be excluded. Also, updated timeframe in exclusion 8 from 60 days to 8 weeks for consistency with screening window.
Section 5.3.2	Updated screening window to reflect it in weeks instead of days for clarity and consistency.
Section 8.1	Revised section title for accuracy and clarified that this is a small scale study.
Appendix B	Updated the changes made to Appendix B in the table of changes made from study protocol version 2 to 3 for accuracy. In addition, added the list of changes made to the study protocol from version 3 dated November 17, 2014 to version 4 dated December 16, 2014.

The following is a list of changes made to the study protocol from version 4 dated December 16, 2014 to version 5 dated January 7, 2015:

Protocol Section	Rationale for Change
Page 1 and footer	Updated the version number.
Protocol Table of Contents	Updated to reflect new page numbers.
Section 4.1	Corrected a typographical error to refer to the correct group.
Section 5.1	Deleted extra space.
Section 5.3.4	Clarified IMP study drug dispensing for both groups.
Section 7.2	Minor grammatical correction.
Appendix A	Corrected the following: • Week 16 footnote for ECG by adding footnote 6. All subsequent numbering of footnotes have been updated. • Weeks 16 and 24 footnotes for NS5A and NS5B gene resistance analysis. • Footnote 1 description.

The following is a list of changes made to the study protocol from version 5 dated January 7, 2015 to version 6 dated February 3, 2015:

Protocol Section	Rationale for Change
Page 1 and footer	Updated the version number.
Protocol Table of Contents	Updated to reflect new page numbers.
Section 4.5	Added amiodarone or any of its trade/brand names/formulas to the list of prohibited treatments.
Section 7.1	Added summary information on the adverse events reports regarding the use of amiodarone and DCV.

The following is a list of changes made to the study protocol from version 6 dated February 3, 2015 to version 7 dated September 5, 2015:

Protocol Section	Rationale for Change
Page 1 and footer	Updated the version number.
Page 1	Changed the study phase as the study drug has been approved by the U.S. FDA on July 24, 2015.
Protocol Table of Contents	Updated to reflect new page numbers.
Section 2.7	Added information on the approval of study drug by the U.S. FDA.
Section 4.2.2	Updated exclusion criterion # 6 for accuracy to exclude only subjects with decompensated cirrhosis and not those with stable cirrhosis.