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Title: All-Oral 12-Week Treatment With Daclatasvir Plus Sofosbuvir in Patients With Hepatitis C Virus Genotype 3 Infection: ALLY-3 Phase 3 Study

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List of abbreviations

HCV, hepatitis C virus; SVR12, sustained virologic response at posttreatment Week 12; APRI, aspartate aminotransferase to platelet ratio index; LLOQ, lower limit of quantitation; AE, adverse event; RAV, resistance-associated variant; INR, international normalized ratio.

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Abstract

Treatment options for patients with hepatitis C virus (HCV) genotype 3 infection are limited, with the currently approved all-oral regimens requiring 24-week treatment and the addition of ribavirin. This phase 3 study (ALLY-3; ClinicalTrials.gov NCT02032901) evaluated the 12-week regimen of daclatasvir (pangenotypic NS5A inhibitor) plus sofosbuvir (pangenotypic NS5B inhibitor) in patients infected with genotype 3. Patients were either treatment-naive (n=101) or treatment-experienced (n=51) and received daclatasvir 60 mg plus sofosbuvir 400 mg once daily for 12 weeks. Co-primary endpoints were the proportions of treatment-naive and treatment-experienced patients achieving a sustained virologic response at posttreatment Week 12 (SVR12). SVR12 rates were 90% (91/101) and 86% (44/51) in treatment-naive and treatment-experienced patients, respectively; no virologic breakthrough was observed, and ≥99% of patients had a virologic response at the end of treatment. SVR12 rates were higher in patients without cirrhosis (96% [105/109]) than in those with cirrhosis (63% [20/32]). Five of 7 patients who previously failed treatment with a sofosbuvir-containing regimen and 2 of 2 patients who previously failed treatment with an alisporivir-containing regimen achieved SVR12. Baseline characteristics, including gender, age, HCV RNA levels, and *IL28B* genotype, did not impact virologic outcome. Daclatasvir plus sofosbuvir was well tolerated; there were no adverse events leading to discontinuation and only 1 serious adverse event on-treatment, which was unrelated to study medications. The few treatment-emergent grade 3/4 laboratory abnormalities that were observed were transient. ***Conclusion:*** A 12-week regimen of daclatasvir plus sofosbuvir achieved SVR12 in 96% of patients with genotype 3 infection without cirrhosis and was well tolerated. Additional evaluation to optimize efficacy in genotype 3-infected patients with cirrhosis is underway.

Chronic infection with hepatitis C virus (HCV) genotype 3 is common throughout the world and remains a significant disease burden for many patients.[1, 2] Infection with HCV genotype 3 has been associated with an increased risk of progression to cirrhosis, as well as development of steatosis or hepatocellular carcinoma, compared with other HCV genotypes.[3-5] In an observational cohort study, analysis of real-world data from the Veterans Affairs HCV clinical registry found that the risks of cirrhosis, hepatocellular carcinoma, liver-related hospitalization, and death were significantly higher in genotype 3–infected patients compared with genotype 1–infected patients,[6] underscoring the medical need for safe and effective treatment options for patients with genotype 3 infection. Recent advances have led to the approval of interferon-free and/or ribavirin-free therapies for chronic infection with HCV genotypes 1, 2, 3, and 4. However, for both treatment-naive and treatment-experienced patients with genotype 3 infection, interferon- and ribavirin-free therapy options are currently limited.

Therapies approved in the United States and Europe for the treatment of genotype 3 infection include a 24-week, all-oral regimen of sofosbuvir (a pangenotypic NS5B inhibitor) in combination with ribavirin[7, 8] and a 24-week regimen of peginterferon plus ribavirin.[9, 10] In addition, a 12-week, interferon-based regimen of sofosbuvir plus peginterferon and ribavirin[8] is approved in Europe for treating genotype 3 infection, as are all-oral, 24-week regimens of daclatasvir (a potent, pangenotypic NS5A inhibitor) plus sofosbuvir with ribavirin[11] and ledipasvir (an NS5A inhibitor) plus sofosbuvir with ribavirin[12] for patients with compensated cirrhosis and/or prior treatment experience. The all-oral combination of sofosbuvir plus ribavirin requires 24 weeks of treatment because 12-week and 16-week treatment durations were associated with lower response rates (30%-61% and 62%, respectively) in genotype 3–infected patients.[7, 13, 14] With 24-week treatment, lower response rates were observed in genotype 3–infected patients who were treatment-experienced (77%), particularly those with cirrhosis (60%), compared with those who were treatment-naive (93%).[7, 15] In addition, there was an increased incidence of

anemia, which is consistent with the hemolytic anemia known to occur with ribavirin treatment.[15, 16] Thus, patients with genotype 3 infection have a need for improved treatment options, preferably with therapies of shorter duration and without the addition of peginterferon or ribavirin.

Daclatasvir was evaluated in combination with sofosbuvir in a phase 2 study.[17] Treatment for 24 weeks with daclatasvir plus sofosbuvir, with or without the addition of ribavirin, resulted in an 89% rate of sustained virologic response at posttreatment Week 12 (SVR12) among 18 treatment-naive patients with genotype 3 infection.[11, 17] Of 5 genotype 3–infected patients who had ≥F3 fibrosis (based on FibroTest scores), all 5 achieved SVR12.[11] In this phase 3 study, the efficacy and safety of 12-week, ribavirin-free treatment with daclatasvir plus sofosbuvir were evaluated in treatment-naive and treatment-experienced patients chronically infected with HCV genotype 3.

Experimental Procedures

Study Design and Patients

This was an open-label, two-cohort phase 3 study (ClinicalTrials.gov NCT02032901) of a 12-week regimen of daclatasvir plus sofosbuvir in genotype 3 infection. Eligible patients were men and women ≥18 years of age with chronic genotype 3 infection who were either treatment-naive or treatment-experienced and had HCV RNA levels ≥10,000 IU/mL at screening. Treatment-naive patients had no previous exposure to any interferon formulation, ribavirin, or any HCV direct-acting antiviral agent, whereas treatment-experienced patients received prior therapy with interferon alfa (with or without ribavirin), sofosbuvir plus ribavirin, or other anti-HCV agents, such as inhibitors of cyclophilin or microRNA. Patients who received prior therapy with NS5A inhibitors and those who previously discontinued treatment with sofosbuvir plus ribavirin prematurely due to intolerance (other than exacerbation of anemia) were excluded. All permitted

prior anti-HCV therapies must have been completed or discontinued at least 12 weeks prior to screening.

Patients with compensated cirrhosis were eligible (up to 50% in each cohort), with cirrhosis determined by liver biopsy (METAVIR F4) at any time prior to screening, FibroScan (>14.6 kPa) within 1 year of baseline (Day 1), or a FibroTest score ≥0.75 coupled with an aspartate aminotransferase to platelet ratio index (APRI) >2. Per the study protocol, FibroTest assessments (scores determined by BioPredictive) were performed during screening; a FibroTest score ≤0.74 corresponded to a fibrosis stage of F0 to F3, and a score >0.74 corresponded to a fibrosis stage of F4. Key patient exclusion criteria included chronic liver disease other than that related to HCV infection, infection with HCV genotypes other than genotype 3 or with mixed genotypes, coinfection with HIV or hepatitis B virus, documented or suspected hepatocellular carcinoma, or evidence of hepatic decompensation.

All patients received open-label treatment with daclatasvir 60 mg plus sofosbuvir 400 mg once daily for 12 weeks, with a subsequent 24-week follow-up. The study was conducted in accordance with the ethical principles that originated in the Declaration of Helsinki, and the study protocol was approved by the institutional review board or independent ethics committee at each study site. All patients provided written informed consent prior to participation in the study.

Study Assessments

Adherence to study treatment was assessed at each study visit based on tablet counts and dosing information recorded in patient diaries. HCV RNA levels were determined at baseline; on-treatment Weeks 1, 2, 4, 6, 8, and 12; and posttreatment Weeks 4, 12, and 24 using the COBAS TaqMan HCV test version 2.0 (Roche Molecular Systems, Pleasanton, CA), with a

lower limit of quantitation (LLOQ) of 25 IU/mL. HCV genotype or subtype was determined using the RealTime HCV genotype II assay (Abbott Molecular, Abbott Park, IL) and confirmed by viral sequence analysis. *IL28B* genotype (rs12979860 single-nucleotide polymorphism) was determined by polymerase chain reaction amplification and sequencing. Resistance testing was performed by population-based sequencing of plasma samples from all patients at baseline and from patients with virologic failure who had HCV RNA levels of ≥1000 IU/mL. Virologic failures included virologic breakthrough, defined as a confirmed, on-treatment HCV RNA increase of ≥1 $\log_{10}$ IU/mL from nadir or a confirmed HCV RNA measurement of ≥LLOQ following a previous measurement of <LLOQ; relapse, defined as a confirmed HCV RNA measurement of ≥LLOQ posttreatment following an undetectable HCV RNA measurement at the end of treatment; and HCV RNA measurement of ≥LLOQ at any time point not meeting the definition of virologic breakthrough or relapse. Safety and tolerability were assessed based on adverse event (AE) reporting, clinical laboratory tests, vital signs, and physical examinations.

Statistical analyses

The co-primary endpoints were the proportions of treatment-naive and treatment-experienced patients achieving SVR12 (defined as HCV RNA levels <LLOQ, either detectable or undetectable). Target sample sizes of 100 treatment-naive and 50 treatment-experienced patients would provide 95% CI for the observed SVR12 rates of within 9.7% and 14.2%, respectively, when the observed SVR12 rates were ≥75%. In the treatment-naive cohort, a target sample size of 100 patients would provide a 95% CI lower bound of >76% with an observed SVR12 rate of 85%. In the treatment-experienced cohort, a target sample size of 50 patients would provide a 95% CI lower bound of >73% with an observed SVR12 rate of 86%.

Secondary efficacy endpoints included the proportion of patients achieving HCV RNA levels <LLOQ, detectable or undetectable, at on-treatment Weeks 1, 2, 4, 6, and 8, the end of

treatment, and posttreatment Weeks 4 and 24; the proportion achieving HCV RNA levels <LLOQ, undetectable, at on-treatment Weeks 1, 2, 4, 6, and 8 and the end of treatment; and SVR12 rates by baseline cirrhosis status and *IL28B* genotype. Efficacy analyses included all patients who received ≥1 dose of study medications, and response rates and two-sided 95% exact binomial CI were estimated by cohort for efficacy endpoints.

Results

Patients

A total of 152 patients received ≥1 dose of study medications; of these, 101 (66%) were treatment-naive and 51 (34%) were treatment-experienced. Treatment-experienced patients included those who had previously failed treatment with interferon-based therapies or other anti-HCV therapies, including sofosbuvir- and alisporivir-containing regimens (Table 1). One hundred (99%) treatment-naive patients and all 51 (100%) treatment-experienced patients completed 12 weeks of treatment; 1 treatment-naive patient discontinued treatment after Week 8 due to pregnancy but achieved SVR12.

Overall, patients were 90% white and 59% male, with a median age of 55 years; the majority of patients had baseline HCV RNA levels of ≥800,000 IU/mL (71%) and a non-CC *IL28B* genotype (61%; Table 1). All patients were chronically infected with HCV genotype 3. Cirrhosis, as determined by liver biopsy, FibroScan, or FibroTest/APRI per protocol, was present in 21% of patients overall (treatment-naive, 19%; treatment-experienced, 25%). Fibrosis stage was also determined using FibroTest scores, based on which 119 (78%) patients had a fibrosis stage of F0 to F3 and 30 (20%) had a fibrosis stage of F4; FibroTest scores were not reported for 3 patients (all 3 achieved SVR12). Baseline albumin levels were similar in patients with cirrhosis (median 41 g/L, range 33-47) and without cirrhosis (median 44 g/L, range 36-53); baseline

platelet counts were lower in patients with cirrhosis (median 124.5 × 10^9/L, range 62-382) than in those without cirrhosis (median 200 × 10^9/L, range 89-334).

Virologic Response

Daclatasvir plus sofosbuvir for 12 weeks achieved SVR12 rates of 90% in treatment-naive patients and 86% in treatment-experienced patients with genotype 3 infection, with an overall SVR12 rate of 89% (Table 2). Rapid and sustained reductions from baseline in HCV RNA levels were observed, with mean decreases of 4.3 to 4.5 $\log_{10}$ IU/mL at on-treatment Week 1 and 4.7 to 4.9 $\log_{10}$ IU/mL at on-treatment Week 2. The proportion of patients achieving HCV RNA levels <LLOQ, detectable or undetectable, at early on-treatment time points in the treatment-naive and treatment-experienced cohorts, respectively, was 40% and 24% for Week 1, 77% and 69% for Week 2, and 94% and 98% for Week 4. HCV RNA levels were undetectable at the end of treatment in ≥99% of patients.

The relationship between virologic response at early on-treatment time points and achievement of SVR12 was assessed. SVR12 was achieved by 94% of patients with HCV RNA levels <LLOQ, detectable or undetectable, and 86% of patients with HCV RNA levels ≥LLOQ, at Week 1; 92% and 79% of patients with HCV RNA levels <LLOQ, detectable or undetectable, or ≥LLOQ, respectively, at Week 2 achieved SVR12. Among patients with HCV RNA levels <LLOQ, detectable or undetectable, at Week 4, 90% achieved SVR12 compared with 71% of patients with HCV RNA levels ≥LLOQ. When virologic response at Week 4 was assessed based on undetectable HCV RNA levels, the proportion of patients with a Week 4 response who achieved SVR12 was 91%.

Analysis of SVR12 in patient subgroups based on baseline characteristics showed no notable differences by gender, age, HCV RNA levels, or *IL28B* genotype (Figure 1). Among treatment-

experienced patients, SVR12 was achieved by 25 of 31 patients with previous relapse and by all 7 null responders, 2 partial responders, and 2 patients who experienced virologic breakthrough with prior treatment. In addition, all 6 patients who were intolerant of prior treatment achieved SVR12, as did 2 of 3 patients with other types of prior treatment failure (HCV RNA never undetectable on treatment or indeterminate). SVR12 was achieved in 5 of 7 patients who previously failed treatment with a sofosbuvir-containing regimen and in both patients who previously failed treatment with an alisporivir-containing regimen.

SVR12 rates were higher in patients without cirrhosis (96%) than in patients with cirrhosis (63%; Figure 2A), although high response rates at the end of treatment were seen both in patients with and without cirrhosis (97% and 100%, respectively). A similar trend was observed when SVR12 was analyzed by fibrosis stage, based on FibroTest scores, of F0 to F3 (93%) and F4 (70%; Figure 2B). Overall, results by cirrhosis status or by fibrosis stage based on FibroTest scores were generally consistent between the treatment-naive and treatment-experienced cohorts. Virologic response at early on-treatment time points did not appear to impact SVR12 rates in patients with cirrhosis, as the proportion of patients with cirrhosis who achieved SVR12 was the same among those who did or did not have undetectable HCV RNA levels at on-treatment Week 4 (10 of 16 patients with undetectable HCV RNA levels at Week 4 and 10 of 16 patients without undetectable HCV RNA levels at Week 4 achieved SVR12).

The relationship between resistance-associated variants (RAVs) at NS5A amino acid positions M28, A30, L31, and Y93 at baseline and SVR12 was assessed. No patients had L31 polymorphisms at baseline; one patient without cirrhosis had M28V at baseline and achieved SVR12. NS5A-A30 polymorphisms were detected in 14 of 147 patients at baseline. Of the 14 patients with A30 polymorphisms, 9 of 9 patients without cirrhosis and 1 of 5 with cirrhosis achieved SVR12. Among the 4 cirrhotic patients with baseline A30 polymorphisms who did not

achieve SVR12, 2 also had Y93H at baseline, 1 had A30T which has no effect on daclatasvir potency in vitro, and 1 had A30K which was associated with SVR12 in the 5 remaining patients with this polymorphism.[18] NS5A-Y93H was detected in 13 of 147 patients who had NS5A sequence at baseline; of these 13 patients, 6 of 9 patients without cirrhosis and 1 of 4 patients with cirrhosis achieved SVR12. No NS5B RAVs were detected at amino acid positions associated with resistance to sofosbuvir (159, 282, or 321) at baseline.

Virologic Failure

The occurrence of virologic failure was low, with no virologic breakthroughs observed (Table 2). One treatment-naive patient with cirrhosis had a quantifiable HCV RNA level of 53 IU/mL at the end of treatment; this event did not meet the protocol definition of virologic breakthrough, which required on-treatment confirmation of the HCV RNA measurement. The patient was a slow responder through Week 4 and had a low baseline platelet count (83×10^9 cells/L), reflecting advanced cirrhosis. Sixteen patients (9 treatment-naive and 7 treatment-experienced) had posttreatment relapse, of whom 11 (7 treatment-naive and 4 treatment-experienced) had cirrhosis at baseline. All of the relapses occurred by posttreatment Week 4 except for one, which occurred between posttreatment Week 4 and posttreatment Week 12 in a treatment-naive patient without cirrhosis. Factors that may have contributed to treatment failure in this patient included a very high baseline HCV RNA level (27.5×10^6 IU/mL), presence of the NS5A-Y93H RAV at baseline, and incomplete treatment adherence (93% adherent), although no relapses occurred among the other 4 patients who were not completely adherent to treatment (3 with 90%-95% adherence and 1, who discontinued after Week 8 due to pregnancy, with 66% adherence). The NS5A-Y93H RAV emerged in 9 of 16 patients with relapse; of the remaining 7 patients with relapse, 6 had NS5A-Y93H at baseline and 1 had emergent NS5A-L31I. NS5B RAVs at amino acid positions associated with resistance to sofosbuvir (159, 282, or 321) were not detected at relapse.

Safety and Tolerability

Daclatasvir plus sofosbuvir was well tolerated, with no AEs leading to discontinuation of treatment (Table 3). There were no deaths and only 1 serious AE was reported on-treatment: an event of gastrointestinal hemorrhage that was considered not related to study medications. The most common AEs (in >10% of patients) were headache, fatigue, and nausea, and the incidence of grade 3 AEs was low (2%), with no grade 4 AEs reported.

Few treatment-emergent grade 3/4 laboratory abnormalities were observed with daclatasvir plus sofosbuvir, with such events reported only for absolute lymphocytes, platelets, international normalized ratio (INR), and lipase. The incidences of these grade 3/4 laboratory abnormalities were low (≤2% each), and none led to clinically significant bleeding or pancreatitis, or to treatment discontinuation. Moreover, these abnormalities were primarily transient increases or decreases that were not present for prolonged periods during treatment. No treatment-emergent grade 3/4 abnormalities were observed in hemoglobin or liver-related parameters, including alanine and aspartate aminotransferase and total bilirubin.

Discussion

In patients chronically infected with HCV genotype 3, the all-oral, 12-week regimen of daclatasvir plus sofosbuvir achieved SVR12 rates of 90% in treatment-naive patients and 86% in treatment-experienced patients; SVR12 was achieved in 96% of patients without cirrhosis and in 63% of patients with cirrhosis. No virologic breakthroughs were observed, and all but 1 patient achieved a virologic response at the end of treatment. The combination of daclatasvir plus sofosbuvir was well tolerated, with a low incidence of serious AEs, no deaths or AEs leading to discontinuation, and few treatment-emergent grade 3/4 laboratory abnormalities. These results are generally consistent with those from a phase 2 study demonstrating the

efficacy and tolerability of daclatasvir plus sofosbuvir, with or without ribavirin, in patients with genotype 3 infection.[17] Overall, findings from the present study show that in genotype 3–infected patients without cirrhosis, a 12-week treatment with daclatasvir plus sofosbuvir is efficacious compared with the current 24-week, all-oral regimens containing ribavirin.

SVR12 rates were comparable across subgroups based on gender, age, baseline HCV RNA levels, and *IL28B* genotype. Notably, this study included patients who previously failed treatment with sofosbuvir- or alisporivir-containing regimens, of whom 71% and 100%, respectively, achieved SVR12. A limitation of the study is that the impact of race on SVR12 rates could not be fully assessed due to the high proportion of white patents enrolled (90% overall); however, all 6 of the black patients enrolled in the study achieved SVR12.

SVR12 rates with daclatasvir plus sofosbuvir were higher in patients without cirrhosis than in those with cirrhosis, and in patients with a fibrosis stage (based on FibroTest scores) of F0 to F3 than in those with F4. However, the 63% SVR12 rate in patients with cirrhosis is comparable to that achieved with 16 weeks (61%) or 24 weeks (67%) of sofosbuvir plus ribavirin, with the advantages of an interferon-free and shorter-duration regimen.[7] On-treatment and end-of-treatment response rates were similar in patients with or without cirrhosis, with relapse accounting for all but one of the treatment failures: among the 16 patients with relapse, 11 had cirrhosis. Relapse was more frequent in the 4 patients with cirrhosis who had Y93H RAVs at baseline, although these RAVs did not measurably affect on-treatment response. Other possible reasons for the higher relapse rate in genotype 3-infected patients with cirrhosis remain uncertain. Since high relapse rates have also been observed with other all-oral regimens following treatment of genotype 3 infection,[14,18] this HCV genotype may be more difficult than others to eradicate with direct-acting antivirals, particularly in patients with cirrhosis. Multiple factors may contribute to this effect and require further study.

The robust on-treatment virologic response with daclatasvir plus sofosbuvir, with nearly all virologic failures due to posttreatment relapse, suggests that optimizing treatment outcomes in patients with cirrhosis could include the addition of ribavirin or a longer treatment duration. A randomized study has been initiated (clinicaltrials.gov NCT02319031)[19] in which patients with genotype 3 infection and compensated advanced cirrhosis are receiving daclatasvir in combination with sofosbuvir and ribavirin for 12 or 16 weeks, with the objective of determining whether adding ribavirin and extending treatment will improve the durability of response posttreatment. This strategy has been successful with other all-oral regimens. A recent report regarding a phase 2 study of sofosbuvir plus GS-5816, with or without ribavirin, suggests that the addition of ribavirin improves response rates in genotype 3–infected patients with cirrhosis. In treatment-experienced patients with cirrhosis treated for 12 weeks, SVR12 rates were higher with sofosbuvir plus GS-5816 with the addition of ribavirin (85%-96%) than with sofosbuvir plus GS-5816 alone (58%-88%).[20] The combination of ledipasvir plus sofosbuvir with ribavirin for 12 weeks has been reported to provide SVR12 rates of 89% in genotype 3–infected, treatment-experienced patients without cirrhosis and a lower rate of 77% in those with cirrhosis.[21] Because daclatasvir has shown greater potency *in vitro* against genotype 3 compared with ledipasvir,[11, 22-24] the combination of daclatasvir plus sofosbuvir, with the addition of ribavirin, may be expected to provide improved response rates relative to the current results in patients with cirrhosis. Daclatasvir plus sofosbuvir, with or without ribavirin, is also being evaluated in additional patient populations with high unmet medical needs in other studies of the ALLY phase 3 program. These include patients who have cirrhosis or who are post–liver transplant (ALLY-1; ClinicalTrials.gov NCT02032875) and patients who are coinfected with HIV (ALLY-2; ClinicalTrials.gov NCT02032888). Daclatasvir has been approved in combination with other anti-HCV agents in Europe and Japan.

Daclatasvir plus sofosbuvir was associated with a favorable safety profile. Incidences of serious AEs and grade 3/4 AEs were low, and no deaths or AEs leading to discontinuation were reported. Few grade 3/4 laboratory abnormalities were reported, and the events that were observed were primarily transient changes and did not lead to treatment discontinuation. No grade 3/4 abnormalities in hemoglobin emerged during treatment, whereas previous studies have reported reductions in hemoglobin levels with the combination of sofosbuvir plus ribavirin.[14, 15] Overall, no notable safety concerns were observed with the combination of daclatasvir plus sofosbuvir.

In summary, a 12-week regimen of daclatasvir plus sofosbuvir achieved SVR12 in 96% of treatment-naive and experienced patients with genotype 3 infection without cirrhosis and was well tolerated. This regimen, without the addition of ribavirin and with a shorter treatment duration relative to currently approved all-oral regimens, demonstrated high SVR12 rates across patient subgroups, except in patients with cirrhosis and regardless of prior treatment response. These findings support the 12-week regimen of daclatasvir plus sofosbuvir as an efficacious and well tolerated treatment option. Additional evaluation to optimize efficacy in genotype 3-infected patients with cirrhosis is underway.[19]

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Conflicts of Interest

D.R.N. has received research support from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, and Merck. J.P.L. has received research support from Bristol-Myers Squibb. E.L. has received research support from AbbVie, Achillion Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Idenix Pharmaceuticals, Janssen, Merck, Novartis, Presidio Pharmaceuticals, Roche, Santaris Pharmaceuticals, Theravance, and Vertex Pharmaceuticals; served as an advisor or consultant for AbbVie, Achillion Pharmaceuticals, BioCryst Pharmaceuticals, Biotica, Bristol-Myers Squibb, Enanta Pharmaceuticals, Gilead Sciences, Idenix Pharmaceuticals, Janssen, Merck, Novartis, Santaris Pharmaceuticals, Regulus Therapeutics, Theravance, and Vertex Pharmaceuticals; and served as a speaker for AbbVie, Gilead Sciences, Janssen, Kadmon, Merck, and Vertex Pharmaceuticals. P.J.P. has received research support and personal fees from Janssen, Bristol-Myers Squibb, Gilead Sciences, AbbVie, and Merck. N.G. has received research support from and served as a speaker for Bristol-Myers Squibb. B.F.F. has received research support from Bristol-Myers Squibb. Z.H.Y. has received research support from Bristol-Myers Squibb, AbbVie, Gilead Sciences, Vertex Pharmaceuticals, Idenix Pharmaceuticals, Merck, and Janssen and served as a speaker for Vertex Pharmaceuticals. R.G. has received research support from Bristol-Myers Squibb, Vertex Pharmaceuticals, Janssen, Merck, Idenix Pharmaceuticals, Boehringer Ingelheim, Gilead, Salix Pharmaceuticals, Pfizer, Evoke Pharma, Debiopharm, Takeda, and AbbVie. P.J.T. has received research support from Gilead Sciences, Bristol-Myers Squibb, and AbbVie and served as a speaker for Gilead Sciences, AbbVie, and Onyx. M.R. has received research support from Bristol-Myers Squibb, AbbVie, Gilead Sciences, Merck, Janssen, and Vertex Pharmaceuticals. D.B. has received research support from Bristol-Myers Squibb and received research support and personal fees from Gilead Sciences, AbbVie, Merck, and Janssen. T.H. has received research support from Bristol-Myers Squibb and ViiV

Healthcare and received research support and personal fees from Gilead Sciences, AbbVie, and Janssen. N.R. has received research support from and served on an advisory board for Bristol-Myers Squibb. A.M.S. has received research support, personal fees, and nonfinancial support from Genentech, Vertex Pharmaceuticals, Gilead Sciences, and Janssen; research support and nonfinancial support from Bristol-Myers Squibb; and research support from Idenix Pharmaceuticals, Achillion Pharmaceuticals, Merck, and Hologic. P.V. has served as a speaker for AbbVie, Merck, and Forest Pharmaceuticals. K.V.K. has received research support and personal fees from Bristol-Myers Squibb, AbbVie, Gilead Sciences, and Merck; research support from Beckman, Boehringer Ingelheim, Ikaria, Intercept Pharmaceuticals, Janssen, Mochida Pharmaceutical, Novartis, and Vertex Pharmaceuticals; and personal fees from Achillion Pharmaceuticals and Trio Health. D.H., F.M., K.R., and E.A.H. are employees of Bristol-Myers Squibb. J.N.C., W.H., G.O., G.O.-L., and M.B. have no conflicts of interest to disclose.

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Figure Legends

Figure 1. Virologic Response by Baseline Characteristics

HCV, hepatitis C virus; LLOQ, lower limit of quantitation; SVR12, sustained virologic response at posttreatment Week 12.

[a] HCV RNA <LLOQ (25 IU/mL), detectable or undetectable; error bars reflect 95% CI.

Figure 2. Virologic Response in Patients With (A) Cirrhosis or (B) Fibrosis Stage of F4 (FibroTest)

APRI, aspartate aminotransferase to platelet ratio index; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; SVR12, sustained virologic response at posttreatment Week 12.

[a] HCV RNA <LLOQ (25 IU/mL), detectable or undetectable; error bars reflect 95% CI.

[b] Among 32 patients with cirrhosis, 11 (34%) had baseline platelet counts ≤100×10^9 cells/mL.

[c] Cirrhosis status determined in 141 patients by liver biopsy (METAVIR F4), FibroScan (>14.6 kPa), or FibroTest score ≥0.75 and APRI >2; for 11 patients, cirrhosis status was missing or inconclusive (FibroTest score >0.48 to <0.75 or APRI >1 to ≤2).

[d] Per the study protocol, FibroTest assessments were performed during screening (FibroTest scores not available for 3 treatment-naive patients); F0-F3 defined as FibroTest score of ≤0.74 and F4 defined as FibroTest score of >0.74.

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Table 1. Demographic and Baseline Disease Characteristics

Parameter	Treatment-Naive (N=101)	Treatment-Experienced[a] (N=51)
Age, median (range) years	53 (24-67)	58 (40-73)
Male, n (%)	58 (57)	32 (63)
Race, n (%)		
White	92 (91)	45 (88)
Black	4 (4)	2 (4)
Asian	5 (5)	2 (4)
Other	0	2 (4)[b]
Body mass index, mean kg/m^2 (SD)	26.55 (4.25)	28.22 (3.77)
HCV RNA level, n (%)[c]		
<800,000 IU/mL	31 (31)	13 (25)
≥800,000 IU/mL	70 (69)	38 (75)
IL28B genotype, n (%)		
CC	40 (40)	20 (39)

CT	47 (47)	21 (41)
TT	14 (14)	10 (20)
Cirrhosis, n (%)[d,e]	19 (19)	13 (25)
Fibrosis stage by FibroTest, n (%)[f]		
F0-F3	76 (75)	43 (84)
F4	22 (22)	8 (16)
Prior treatment category, n (%)		
Relapse	NA	31 (61)
Null response	NA	7 (14)
Partial response	NA	2 (4)
Other treatment failures[g]	NA	11 (22)

APRI, aspartate aminotransferase to platelet ratio index; HCV, hepatitis C virus; NA, not applicable.

[a] Includes patients who previously failed treatment with interferon-based therapies or other anti-HCV therapies, including sofosbuvir (n=7) and alisporivir (n=2).

[b] American Indian/Alaska native.

[c] All patients were infected with HCV genotype 3a.

[d] Cirrhosis was determined by liver biopsy (METAVIR F4; n=14), FibroScan (>14.6 kPa; n=11), or FibroTest score ≥0.75 and APRI >2 (n=7); for 11 patients, cirrhosis status was missing or inconclusive (FibroTest score >0.48 to <0.75 or APRI >1 to ≤2).

[e] Of the 32 patients with cirrhosis, 11 (34%) had baseline platelet counts of ≤100×10^9 cells/L.

[f] Per the study protocol, FibroTest assessments were performed during screening (FibroTest scores not available for 3 treatment-naive patients); F0-F3 defined as FibroTest score of ≤0.74 and F4 defined as FibroTest score of >0.74.

[g] Includes intolerance (n=6), breakthrough (n=2), HCV RNA never undetectable on treatment (n=2), and indeterminate (n=1).

Table 2. Virologic Response

Parameter	Treatment-Naive (N=101)	Treatment-Experienced (N=51)
SVR12, n (%) [95% CI][a]	91 (90) [83, 95]	44 (86) [74, 94]
On-treatment response, n (%) [95% CI]		
Week 1		
HCV RNA <LLOQ, detectable or undetectable	40 (40) [30, 50]	12 (24) [13, 37]
Week 2		
HCV RNA <LLOQ, detectable or undetectable	78 (77) [68, 85]	35 (69) [54, 81]
Week 4		
HCV RNA <LLOQ, detectable or undetectable	95 (94) [88, 98]	50 (98) [90, 100]
HCV RNA undetectable	64 (63) [53, 73]	37 (73) [58, 84]
End of treatment		
HCV RNA <LLOQ, detectable or undetectable	100 (99) [95, 100][b]	51 (100) [93, 100]
HCV RNA undetectable	100 (99) [95, 100][b]	51 (100) [93, 100]
Patients without SVR12		
Virologic breakthrough, n (%)[c]	0	0
Other on-treatment failure, n (%)	1 (1)[d]	0

Posttreatment relapse, n/N (%)[e,f]	9/100 (9)	7/51 (14)

HCV, hepatitis C virus; LLOQ, lower limit of quantitation; SVR12, sustained virologic response at posttreatment Week 12.

[a] HCV RNA <LLOQ (25 IU/mL), detectable or undetectable.

[b] One patient who discontinued after Week 8 (due to pregnancy) and achieved SVR12 was included in the number of patients achieving a virologic response at the end of treatment (n=100) but not at Week 12 (n=99).

[c] Defined as a confirmed HCV RNA increase from nadir of ≥1 $\log_{10}$ IU/mL on-treatment or a confirmed HCV RNA measurement of ≥LLOQ following a previous measurement of <LLOQ.

[d] One patient with cirrhosis who had a quantifiable HCV RNA level (53 IU/mL) at the end of treatment (did not meet the protocol definition of virologic breakthrough, which required on-treatment confirmation of the HCV RNA measurement).

[e] Defined as a confirmed HCV RNA measurement of ≥LLOQ posttreatment following an undetectable HCV RNA measurement at the end of treatment; percentages are based on the numbers of patients with undetectable HCV RNA at the end of treatment.

[f] Of the 16 patients with posttreatment relapse, 11 had cirrhosis at baseline; 1 relapse, in a treatment-naive patient without cirrhosis, occurred between posttreatment Week 4 and posttreatment Week 12.

Table 3. Safety and Tolerability

Parameter, n (%)[a]	All Patients (N=152)
Death	0
Serious adverse events	1 (1)[b]
Adverse events leading to discontinuation	0
Grade 3 adverse events	3 (2)[c]
Grade 4 adverse events	0
Adverse events in ≥5% of patients (all grades)	
Headache	30 (20)
Fatigue	29 (19)
Nausea	18 (12)
Diarrhea	13 (9)
Insomnia	9 (6)
Abdominal pain	8 (5)
Arthralgia	8 (5)
Grade 3/4 laboratory abnormalities[d]	
Hemoglobin <9.0 g/dL	0
Absolute neutrophils <0.75×10^9 cells/L	0
Absolute lymphocytes <0.5×10^9 cells/L	1 (1)
Platelets <50×10^9 cells/L	2 (1)
INR >2×ULN	2 (1)
Alanine aminotransferase >5×ULN	0
Aspartate aminotransferase >5×ULN	0
Total bilirubin >2.5×ULN	0

Lipase >3×ULN	3 (2)

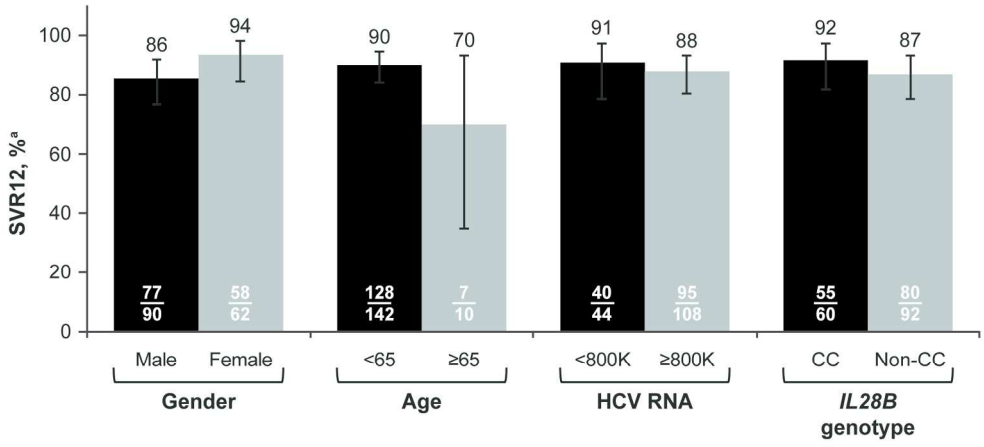
INR, international normalized ratio; ULN, upper limit of normal.

[a] On-treatment events for death and adverse events; treatment-emergent events for grade 3/4 laboratory abnormalities.

[b] One event of gastrointestinal hemorrhage at Week 2, considered not related to study treatment.

[c] Arthralgia in 1 patient; food poisoning, nausea, and vomiting in 1 patient; and serious adverse event of gastrointestinal hemorrhage in 1 patient.

[d] Primarily transient increases or decreases that were not present for prolonged periods during treatment.



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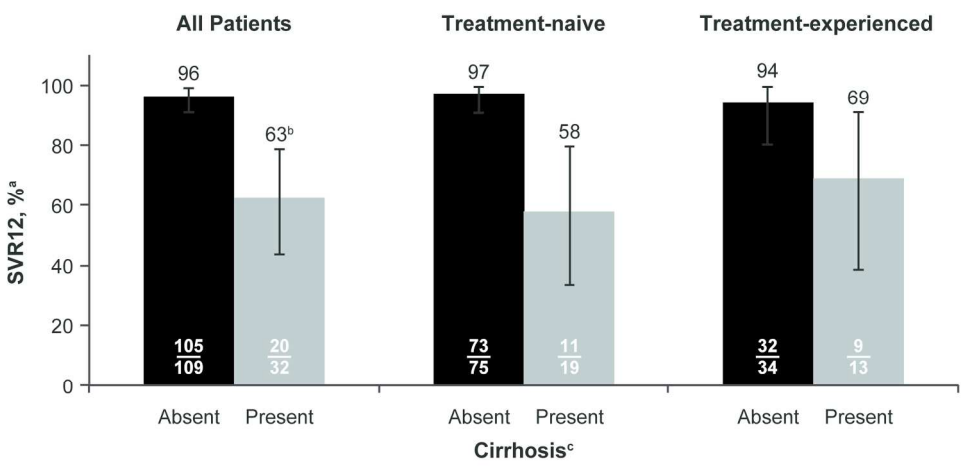

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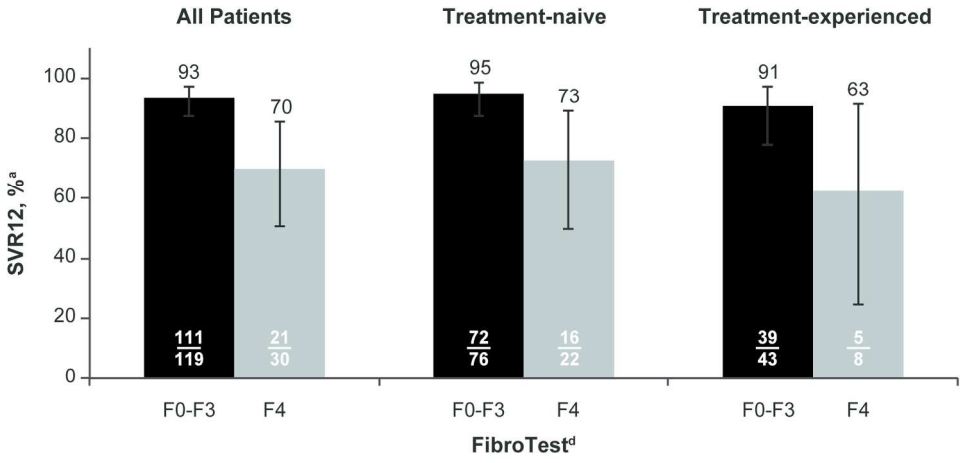

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Supplemental Material

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Clinical Protocol AI444218

A Phase 3 Evaluation of Daclatasvir and Sofosbuvir in Treatment Naïve and Treatment Experienced Subjects with Genotype 3 Chronic Hepatitis C Infection

Revised Protocol: 02
Incorporate Amendment: 03

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 02	15-May-2014	Incorporates Amendment 03
Amendment 03	15-May-2014	Adds interim analysis at SVR4, removes exclusion criteria for fertile men with pregnant partners, increases samples for resistance testing
Revised Protocol 01	19-Dec-2013	Incorporates Amendment 02
Amendment 02	19-Dec-2013	Removes the option for WOCBP to use hormonal contraceptives as a highly effective method of contraception
Original Protocol	25-Nov-2013	Not applicable

SYNOPSIS

Clinical Protocol AI444218

Protocol Title: **A** Phase 3 Evaluation of Daclatasvir and Sofosbuvir in Treatment Naïve and Treatment Experienced Subjects with Genotype 3 Chronic Hepatitis C Infection

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

- Daclatasvir (DCV): in tablet form at the dose 60 mg once daily, by mouth, for 12 weeks;
- Sofosbuvir (SOF): in tablet form at the dose 400 mg once daily, by mouth, for 12 weeks.

Study Phase: Phase III

Research Hypothesis:

Combination therapy with DCV and SOF for 12 weeks is safe and effective in treatment-naive or treatment-experienced subjects chronically infected with HCV GT3 based upon SVR12 (defined as HCV RNA < LLOQ [TND or TD] at post treatment Week 12).

Objectives:

Primary Objectives:

- To estimate the SVR12 rate, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12 in treatment-naive subjects treated with 12 weeks of DCV+SOF therapy.
- To estimate the SVR12 rate, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12 in treatment-experienced subjects treated with 12 weeks of DCV+SOF therapy.

Secondary Objective(s):

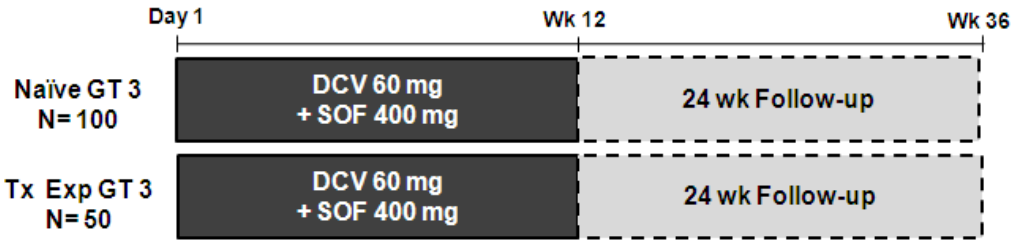
- To assess safety, as measured by the frequency of deaths, serious adverse events (SAE)s, discontinuation due to adverse events (AE)s, Grade 3/4 AEs and Grade 3/4 lab abnormalities observed from clinical laboratory testing.
- To assess antiviral activity, as measured by:
  - The proportion of subjects who achieve HCV RNA < LLOQ-TD/TND at each of the following Weeks: 1, 2, 4, 6, 8, 12 and EOT; post-treatment Week 4 and 24;
  - The proportion of subjects who achieve HCV RNA < LLOQ-TND at each of the following Weeks: 1, 2, 4, 6, 8, 12 and EOT;
- To assess antiviral activity by baseline cirrhosis (presence or absence) as measured by the proportion of subjects who achieve SVR12.
- To assess the relationship between efficacy and the rs12979860 single nucleotide polymorphisms (SNPs) in the IL28B gene.

Exploratory Objective(s)

- To describe genotypic substitutions associated with virologic failure for HCV.
- To explore the relationship between endpoints of safety and/or efficacy and exposure to DCV and/or possibly SOF and its metabolites when co-administered.
- To describe the pharmacokinetics of DCV when administered with SOF.
- To describe EQ-5D utilities at baseline, EOT, and post-treatment Week 24.

Study Design: Study Schematic

Figure -1: Study Schematic



Study Population:

Males and females ≥ 18 years of age who are treatment naive or treatment experienced and are infected with HCV Genotype 3 with a documented HCV RNA ≥ 10,000 IU/mL.

Study Assessments:

On-treatment visits will occur at Weeks 1, 2, 4, 6, 8, and 12. Following discontinuation or completion of therapy, safety will be assessed through the post-treatment Week 4 visit, while efficacy and/or resistance (through measurement of HCV RNA) will be assessed at post-treatment Weeks 4, 12, and 24 visits.

Discontinuation criteria are defined in the protocol.

Statistical Considerations:

Sample Size: The target sample sizes of 100 treatment naive subjects and 50 treatment experienced subjects provide 95% confidence that the observed SVR12 rate can be estimated to within 9.7% and 14.2% of the estimates respectively when the observed SVR12 rate is 75% or higher.

Endpoints:

Primary Endpoints

- Proportion of treatment naive subjects with SVR12, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12.
- Proportion of treatment experienced subjects with SVR12, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12.

Secondary Endpoints

- On treatment safety, as measured by frequency of SAEs, discontinuations due to AEs, Grade 3/4 AEs, and Grade 3/4 laboratory abnormalities through the end of treatment plus 7 days.
- The proportion of subjects who achieve HCV RNA < LLOQ-TD/TND at each of the following Weeks: 1, 2, 4, 6, 8, and 12; EOT; post-treatment Weeks 4 and 24 for each cohort.
- The proportion of subjects who achieve HCV RNA < LLOQ TND at each of the following Weeks: 1, 2, 4, 6, 8, and 12; EOT for each cohort.
- The proportion of subjects who achieve SVR12 (HCV RNA < LLOQ-TD/TND at post treatment week 12) by baseline cirrhosis (presence or absence) for each cohort.
- The proportion of subjects with CC or non-CC genotype at the IL28B rs12979860 single nucleotide polymorphisms (SNPs) who achieve SVR12 for each cohort.

Exploratory Endpoints

- Frequency of genotypic substitutions associated with virologic failure for HCV.
- Summary statistics of trough concentrations of DCV and possibly SOF; summary statistics of plasma concentrations of DCV and possibly SOF.
- Exposure-response analyses will explore the relationship between endpoints of safety and/or efficacy and exposure to DCV and/or possibly SOF and its metabolites.
- Summary statistics of the EQ-5D utilities at baseline, EOT and post-treatment Week 24 by cohort.

Analyses:

Results will be presented by cohort for treated subjects. Demographics, baseline characteristics and safety data will also be presented by cohort.

Categorical variables will be summarized using counts and percents. Continuous variables will be summarized with univariate statistics (eg, mean, median, standard deviation).

Longitudinal summaries of safety and efficacy endpoints will use pre-defined visit week windows. Windows around planned measurement times will be constructed based on the midpoint between planned study visits. Laboratory measures will be summarized using standard international values and units, and US units will be provided in the appendix.

On-treatment endpoints will be assessed using measurements from the start of study therapy through the last dose of study therapy plus 7 days. Follow-up endpoints will be assessed with measurements after the last dose of study therapy plus 7 days.

- **Schedule of Analyses:**
- An interim analysis will be performed after all subjects have completed post-treatment Week 4 (SVR4) (the analysis for the primary endpoint of SVR12 will not be performed at this interim analysis);
- The analysis for the primary endpoint will be performed after all subjects have completed post-treatment Week 12 (SVR12).
- The final analysis (SVR24) will be performed at study completion.

TABLE OF CONTENTS

1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

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, 3, 4]

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. Both regimens have demonstrated improved treatment outcomes compared with pegIFNα/ribavirin (RBV) and also offer potentially shorter duration of therapy (24 weeks vs. 48 weeks) for those patients who achieve rapid virologic responses (RVR).[5,6] However, both these agents must be administered with pegIFNα/RBV, and are therefore associated with the known adverse effects of the IFN/RBV backbone. In addition, each agent brings a unique adverse event profile which adds to the safety burden of pegIFNα/RBV limiting their widespread use. Furthermore, numerous drug interactions, emerging real-world safety in cirrhotic patients, the emergence of drug resistance in the setting of virologic failure, and the lack of activity in key HCV genotypes leave several populations with acutely high unmet medical need for improved therapies.

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. The absence of cross-resistance to the NS3 protease inhibitors also makes the combination DCV and SOF well suited to treat PI-failures. 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.

1.1.1 Infection with Genotype 3 HCV

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 south-east Asia and is variably distributed in different countries. For example GT3 is the predominant genotype in India, Pakistan and Brazil,[7,8,9] and accounts for > 30% cases in Australia, Greece, Poland, and Netherlands.[10,11,12,13,14] Compared with other genotypes, genotype 3 is associated with a higher incidence of hepatic steatosis and the rapid progression of liver fibrosis.[15] According to a recent meta-analysis, the odds ratio for the association of genotype 3 infection and accelerated progression of liver fibrosis was 1.52 in single biopsy studies suggesting faster fibrosis progression compared with other genotypes.[16] In a retrospective study of 353 patients, Nkontchou et al [17] showed that hepatitis C genotype 3 was associated with a higher incidence of hepatocellular carcinoma (HCC) in patients with ongoing cirrhosis. The observations that the HCV genotype 3 core protein induces steatosis support the hypothesis that GT-3 HCV infection may lead to oxidative stress and reactive oxygen species predisposing to carcinogenesis by inducing steatosis.[18,19,20]

Twenty-four weeks treatment with pegIFNα/RBV has been widely used for treating the patients with chronic genotype 2 and genotype 3 HCV infection. The treatment resulted in a sustained virologic response (SVR) in 70 to 85% of patients with HCV genotype (GT) 2 or 3 infection who had not received prior treatment and in 55 to 60% of those who had received treatment.[21,22,23,24] However, relatively lower rates of sustained response have been reported in HCV GT-3 infected patients compared to HCV GT-2 infected patients.[25] A meta-analyses was carried out on SVR data of 2275 patients treated with pegIFNα/RBV for 24 weeks in eight individual trials. The results showed SVR rates were 74% and 68% for GT-2 and GT-3 patients, respectively. Larger differences were observed among subjects with high baseline viral loads (HCV RNA > 600,000 IU/mL), in which SVR rate was 75% in HCV GT-2 infected patients compared to only 58% in HCV GT-3 infected patients[26] also showed pegIFNα-2b 1.5 μg/kg/wk plus RBV 800-1400 mg/d treatment for 24 weeks resulted in a SVR of 93% (39/42) in GT-2 subjects compared to a SVR of 79% (143/182) in GT-3 subjects. The reasons for lower SVR rates in GT-3 patients are not fully understood. It may due to the predisposition of fibrosis in these patients. As reported by Aghemo,[27] SVR was significantly higher in non-cirrhotic subjects compared to cirrhotic subjects who were infected with GT-3 HCV and were treated with pegIFNα/RBV (SVR 33% versus 79%). Higher rates of post-treatment relapse in cirrhotic subjects was the major reason for the difference (relapse rate was 61% and 12% in cirrhotic and non-cirrhotics respectively). By multivariate analysis, cirrhosis was an independent predictor of treatment failure in GT-3 patients. In addition, steatosis has also been identified as a negative predictor for achieving SVR in GT-2 or 3 infected patients. In the Zeuzem study,[26] lower SVR was observed in subjects with steatosis, defined as > 5% hepatocytes containing visible macrovesicular steatosis, compared to subjects without steatosis (SVR 74% vs. 89%). The multiple logistic regression analysis showed the steatosis status was a significant prognostic

factor for sustained response. Consistent with the findings in other studies, steatosis was more common in GT-3 HCV infected subjects compared to GT-2 infected subjects (44% vs. 14%). Stepwise logistic regression suggested GT-3 HCV infection was a factor significantly associated with steatosis status. In a cohort of 932 treatment-naive patients (study ACHIEVE-2/3), the investigators also showed that hepatic steatosis significantly increased the risk of relapse in the patients who were infected with HCV GT-3 and have achieved RVR with IFN-based treatment.[28] The higher relapse rate related to steatosis may due to the altered interferon signaling, increased intrahepatic RNA levels or increased quasispecies diversity.[28]

The treatment paradigm for chronic genotype-1 HCV infection has evolved very quickly since 2011 when the first two protease inhibitors, telaprevir and boceprevir received approval in the United States and later on in other regions. However, new drug development for the treatment of genotype 2/3 has not been as rapid, this is in part due to the perception that pegIFNα/RBV was already effective and because many of the first generation DAAs, such as the protease inhibitors telaprevir and boceprevir, lack of potent antiviral activity against HCV genotype 3 viruses. With the development of new DAA classes with broader and more potent antiviral activity, the future of genotype 3 therapy has the potential to improve. This promise has been demonstrated in three phase 3 studies investigating the all oral combination of NS5B nucleoside inhibitors, Sofosbuvir (SOF), and RBV(SOF/RBV) in various genotype 2 (GT-2) or genotype 3 (GT-3) HCV infected populations, including treatment naive population (FISSION), interferon intolerant / ineligible / unwilling population (POSITRON) and treatment experienced population (FUSION).[29,30] The results from all three studies demonstrated that SOF/RBV combination was efficacious as treatment of HCV GT-2 infection in various populations (SVR12 86%-97%), whereas SVRs were consistently lower in subjects infected with HCV GT- 3 (SVR12 30%-61%). In fact, in one study comparing SOF + RBV to pegIFNα/RBV control, SVR following treatment with SOF/RBV appeared inferior to control in subjects infected with HCV GT-3 (SVR12 56% in SOF/RBV arm vs. 63% in pegIFNα/RBV arm).[29] In addition, typical RBV-related hematological side effects cannot be avoided with these regimens. The incidence rate of anemia in SOF/RBV groups was 8%, 13% and 4%-11% in FISSION, POSITRON and FUSION respectively.[29, 30]Although the regimen of SOF plus RBV is anticipated to gain approval for the indication of treating GT-3 HCV infection in USA in light of its better tolerability and shorter treatment duration compared to pegIFNα/RBV, the efficacy of this regimen is far from satisfactory. The issue underlines the high unmet needs in the patients infected with GT-3 HCV for new pegIFNα/RBV sparing treatment with better efficacy and favorable tolerability.

1.1.2 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.[31]

Table 1.1.2-1: 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.[32]

Daclatasvir and sofosbuvir demonstrates activity as treating genotype 1-3 HCV infection (Study AI444040)

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. This study also included some subjects who had experienced virologic failure on or after treatment with therapy including BOC or TVR. The efficacy results are presented in Table 1.1.2-1.

Using a modified intent to treat (mITT) analysis approach, the SVR12 achieved in GT-1 infected treatment naive subjects who were treated with dual DCV and SOF therapy for 12 or 24 weeks was 98.4% (124/126). Two subjects did not present for their SVR12 visits and were counted as treatment failures. In the group of GT-1 PI-failures who were retreated with DCV plus SOF with or without RBV for 24 weeks, the SVR12 was 97.6% (40/41); one subject missed their SVR12 visit but returned to the clinic and demonstrated undetectable HCV RNA. Thus, there were no confirmed treatment failures among 167 GT-1 infected subjects. The overall SVR12 in GT-2/3 infected subjects (n = 44) following 24 weeks of treatment was 90.9% (40/44). Two of the 4 subjects who did not achieve SVR12 were treated by lead-in SOF monotherapy for 7 days followed by DCV and SOF combination therapy for 23 weeks. One had virologic breakthrough and one had relapse. The other two subjects not achieving SVR12 were treated by DCV and SOF plus RBV combination for 24 weeks. Both of them missed the visit and were counted as failures. One later returned and demonstrated SVR24. The other one was lost to follow-up after treatment week 18. The last on-treatment HCV RNA level available (Week 14) was < LLOQ-TND. The treatment response was not influenced by HCV genotype or subtype (GT-1a/1b), IL28B genotype, or RBV use. 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.[33,34]

Table 1.1.2-2: Summary of Efficacy Results for Study AI444040

Treatment group	Patient population	Treatment regimen	Treatment duration	Efficacy results % (N achieving endpoint/N treated)
A	GT-1a,-1b naive	SOF 400 mg QD Lead in for 7 days then add DCV 60 mg QD	24 weeks	SVR 12 100% (15/15)
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)
C	GT-1a,-1b naive	SOF 400 mg QD + DCV 60 mg QD	24 weeks	SVR 12 100% (14/14)
D	GT-2, -3 naive	SOF 400 mg QD + DCV 60 mg QD	24 weeks	SVR 12 100% (14/14)

Table 1.1.2-2: Summary of Efficacy Results for Study AI444040				
Treatment group	**Patient population**	**Treatment regimen**	**Treatment duration**	**Efficacy results % (N achieving endpoint/N treated)**
E	GT-1a,-1b naive	SOF 400 mg QD + DCV 60 mg QD+RBV	24 weeks	SVR 12 100% (15/15)
F	GT-2,-3 naive	SOF 400 mg QD + DCV 60 mg QD + RBV	24 weeks	SVR 24 86% (12/14)
G	GT-1a,-1b naive	SOF 400 mg QD + DCV 60 mg QD	12 weeks	SVR 12 100% (41/41)
H	GT-1a, 1b naive	SOF 400 mg QD + DCV 60 mg QD + RBV	12 weeks	SVR 12 95% (39/41)
I	GT-1a,1b PI-failure	SOF 400 mg QD + DCV 60 mg QD	24 weeks	SVR 12 100% (21/21)
J	GT-1a,-1b PI-failure	SOF 400 mg QD + DCV 60 mg QD + RBV	24 weeks	SVR 12 95% (19/20)

Addition of the NS5A inhibitor, ledipasvir (LDV), to SOF confirms the NS5A/NS5B inhibitor paradigm : Results of the LONESTAR study (Gilead)

The LONESTAR study treated naive and protease-inhibitor (PI) failure subjects for 8 or 12 weeks with the DAA combination of LDV/SOF and provide additional confirmation that the combination of a potent NS5A inhibitor and NS5B nucleotide inhibitor is a highly effective and tolerable treatment paradigm. Further, half of the PI-failure subjects had documented compensated cirrhosis. Almost all subjects achieved either SVR4 or SVR8 based on this interim analysis.[35] The results are summarized in the Table 1.1.2-3.

Table 1.1.2-3: Summary of Efficacy Results of the LONESTAR Study				
Treatment	**Duration**	**GT-1 Population**	**Efficacy Results**	
SOF + ledipasvir	8 Weeks	Naive	SVR8	19/20 (95%)
SOF + ledipasvir + RBV	8 Weeks	Naive	SVR8	21/21 (100%)
SOF + ledipasvir	12 Weeks	Naive	SVR4	19/19 (100%)
SOF + ledipasvir	12 Weeks	PI-exp	SVR4	18/19 (95%)
SOF + ledipasvir + RBV	12 Weeks	PI-exp	SVR4	20/21 (95%)

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, following as little as 12 weeks of treatment. Thus, this regimen offers a significant improvement in the

tolerability and supports further investigation of the combination of DCV and SOF regimens especially in the patients with highest unmet medical needs.

1.1.3 Rationale for Study Design

This study is designed to evaluate the safety and efficacy of the combination of DCV+SOF in subjects infected with Genotype-3 HCV including treatment experienced subjects. The rationale for studying this combination in this population is described below.

1.1.3.1 Rationale for use of DCV and SOF in patients infected with GT-3 HCV

Given the higher risk of disease progression compared to other genotypes, patients with chronic GT-3 HCV infection represent a population with high unmet medical need. However, the efficacy and safety profile with the current standard of care (pegIFNα/RBV) is greatly limited by adverse events and the SVR rate can be greatly improved. New DAA-based treatments that may be available in near future (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.

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.[17, 18]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. Replacement of RBV with potent DAAs is anticipated to eliminate the impact of these negative factors. This possibility is supported by the data from the LONESTAR study, in which half of participants had cirrhosis at baseline and 97% (97/100) achieved SVR12 after 8-12 weeks treatment with SOF plus ledipasvir, another NS5A inhibitor.

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.[32, 36] 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.

The combination of DCV and SOF has been demonstrated as a regimen with the potential for enhanced efficacy and tolerability that does not require the administration of interferon or RBV. More than 200 subjects infected with HCV GT-1, -2 or -3 have received DCV and SOF combination therapy for 12 week to 24 weeks in study AI444040. The result showed that without IFN, the once-daily combination of DCV plus SOF was very potent with or without RBV, providing high efficacy with across different HCV genotypes. SVR12 was achieved in 98% (166/167) of GT-1 HCV infected patients who were treatment naive or failed previous PI treatment and in 90.9% (40/44) of GT-2/3 HCV infected subjects who were treatment naive, with only two confirmed treatment failures in subjects receiving SOF lead-in regimen. DCV and SOF combination regimen was also well tolerated. Most AEs were mild or moderate and did not lead to treatment discontinuation. There were no cases of pDILI (potential drug induced liver injury) reported in AI444040. So far, more than 6000 subjects and more than 3100 subjects have been exposed to DCV and SOF respectively in clinical studies, no safety signal has been identified to be specific to DCV or SOF.

1.1.3.2 Rationale for Treatment of Cirrhotics

Available evidence suggests the combination of DCV+SOF will have significant antiviral activity and efficacy in cirrhotic patients.

The importance of cirrhosis as a predictor of SVR

Cirrhosis is a known negative predictor of SVR in patients treated with pegIFNα/RBV based regimen. Recently, lower SVRs were also reported in cirrhotic patients treated with IFN-free regimens. For example, in the FISSION study,[37] the combination of SOF and the weak antiviral RBV for 12 weeks resulted in 56% SVR12 in GT-3 treatment-naive patients with a large difference between non-cirrhotic patients and cirrhotic patients (61% in non-cirrhotic vs. 34% in cirrhotic). A similar yet less dramatic difference in SVR was also observed between GT-2 infected non-cirrhotic and cirrhotic patients (98% in non cirrhotic vs. 91% in cirrhotic). Similar results were observed in the POSITRON study.[38] The weak potency of RBV may contribute to the difference of SVR between non-cirrhotic and cirrhotic patients when multiple negative predictors are involved, eg GT-3 infection, cirrhosis etc. Replacement of RBV with potent DAAs would be predicted to further increase sustained responses and reduce or eliminate the difference in SVR between non-cirrhotic and cirrhotic patients. This possibility is supported by the data from the LONESTAR study discussed previously.

No dose adjustment is required for DCV or SOF in subjects with hepatic impairment

BMS Study AI444013 examined the exposure of DCV in non-HCV infected individuals with hepatic impairment. In this study, a total of 18 hepatically impaired non-HCV-infected subjects were dosed with DCV; 6 subjects each in Child Pugh class A (mild), B (moderate), and C (severe). Twelve healthy volunteers were dosed as a control group. Results demonstrated that subjects with mild, moderate or severe hepatic impairment did not have clinically significant differences in free drug concentrations of DCV when compared to subjects with normal hepatic function. The study concluded that no dose adjustment of DCV is required in subjects with hepatic impairment.

SOF was evaluated in HCV-infected subjects with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment after administration of SOF 400 mg for 7 days. SOF mean plasma exposure parameters (AUC_{tau} and C_{max}) were similar in subjects with moderate or severe hepatic impairment and were modestly higher than those achieved in subjects with normal hepatic function. Based on these PK results, it was concluded that no dose adjustment of SOF 400 mg is recommended in subjects with hepatic impairment.

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 pegIFN α/RBV and as part of dual combination of DCV and asunaprevir (ASV).

There were no clear differences in response between non-cirrhotic and cirrhotic subjects in BMS Study AI444010. This is a Phase 2b study that examined DCV (20 mg or 60 mg) with pegIFNα/RBV compared to pegIFNα/RBV alone in treatment-naive patients with GT-1 and GT-4 infection. Analyses of SVR12 by baseline cirrhosis status (present or absent) were limited due to small sample size for cirrhotic subgroup. However, according to available data, In the DCV 20 mg pegIFNα/RBV arm, SVR12 was 54.5% (73/134) in non-cirrhotic patients compared to 53.8% (7/13) in cirrhotic patients. Similarly, in DCV 60mg pegIFNα/RBV arm, the SVR12 was 53.3% (73/137) in non-cirrhotic patients compared to 75% (6/8) in cirrhotic patients.

Similarly, no clear difference in response was observed between non-cirrhotic and cirrhotic subjects treated with IFN and RBV free combinations such as DCV in combination plus ASV (DUAL). BMS Study AI447026 is an ongoing Phase 3 study investigating the DUAL therapy of DCV plus ASV in combination alone in Japanese subjects infected with HCV GT-1b who had either previously failed treatment with pegIFNα/RBV or were otherwise intolerant or ineligible for IFN-based therapy. Preliminary data showed that SVR12 following 24 weeks of DUAL treatment was 85% (170/200) in non-cirrhotics compared to 91% (20/22) in cirrhotics.

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.

Ledipasvir and Sofosbuvir demonstrates efficacy in cirrhotic patients

As observed in the LONESTAR study, 95% (38/40) SVR4 was achieved in the GT-1 HCV infected patients who had previously failed therapy with an HCV-specific PI-based regimen and were treated by a 12-week course of the fixed-dose combination of SOF and ledipasvir with or without RBV. Half of these treatment-experienced patients had documented, compensated cirrhosis and almost all achieved SVR4. In addition, there was no on-treatment failure or resistance that was detected in the subjects treated with the combination of SOF and ledipasvir with or without RBV so far.

Based upon these data, BMS concludes that the combination of DCV and SOF will provide significant antiviral activity and efficacy in cirrhotic patients infected with HCV.

1.1.3.3 Rationale for Dose Selection

Dose Selection for DCV 60 mg

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.

Dose Selection for SOF 400 mg

The SOF dose selected for study AI444218 is 400 mg QD, which is the dose currently being evaluated in current BMS sponsored DCV/SOF Phase 3 studies. Available data supporting the 400 mg dose include:

- Lack of identified dose-limiting toxicity in studies conducted to date with single doses up to 1200 mg. At this dose in healthy subjects there was no effect of SOF on QTc and therefore, the potential to induce clinically meaningful QT prolongation is considered low;
- Greater initial antiviral activity observed as early as Day 3 with 200 mg and 400 mg QD compared to the 100 mg QD dose in both 3-day monotherapy and in the 28-day study in combination with pegIFNα/RBV.

In the Phase 2a study investigating 28-day combination of SOF and pegIFNα/RBV, more rapid suppression to below the limit of detection and slightly higher RVR rates at Week 4 were

observed in 200 mg and 400 mg QD dose groups. In addition, a greater proportion of patients who achieved an RVR demonstrated continued suppression of HCV RNA following discontinuation of SOF in the 200 mg and 400 mg QD dose groups; No clinically relevant difference in the safety and tolerability profile of the SOF treatment groups as compared to the placebo/pegIFNα/RBV group.

SOF 400 mg containing regimens, including combination with pegIFNα/RBV or other direct antiviral agents, have been or are being investigated in multiple Phase 2 and Phase 3 studies. High rates of sustained virological response were observed across various populations with different genotypes or treatment experience. Thus far, no safety signal is reported to be specifically related to SOF.

The results from in study AI444040 showed the treatment of SOF 400 mg in combination with DCV 60 mg for 12 or 24 weeks achieved high SVR in treatment-naive GT-1, -2, and -3 subjects with a favorable safety profile.

Therefore, based on the safety and efficacy of the 400 mg SOF observed in these studies, this dose will be used for this study.

1.1.3.4 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.

There are several IFN-free regimens that confirm that high SVRs can be achieved in HCV-infected patients after 12 weeks of treatment. These include study AI444040, LONESTAR, and the AVIATOR study (AbbVie).[39] Data from the two former studies have been described in previous sections and indicate that 12 weeks of treatment with a highly potent combination of DAAs will deliver very high rates of SVRs in most patients. The latter study provides further support that potent DAA combinations, including those without a nucleotide NS5B inhibitor can achieve high SVR after 12 weeks of treatment.

In the AVIATOR study, the IFN-free regimens of ABT-450/ritonavir(r) (HCV NS3/4A PI with ritonavir booster), ABT-267 (NS5A inhibitor), ABT-333 (NS5b inhibitor) with or without RBV were investigated in GT-1 treatment-naive subjects and pegIFNα/RBV null responders. After 12 weeks of treatment with ABT-450/ABT-267/ABT-333/r with or without RBV, there were 87% who achieved SVR with ABT-450/ABT-267/ABT-333/r only and 96% following treatment with three ABT-450/ABT-267/ABT-333/r and RBV in treatment-naive subjects. In pegIFNα/RBV null responders, there were 93% who achieved SVR with ABT-450/ABT-267/ABT-333/r and RBV. In addition, a very high SVR24 (88%) was also observed in treatment-naive subjects who were treated with ABT-450/ABT-267/ABT-333/r and RBV for 8 weeks.

Additional 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. This is supported by the data recently reported by Osinusi.[40] In the Osinusi study,[40] 50 HCV GT-1 infected treatment naive subjects with all stages of liver fibrosis were randomized 1:1 to receive 400 mg of sofosbuvir with either weight-based or low-dose ribavirin for 24 weeks. 7 subjects (28%) in the weight-based group and 10 (40%) in the low-dose group relapsed after treatment completion leading to SVR24 rates of 68% in the weight-based group and 48% in the low-dose group. The pharmacokinetic-viral kinetic sub-study demonstrated a slower loss of infectious virus in relapsers than in participants who achieved SVR (clearance, 3.57/d vs. 5.60/d; P = 009).[40] 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. Replacement of RBV with the potent antiviral DCV would be predicted to provide more rapid and intensive viral suppression and enhanced viral clearance. This hypothesis is supported by the data from the LONESTAR study where LDV was combined with SOF in HCV GT1 patients with underlying cirrhosis as well as the high SVR rates following treatment of HCV GT3 with DCV and SOF in study AI444040.

In summary, we conclude that the combination of DCV and SOF is likely to have a high rate of SVR following 12 weeks of treatment in patients infected with GT-3 HCV.

1.2 Research Hypothesis

Combination therapy with DCV and SOF for 12 weeks is safe and effective in treatment-naive or treatment-experienced subjects chronically infected with HCV GT3 based upon SVR12 (defined as HCV RNA < LLOQ [TND or TD] at post treatment Week 12).

1.3 Objectives(s)

1.3.1 Primary Objectives

- To estimate the SVR12 rate, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12 in treatment-naive subjects treated with 12 weeks of DCV+SOF therapy.
- To estimate the SVR12 rate, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12 in treatment-experienced subjects treated with 12 weeks of DCV+SOF therapy.

1.3.2 Secondary Objectives

- To assess safety, as measured by the frequency of deaths, serious adverse events (SAE)s, discontinuation due to adverse events (AE)s, Grade 3/4 AEs and Grade 3/4 lab abnormalities observed from clinical laboratory testing.
- To assess antiviral activity, as measured by
  - The proportion of subjects who achieve HCV RNA < LLOQ-TD/TND at each of the following Weeks: 1, 2, 4, 6, 8, 12, and EOT; post-treatment Week 4 and 24.
  - The proportion of subjects who achieve HCV RNA < LLOQ-TND at each of the following Weeks: 1, 2, 4, 6, 8, 12 and EOT;

- To assess antiviral activity by baseline cirrhosis (presence or absence) as measured by the proportion of subjects who achieve SVR12.
- To assess the relationship between efficacy and the rs12979860 single nucleotide polymorphisms (SNPs) in the IL28B gene

1.3.3 Exploratory Objectives

- To describe genotypic substitutions associated with virologic failure for HCV
- To explore the relationship between endpoints of safety and/or efficacy and exposure to DCV and/or possibly SOF and its metabolites when co-administered
- To describe the pharmacokinetics of DCV (total and unbound) when administered with SOF
- To describe EQ-5D utilities at baseline, EOT, and post-treatment Week 24

1.4 Product Development Background

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)

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. (Refer to Section 1.1.2 for more details).

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[33] 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 in Table 1.4-1.

Table 1.4-1: 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%

Table 1.4-1: 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
FUSION	GT-2, -3 treatment - experienced	SOF + RBV for 12 weeks or	50%	86%	30%
		SOF + RBV for 16 weeks	73%	94%	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.[32,36] 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.

1.4.1 Safety of DCV and SOF

1.4.1.1 Safety of 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/pegIFNα/RBV, DCV/ASV Dual, DCV/ASV/pegIFNα/RBV 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/pegIFNα/RBV [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 ($\geq 0.6 \times 10^3$ 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.

1.4.1.2 Safety of SOF

Thus far, more than 3300 subjects with HCV infection have been dosed with SOF in ongoing or completed clinical efficacy studies.

Clinical pharmacology studies have been completed or are ongoing in subjects with renal or hepatic impairment, transplant patients, subjects on methadone maintenance therapy, subjects taking oral contraceptives, subjects who are coinfected with HIV and HCV, and healthy Japanese subjects. Clinical efficacy studies have been completed or are being conducted in subject populations with chronic GT-1-6, including HCV infection of indeterminate genotpyes

Across clinical studies, SOF + pegIFNα/RBV and SOF+RBV regimens were generally safe and well tolerated. Other than the expected AEs and laboratory abnormalities associated with RBV, the SOF+RBV for up to 24 weeks had a safety profile similar to that of placebo. Most AEs were mild to moderate. Severe and serious AEs were uncommon with SOF-based treatment and there were no consistent trends in type or timing of these events other than what would be expected with RBV with or without pegIFNα.

The proportion of patients who permanently discontinued treatment with SOF due to adverse events was low in all SOF-containing regimens. In the SOF+RBV groups, AEs leading to permanent discontinuation of SOF+RBV occurred in 1% of patients while in the SOF + pegIFNα/RBV group, AEs leading to treatment discontinuation occurred in 2% of patients.

1.4.2 PK interaction

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.

1.5 Overall Risk/Benefit Assessment

Thus far, more than 6000 subjects and more than 3300 subjects with HCV infection have been randomized and exposed to DCV and SOF, respectively, in ongoing or completed clinical efficacy studies. The consistently high efficacy was observed when DCV or SOF was investigated in combination with pegIFNα/RBV or other DAAs. The safety profile of DCV and SOF are favorable and the drugs remain well tolerated. In the 4 registrational Phase 3 studies (three were conducted in GT-2 and GT-3 subjects), adverse reactions of SOF+RBV and SOF and pegIFNα/RBV were consistent with the safety profile of RBV and pegIFNα/RBV. Based on nonclinical and clinical studies, especially in study AI444040, no clinically reported safety risk was identified for DCV or SOF. However, the following general potential risks should be considered:

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 pegIFNα/RBV.

Most common AEs with SOF

No AEs or clinical laboratory abnormalities directly attributable to SOF are identified. The most common AEs reported in the registrational studies were fatigue, headache, nausea, insomnia and anemia. These AEs are consistent with those observed with pegIFNα/RBV treatment when SOF was given with pegIFNα and RBV.

Development of Resistance

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. [37]

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 pegIFNα/RBV) 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.

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 pegIFNα/RBV
- Convenient once daily dosing schedule and low pill burden

In summary, BMS concludes that 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 pegIFNα/RBV side effects. Thus, this pegIFNα/RBV 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.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC’s written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject’s legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects’ signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

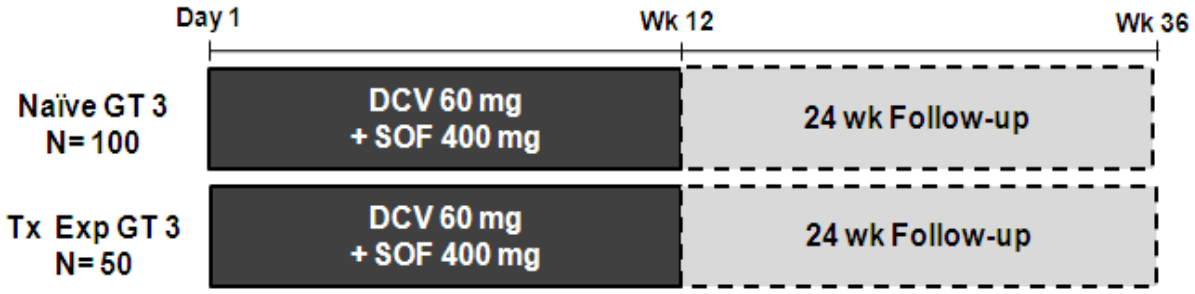
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

Study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



AI444218 is an open label, two cohort trial evaluating the combination therapy of DCV and SOF for 12 weeks duration in GT-3 subjects.

The study will include a total of approximately 150 treated subjects, with approximately 100 treatment-naive subjects and approximately 50 treatment-experienced subjects. The subject population will be HCV treatment-naive and treatment-experienced subjects chronically infected with HCV GT-3 infection with or without cirrhosis (up to 50% cirrhotics will be allowed). Subjects who have been previously treated with SOF may also be permitted.

Subjects will receive 60 mg DCV QD + 400 mg SOF QD administered for 12 weeks.

As an open label study, HCV RNA will be available for review by the subject and clinical site personal. Study duration will be a maximum of 36 weeks (12 weeks therapy + 24 weeks follow-up). Any subject who discontinues therapy before the protocol-defined treatment duration should have 24 weeks of post-treatment follow up.

Any subject who receives anti-HCV therapy in the post-treatment period prior to Week 4 (ie, a subject who discontinued therapy due to an AE or virologic failure, who then chooses to receive an alternative therapy outside of the study), should discontinue from the study after completing the post-treatment Week 4 safety visit (see Table 5.1-3). If the subject receives HCV therapy after post treatment Week 4, the subject should be discontinued from the study as soon as possible, following completion of the procedures outlined in the Post-treatment Week 24 visit.

The end of the study is defined as the date of the last visit for the last subject to complete the study. The last visit is defined as the last post-treatment follow up subject visit. Following completion of the follow-up period of the study, select subjects at selected sites may be asked to

enroll into a separate observational study for an additional 3-year follow up to assess long-term SVR, natural history of HCV resistance, and liver-related complications. It is not a requirement for all subjects to enroll into the long term follow-up, and this option may not be available.

3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to supply study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

No rescue therapy (the addition of pegIFNα/RBV following identification of viral breakthrough) will be offered in this study and a post-study drug program is not anticipated for any molecules within this HCV program.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Before any program procedures are performed, the details of the program will be described to the patient and the patient will be given a written informed consent document to read. If the patient agrees to participate in the program, consent will be indicated by signing and dating of the informed consent document in the presence of program personnel.

2. Target Population

a) Subjects must be able to understand and agree to comply with the prescribed dosing regimens and procedures, report for regularly scheduled study visits, and reliably communicate with study personnel about adverse events and concomitant medications.

b) Subjects chronically infected with HCV genotype 3, as documented by positive HCV RNA at screening and either

i) Positive anti-HCV antibody, HCV RNA , or a positive HCV genotype test at least 6 months prior to screening; or

ii) Liver biopsy consistent with chronic HCV infection.

c) Subjects who are HCV-Treatment-naive

i) No previous exposure to any interferon formulation (ie, IFNα, peg-IFNα) or RBV

ii) No previous exposure to any HCV direct acting antivirals (DAAs).

d) Subjects who are HCV-treatment-experienced

i) All permitted prior anti-HCV therapies must be discontinued or completed ≥ 12 weeks prior to screening

(1) Previous treatment with IFNα, with or without RBV is permitted. Documentation of prior virologic response to treatment is desirable but not strictly required.

Subjects who did not complete treatment due to laboratory abnormality or intolerable side effect are eligible.

(2) Subjects who experienced virologic failure on a previous course of SOF with RBV are permitted. Subjects who discontinued SOF/RBV due to intolerance other than exacerbations of anemia are excluded.

(3) Previous exposure to anti-HCV agents in the following drug classes is also permitted, including but not limited to cyclophilin inhibitors and inhibitors of microRNA.

ii) Previous exposure to NS5A inhibitors is prohibited.

e) HCV RNA ≥ 10^4 IU/ml (10,000 IU/mL) at Screening;

f) Body Mass Index (BMI) of 18 to 35 kg/m^2, inclusive at screening.

g) Subjects with compensated cirrhosis are eligible to enroll in the current study. Determination of cirrhosis status is required prior to randomization. Up to 50% of subjects in each of the 12-week treatment arms (HCV treatment-naive and -experienced subjects) may be cirrhotic. A biopsy is not needed for participation in this study, however.

i) A subject will be considered "cirrhotic" if they meet the following criteria:

(1) Liver biopsy showing cirrhosis (ie, Metavir > F3, Ishak > 4, or the equivalent) at any time prior to screening **OR**;

(2) Fibroscan showing cirrhosis or results > 14.6 kPa within 1 year of Baseline **OR**;

(3) A FibroTest® score of ≥ 0.75 and an aspartate aminotransferase (AST): platelet ratio index (APRI) of > 2 (performed during Screening).

ii) A subject will be considered "non-cirrhotic" if they meet the following criteria:

(1) Most recent liver biopsy (within ≤ 36 months of Screening) showing absence of cirrhosis (Metavir F0-F3, Ishak 0-4, or equivalent) **OR**;

(2) Fibroscan with a result of ≤ 9.6 kPa within 1 year of Baseline/Day 1 **OR**;

(3) A FibroTest® score of ≤ 0.48 and APRI of ≤ 1 (performed during Screening)

iii) If a subject is evaluated by more than one testing method providing conflicting determinations of the subject's liver status, the determination of cirrhosis will be made using the following methodology:

(1) Liver biopsies (performed within the pre-specified time frame outlined above) take precedence over either Fibroscan or FibroTest®/APRI.

(2) In the absence of an acceptable liver biopsy, Fibroscan (performed within the pre-specified time frame outlined above) takes precedence over FibroTest®/APRI.

(3) The combined screening FibroTest®/APRI results are adequate for enrollment and to determine cirrhosis status if an acceptable biopsy or Fibroscan are not available

Note: If results from both Fibroscan and Fibrotest/APRI do not meet the criteria above defining the subject as "cirrhotic" or "non-cirrhotic", the subject is

considered to have an "indeterminate" liver status and a liver biopsy will be required prior to Day 1 for study participation.

h) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). Discussion with the BMS Medical Monitor must occur prior to subject re-enrollment. If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

a) Males and females, ≥ 18 years of age

b) 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.

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the following duration:

i) For DCV and SOF: For the duration of treatment with DCV and SOF plus 5 half-lives of study drugs (5 days) plus 30 days (duration of ovulatory cycle) for a total of 5 weeks post-treatment completion.

e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the following duration:

i) For DCV and SOF: For the duration of treatment with study drugs plus 5 half-lives of the study drug (5 days) plus 90 days (duration of sperm turnover) for a total of 14 weeks 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.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less 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*

* Complete abstinence as 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.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) HCV Genotypes other than GT-3 infection; mixed genotype infections are not permitted.

2. Medical History and Concurrent Diseases

a) Liver or any other organ transplant (including hematopoietic stem cell transplants) other than cornea and hair;

b) Current or known history of cancer (except in situ carcinoma of the cervix or adequately treated basal or squamous cell carcinoma of the skin) within 5 years prior to screening;

c) Documented or suspected HCC, as evidenced by previously obtained imaging studies or liver biopsy (or on a screening imaging study/liver biopsy if this was performed);

d) Evidence of decompensated liver disease including, but not limited to, radiologic criteria, a history or presence of ascites, bleeding varices, or hepatic encephalopathy;

e) Evidence of a medical condition contributing to chronic liver disease other than HCV (such as, but not limited to: hemochromatosis, autoimmune hepatitis, metabolic liver disease, alcoholic liver disease, toxin exposures)

f) History of chronic hepatitis B virus (HBV) as documented by HBV serologies (eg, HBsAg-seropositive). Subjects with resolved HBV infection may participate (eg, HBsAb-seropositive with concurrent HBsAg-seronegative);

g) Subjects who are positive for HIV (confirmed by HIV test performed at Screening);

h) 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);

i) Known history of genetic coagulopathy including, but not limited to, hemophilia

j) Uncontrolled diabetes (any subject with a confirmed screening HbA1c ≥ 8.5 must be excluded);

k) Confirmed, uncontrolled hypertension (any screening systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg should be excluded unless discussed with the BMS medical monitor);

l) Active substance abuse as defined by DSM-IV, Diagnostic Criteria for Drug and Alcohol Abuse (Appendix 1), which in the opinion of the investigator would make the candidate inappropriate for participation in this study

m) Active severe psychiatric disorders including but not limited to, schizophrenia, psychosis, bipolar disorder, post-traumatic stress disorder, mania, etc.;

n) Inability to tolerate oral medication;

o) Poor venous access that would impair the subject's ability to comply with the study protocol.

3. Physical and Laboratory Test Findings

a) Alanine amino transferase (ALT) ≥ 10x ULN

b) Total Bilirubin ≥ 2 mg/dL (≥ 34 μmol/L), unless due to a history of Gilbert's disease;

c) Albumin < 3.5 g/dL (35 g/L);

d) Platelets < 50 x 10^3 cells/μL;

e) ANC < 0.75 x 10^3 cells/μL;

f) Hemoglobin < 10 g/dL (100 g/L);

g) Creatinine Clearance (CrCl) ≤ 50 mL/min (as estimated by Cockcroft and Gault);

h) Alpha fetoprotein (AFP):

i) AFP > 100 ng/mL (> 82.6 IU/mL) OR

ii) AFP ≥ 50 and ≤ 100 ng/mL (≥ 41.3 IU/mL and ≤ 82.6 IU/ mL) requires a liver ultrasound and subjects with findings suspicious for HCC are excluded.

i) QTcF or QTcB > 500 mSec

4. Allergies and Adverse Drug Reaction

a) History of hypersensitivity to drugs with a similar biochemical structure to DCV or SOF

b) Any other criteria or known contraindication that would exclude the subject from receiving SOF (per the local label) or DCV.

5. Sex and Reproductive Status

a) Those males and females who do not or cannot meet the requirements outlined in Inclusion Criteria 3

6. Prohibited Treatments and/or Therapies

a) Any prior treatment with HCV NS5A inhibitors.

b) Refer to Section 3.4 for prohibited and/or restricted treatments during and post-treatment

7. Other Exclusion Criteria

a) Any other medical, psychiatric and/or social reason which, in the opinion of the investigator would make the subject inappropriate for the study

b) Prisoners or subjects who are involuntarily incarcerated

c) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

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.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

3.4.1.1 Prohibited and/or Restricted Treatments for Subjects on DCV and SOF

The following treatments are prohibited during dosing with DCV and SOF and should be discontinued at least one week prior to Day 1 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 (eg, 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.

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

- Substrates of OATP1B1 and OTAP1B3 should be used with caution (eg, glyburide, bosentan, rosuvastatin, pravastatin, and pitavastatin);
- Substrates of BCRP should be used with caution (eg, rosuvastatin);
- P-gp substrates with a narrow therapeutic index (eg, digoxin) should be used with caution and at the lowest efficacious dose with appropriate monitoring (eg, therapeutic drug monitoring)

3.4.2 Other Restrictions and Precautions

- 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;

- Long-term treatment (≥ 2 weeks) with agents that are immunosuppressive, or have a high risk for nephrotoxicity or hepatotoxicity, should be discussed with the central medical monitor.

3.5 Discontinuation of Subjects from Treatment

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
- 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 (eg, 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 and the BMS central medical monitor should be informed. 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 > 2 × ULN or INR > 2;
  - Any Grade 4 AE or clinically significant laboratory abnormality considered study drug-related. (see Section 6.3 for laboratory abnormality AE reporting requirements).
- Virologic Breakthrough:

  Subjects who meet criteria for virologic breakthrough defined as:
  - Confirmed ≥ 1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or
  - Confirmed increase in HCV RNA ≥ LLOQ if HCV RNA previously declined to < LLOQ TD/TND.

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 24 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 as outlined in Section 5. 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 (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post-Treatment Study Follow up

In this study, post-treatment Week 12 is a key endpoint. Post-treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study (Post-treatment Week 24).

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 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.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

Study drugs include both Non-investigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

4.1 Study Treatments

Table 4.1-1: Product Description - On Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Daclatasvir (BMS-790052-05) Film Coated Tablet	60 mg (as the free base)	33 tablets per bottle/ Open Label	N/A	Each tablet is plain, green, biconvex, pentagonal and film-coated.	Store at 15°C-25°C (59°F-77°F). Store in a tightly closed .container..
Sofosbuvir (SOF)	400 mg	28 tablets per bottle/Open Label	N/A	Yellow, capsule-shaped, film-coated tablets containing 400 mg sofosbuvir debossed with “GSI” on one side and “7977” on the other side	Store at room temperature below 30 °C (86 °F). Store in original container.

Note: Daclatasvir will be provided as the Phase 3 clinical presentation/formulation for 60 mg film-coated tablets. Commercially available Sofosbuvir (Sovaldi®) will be procured and distributed by a central pharmacy. Storage for SOF should be in accordance with the package insert.

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) are: daclatasvir, and sofosbuvir. When referring to the program drug in this protocol, references to BMS-790052 or DCV indicate the investigational product (BMS-790052-05/daclatasvir dihydrochloride) as described in this section.

When referring to the program drug in this protocol, references to SOF indicate the investigational product sofosbuvir as described in this section. For additional information on sofosbuvir, please refer to the sofosbuvir package insert.

4.1.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational product(s) is/are: not applicable.

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

4.2 Method of Assigning Subject Identification

Eligible treatment naive and treatment experienced subjects will receive 60 mg DCV and 400 mg SOF, for 12 weeks. At the start of the screening period the site staff will call the Interactive Voice Response System (IVRS) designated by the sponsor to register the patient and to obtain a Patient Identification Number (PID). The site staff will call the IVRS again once protocol eligibility criteria have been determined. For patients who meet the protocol eligibility criteria

during screening, the IVRS will assign the subject to the treatment described above. For patients who do not meet the eligibility criteria, the IVRS will register them as screen failures.

Re-evaluation to confirm eligibility criteria within the 42 day screening period will be allowed. However, beyond this, patients should be re-evaluated only after consultation with the study team.

It is important that the investigative staff reconfirm the patient's willingness to continue in the study prior to calling the IVRS or contacting the central pharmacy to register the patient to treatment.

Investigative staff will call the IVRS every 4 weeks during treatment for the system to assign DCV study medication. SOF will be automatically re-dispensed by the central pharmacy at week 2 and week 6. More detailed information regarding IVRS will be provided in a separate document.

4.3 Selection and Timing of Dose for Each Subject

The screening period for this study is 42 days. Eligible subjects must be dosed within 42 days of the day they were initially enrolled in IVRS.

On Day 1, after all Day 1 study procedures have been performed, eligible subjects will start study drugs. The first Day 1 dose must be administered in the office/clinic.

Selection and timing of dose for each subject is outlined in Table 4.3-1:

Table 4.3-1: Treatment Administration

Cohort	Treatments	Tablet Strength	Number of Tablets Per Dose	Maximum Treatment Duration
1 & 2	Daclatasvir (DCV)	60 mg	1 tablet in the AM	12 Weeks
	Sofosbuvir (SOF)	400 mg	1 tablet in the AM	

Note: DCV & SOF should be taken at the same time each day, with or without a meal

The following applies if a scheduled dose of DCV is missed:

- 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.

The following applies if a scheduled dose of Sofosbuvir is missed:

- If a subject accidentally misses a scheduled dose of Sofosbuvir, the investigator should advise the subject according to the manufacturer's prescribing information for the medication.

4.3.1 Dose Modifications

Dose modifications of DCV or SOF are not permitted.

4.3.2 Dose Interruptions

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. See Section 6.3, Laboratory Test Abnormalities, for reporting guidelines.

When AEs occur that are considered by investigators to be unsafe, the necessity of dose interruption of DCV and/or SOF should be discussed with the central medical monitor. DCV and SOF must be interrupted and restarted at the same time. If interruption is required for more than 7 days, treatment with DCV/SOF must be permanently discontinued.

The safety and efficacy of SOF has not been established in patients with severe renal impairment (creatinine clearance < 30mL/min as estimated by Cockcroft and Gault). Consideration should be given to dose interruption of study drugs (DCV and SOF) but consultation with central medical monitor is required in such circumstances.

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

Assessment of study medication will be performed at each study visit. The patient should be instructed to bring all unused study medication containers to each visit as well as any empty bottles. The dates and number of tablets dispensed and returned must be recorded on the drug accountability form maintained on-site. Opened containers of daclatasvir (BMS-790052-05), as appropriate, are collected every 4 weeks and new bottles are dispensed. Opened containers of sofosbuvir (SOF) should be returned to the subject and dosing should continue from the in-use container. However, if site SOPs do not allow return of open containers of study drug, local SOPs may be followed. All study drug, including in-use containers, should be collected at end of treatment visit.

Patients will be instructed to record dosing in a dosing diary which will be reviewed at each visit, in combination with drug accountability to confirm treatment compliance. Sites should discuss with the patient if there are discrepancies between the diary and the drug log to reconcile actual dosing at each visit.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator or 3rd party) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (AI444218)

Procedure	Screening Visit[a]	Notes
EligibilityAssessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	
HIV Serology (HIV-1 , -2)	X	
HCV Genotype	X	
HCV Serology	X	
HBV Serology	X	
Alpha fetoprotein (AFP)	X	
SafetyAssessments		
Full Physical Examination	X	
Height / Weight	X	BMI must be calculated by site to confirm eligibility.
ECG, Single 12-Lead	X	Performed after supine at least 5 minutes
Liver Biopsy or Fibroscan	Please refer to section 3.3.1, criteria 2g) for details on when a liver biopsy or Fibroscan are required during the Screening Period.	
FibroTest® /APRI Results	X	
Vital Signs	X	Including seated blood pressure and heart rate
Previous and Concomitant medication Review	X	
Laboratory Tests	X	
Pregnancy Test	X	WOCBP Only

Table 5.1-1: Screening Procedural Outline (AI444218)		
Procedure	**Screening Visit[a]**	**Notes**
Serious Adverse Events Assessment	X	Report SAEs that occur after informed consent is obtained
EfficacyAssessments		
HCV RNA and back-up HCV RNA	X	

[a] All screening procedures must be completed in a maximum of 42 days.

Table 5.1-2: On Treatment Procedural Outline (AI444218)

Procedure	Baseline (Day1)	Day 2[a]	Week 1 (± 3 days)	Week 2 (± 3 days)	Week 4 (± 3 days)	Week 6 (± 3 days)	Week 8 (± 3 days)	Week 12 or Early D/C (± 3 days)	Notes
EligibilityAssessments									
Inclusion/Exclusion Criteria	X								Prior to treatment to ensure eligibility criteria are met
SafetyAssessments									
Targeted Physical Examination	X		X	X	X	X	X	X	Performed at investigator's discretion and should include assessment of heart, lung and abdomen.
Vital Signs	X		X	X	X	X	X	X	Including seated blood pressure and heart rate
Weight	X		X	X	X	X	X	X	
Concomitant Medications	X		X	X	X	X	X	X	
Serious Adverse Events Assessment	X		X	X	X	X	X	X	
Adverse Events Assessment	X		X	X	X	X	X	X	Day 1 AE assessment occurs after study drug administration
Laboratory Tests	X		X	X	X	X	X	X	Non-fasting
Pregnancy Test , WOCBP	X				X		X	X	Performed on Day 1, then every 4 weeks while on treatment.
ECG, Single 12-Lead								X	Performed after supine at least 5 minutes

Table 5.1-2: On Treatment Procedural Outline (AI444218)

Procedure	Baseline (Day1)	Day 2[a]	Week 1 (± 3 days)	Week 2 (± 3 days)	Week 4 (± 3 days)	Week 6 (± 3 days)	Week 8 (± 3 days)	Week 12 or Early D/C (± 3 days)	Notes
EfficacyAssessments									
HCV RNA and back up HCV RNA	X		X	X	X	X	X	X	Subjects with suspected on-treatment failure (virologic breakthrough) (see Section 5.8.1) will be retested for HCV RNA and HCV Resistance at an unscheduled visit as soon as possible before their next regular visit.
Storage Specimen for HCV Resistance	X		X	X	X	X	X	X	
HCV Genotype	HCV Genotype to be collected at time of sample collection (HCV RNA) to confirm virologic breakthrough.								
BiomarkerAssessments									
Rs 12979860 IL28B SNP	X								
SNP Analyis (other than Rs12979860)	X								
OtherAssessments									
EuroQol (EQ-5D)	X							X	
DCV/SOF, PK Trough Samples (all subjects)			X	X	X		X	Week 12 only	See Section 5.5
DCV/SOF, PK Samples at 0.5 and 2 hours post dose					X				
DCV Protein binding Sample at 2 hour post dose					X				See Section 5.5
DCV/SOF, PK Sample	PK sample to be collected at time of sample collection (HCV RNA) to confirm virologic breakthrough.								

Table 5.1-2: On Treatment Procedural Outline (AI444218)

Procedure	Baseline (Day1)	Day 2[a]	Week 1 (± 3 days)	Week 2 (± 3 days)	Week 4 (± 3 days)	Week 6 (± 3 days)	Week 8 (± 3 days)	Week 12 or Early D/C (± 3 days)	Notes
Brief Questionnaire	X							X	A brief questionnaire will be completed by the subject to include the subject's e-mail address, name of the subject's primary care physician and 2 non-residing contacts in case the subject cannot be reached for their study assessments unless prohibited by local laws or regulations.
IntensivePKSub-Study									
DCV, SOF, PK Samples: (Intensive PK Sub-Study)	X	X							To be performed on a sub-set of subjects. Refer to Section 5.5 for details on sampling. Day 2 visit is applicable only to subjects participating in the Intensive PK sub-study
HCV RNA Samples: (Intensive PK Sub-Study)	X	X							To be performed on a sub-set of subjects. Refer to Section 5.5 for details on sampling. Day 2 visit is applicable only to subjects participating in the Intensive PK sub-study
Storage Specimen for HCV Resistance		X							To be performed on a sub-set of subjects. Refer to Section 5.5 for details on sampling. Day 2 visit is applicable only to subjects participating in the Intensive PK sub-study

Table 5.1-2: On Treatment Procedural Outline (AI444218)

Procedure	Baseline (Day1)	Day 2[a]	Week 1 (± 3 days)	Week 2 (± 3 days)	Week 4 (± 3 days)	Week 6 (± 3 days)	Week 8 (± 3 days)	Week 12 or Early D/C (± 3 days)	Notes
ClinicalDrugSupplies									
Call IVRS to register eligible subjects for treatment	X								
Dispense DCV Study Drug	X				X		X		IVRS will be responsible for dispensation of DCV.
Dispense SOF Study Drug	X			X		X			Central Pharmacy will be responsible for dispensation of SOF.
Assessment of Study Medication Use / Treatment Compliance			X	X	X	X	X	X	

[a] Day 2 visit is applicable only to subjects participating in the Intensive PK sub-study.

Table 5.1-3: Post Dosing Follow-up Procedural Outline (AI444218)				
Procedure	**Post-Treatment Week 4 (±7 Days)**	**Post-Treatment Week 12 (± 7 Days)**	**Post-Treatment Week 24/EOS (± 7 Days)**	**Notes**
SafetyAssessments				
Targeted Physical Examination	X			Performed at investigator's discretion and should include assessment of heart, lung and abdomen.
Vital Signs	X			Including seated blood pressure and heart rate
Weight	X			
Concomitant Medications	X			Concomitant medication assessment up to post-treatment Week 4. HCV DAA assessment through post-treatment Week 24. If anti-HCV compounds are administered anytime up to post-treatment Week 24, the subject must discontinue from study after post-treatment Week 4 visit. HCV DAAs must be listed on the appropriate eCRF page.
Serious Adverse Events Assessment	X			Refer to Section 6.1.1 for details
Adverse Events Assessment	X			Refer to Section 6.2.1for details
Laboratory Tests	X			Non-fasting
Pregnancy Test, WOCBP	X			For WOCBP only. Pregnancy testing is required every 4 weeks for 8 weeks following discontinuation of DCV and SOF treatment. Home pregnancy testing may be performed at post-treatment Week 8; however any positive result must be verified by serum pregnancy testing. Telephone contacts are required to obtain results for subjects who perform post-treatment, at-home pregnancy testing and subjects will be instructed to record test results in a pregnancy test result log

Hepatology

Table 5.1-3: Post Dosing Follow-up Procedural Outline (AI444218)				
Procedure	**Post-Treatment Week 4 (±7 Days)**	**Post-Treatment Week 12 (± 7 Days)**	**Post-Treatment Week 24/EOS (± 7 Days)**	**Notes**
EfficacyAssessments				
HCV RNA and back up HCV RNA	X	X	X	Subjects with suspected relapse (see Section 5.8.1) will be retested for HCV RNA and HCV Resistance at an unscheduled visit as soon as possible before their next regular visit.
Storage Specimen for HCV Resistance	X	X	X	
HCV Genotype	HCV Genotype to be collected at time of sample collection (HCV RNA) to confirm relapse			
OtherAssessments				
EuroQol (EQ-5D)			X	
Confirm Brief Questionnaire Responses	X	X	X	Responses to brief questionnaire will be confirmed (including the subject's e-mail address, name of the subject's primary care physician, and 2 non-residing contacts in case the subject cannot be reached for their study assessments).
Interim Phone Contacts				Required on a monthly basis between in-office study visits (ie, Weeks 8, 16 & 20 Post-treatment) The purpose of the phone contacts is to verify the subject's continuation in the study and to confirm with the subject the date of his/her next study visit

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital sign assessments. The site will have a monitored refrigerator, and freezer (-20°C or below), as well as containers and dry ice for shipment and storage of blood samples. A refrigerated centrifuge is also recommended. The site will provide all materials required for accurate source documentation of study activities and for housing patients during the study.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required). Case report forms (electronic or hard copy) will be provided by BMS. Central Laboratory will provide labels and tubes for the collection of all required materials for the clinical laboratory tests performed by the Central Laboratory. Investigational products will be supplied by BMS. BMS will also provide the Investigator Brochure, and the IVRS manual. Dosing diaries will be provided by BMS.

5.3 Safety Assessments

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of the subject's standard medical care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested from the sponsor.

5.3.1 Laboratory Assessments

The following assessments listed in Table 5.3.1-1 will be analyzed by a central or other BMSs specified laboratory. Subjects are not required to be fasting prior to laboratory assessments.

Table 5.3.1-1: Laboratory Assessments

	Screening (outlined in Table 5.1-1)	Study Visits On-Treatment (outlined in Table 5.1-2)	Study Visits Post-Treatment Follow-Up (outlined in Table 5.1-3)
Hematology			
Hemoglobin	X	X	X
White Blood Cell (WBC) Count with Differential	X	X	X
ANC (neutrophils plus band)	X	X	X
INR	X	X	X
Platelets	X	X	X
Hematocrit	X	X	X
Chemistry			
Albumin	X	X	X
Total Protein	X	X	X

Table 5.3.1-1: Laboratory Assessments			
	Screening (outlined in Table 5.1-1)	**Study Visits On-Treatment (outlined in Table 5.1-2)**	**Study Visits Post-Treatment Follow-Up (outlined in Table 5.1-3)**
Aspartate aminotransferase (AST)	X	X	X
Alanine aminotransferase (ALT)	X	X	X
Total bilirubin	X	X	X
Direct Bilirubin	X	X	X
Alkaline Phosphatase	X	X	X
Lactate dehydrogenase (LDH)	X	X	X
Creatinine	X	X	X
Creatinine Clearance	X	X	X
Creatinine phosphokinase (CPK)		For AST elevation ≥ Grade 1 without ALT elevation	For AST elevation ≥ Grade 1 without ALT elevation
Creatine Kinase MB Isoenzyme (CK-MB)		Reflex if CPK is elevated > 5xULN	Reflex if CPK is elevated > 5xULN
Lipase	X	X	X
Gamma-Glutamyl Transferase (GGT)	X	X	X
Thyroid stimulating hormone (TSH)	X		Post-Tx Week 4
Electrolytes (sodium, bicarbonate, potassium, chloride)	X		Post-Tx Week 4
Blood Urea Nitrogen (BUN)	X		Post-Tx Week 4
Glucose	X		Post-Tx Week 4
HbA1c	X		Post-Tx Week 4
Calcium	X		Post-Tx Week 4
Phosphate	X		Post-Tx Week 4
Uric Acid	X		Post-Tx Week 4
Alfa fetoprotein (AFP)	X		Post-Tx Week 4
FibroTest® /APRI	X		

Table 5.3.1-1: Laboratory Assessments			
	Screening (outlined in Table 5.1-1)	**Study Visits On-Treatment (outlined in Table 5.1-2)**	**Study Visits Post-Treatment Follow-Up (outlined in Table 5.1-3)**
Other			
Urine pregnancy test (reflex to serum if positive)	24 hours prior to dosing in WOCBP	Every 4 weeks	Every 4 weeks until 8 weeks after the discontinuation of DCV and SOF treatment.
FSH	X		
HCV RNA	X	X	X
HCV resistance specimen for storage		X	X
HIV-1 and -2 antibody	X		
HBsAg	X		
HCV genotype	X	Subjects with suspected on-treatment failure (virologic breakthrough) or relapse will be retested for HCV RNA, HCV Resistance and HCV Genotype at an unscheduled visit as soon as possible before their next regular visit.	
Anti-HCV antibody	X		
SNP analysis of rs12979860		Day 1	
SNP analysis (other exploratory SNPs)		Day 1	
PK samples for DCV/SOF (all subjects)		Day 1 Weeks 1, 2, 4, 8, 12/EOT	
Intensive PK/VK sub-study (approximately N = 10 subjects with liver cirrhosis)		Day 1 and Day 2	

All protocol-specified laboratory tests specified in Table 5.3.1-1 must be analyzed and reported by the central lab. In exceptional cases when local laboratory tests are performed, central lab samples should be submitted at the same time, if possible (in addition to the time points specified in Section 5.1. In an effort to limit laboratory data collection, only relevant local lab results should be reported on the appropriate Supplementary Lab CRF pages. Refer to Section 6.3 for guidance on the reporting of lab abnormalities.

Pregnancy testing must be completed for WOCBP at post-treatment Week 4 and Week 8 in subjects receiving DCV and SOF treatment (see Table 5.1-3 and Table 5.5-1). Pregnancy testing may be performed at home if an in-office visit is otherwise not required. Telephone contacts are required to obtain results for all subjects who perform post-treatment at-home pregnancy testing.

Although testing may be performed with home pregnancy testing kits, any positive result must be confirmed by serum pregnancy testing at study site.

Plasma is utilized for HCV RNA viral load testing and HCV resistance testing. The Roche HCV COBAS® TaqMan Test v. 2.0 (LLOQ = 25 IU/mL) will be used to measure HCV RNA levels. The Abbott RealTime HCV Genotype II assay will be used for all genotype/subtype assessments. For samples where HCV genotype or subtype results are unavailable or inconclusive, the Versant HCV genotype 2.0 assay (LIPA) or viral sequence analysis may used for genotype/subtype assessments. HCV RNA and HCV genotype will be analyzed by Quintiles Central Laboratories, Inc. HCV RNA and HCV genotype subtype samples may be used by BMS or BMS designated third party for assay development and validation purposes, except where prohibited by local laws or regulations.

5.3.2 Adverse Events Assessments

Subjects will be closely monitored throughout the study for AEs. Adverse events should be reported at study visits outlined in Table 5.1-2 and Table 5.1-3. Subjects who discontinue assigned therapy early should proceed to all post-treatment follow-up visits as indicated in Table 5.1-3. All study drug-related AEs must be followed until resolution or stabilization.

5.3.3 Vital Signs and Physical Examinations

Vital signs (seated blood pressure and heart rate), weight, and physical measurements and examinations must be performed at study visits outlined in Table 5.1-1, Table 5.1-2 and Table 5.1-3. Physical measurements including height and weight for calculation of BMI will be performed at screening.

All subjects should be evaluated by qualified study site personnel at every visit, capable of making proper safety assessments based on the clinical history obtained from the subject.

A full physical examination will be performed at the Screening visit. A targeted physical exam should be performed during on treatment visits, when deemed necessary by the investigator when safety or other assessments warrant additional physical examination. A targeted physical examination may be performed by a qualified professional guided by the examiner's observations and/or subject complaints on new or changed conditions, symptoms or concerns. Targeted physical exam includes assessment of heart, lung and abdomen.

5.3.4 Electrocardiogram

A 12-lead ECG performed while the subject is resting in a supine position will be recorded at study visits outlined in Table 5.1-1 and Table 5.1-2. The ECG should be recorded after the subject has been supine for at least 5 minutes.

5.4 Efficacy Assessments

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a CRF. Additional procedures and assessments may be performed as part of the subject's standard medical care; however data for these assessments should remain in the

subject's medical record and should not be provided to BMS, unless specifically requested by the sponsor.

5.4.1 Primary Efficacy Assessment

The HCV RNA collected at post-treatment follow-up Week 12, on patients treated with DCV/ SOF for 12 weeks will be used for the primary antiviral assessment in this study.

5.4.2 Secondary Efficacy Assessments

HCV RNA collected at each of the following Weeks: 1, 2, 4, 6, 8, and 12 (EOT); post-treatment Weeks 4 and 24 will be used for the secondary antiviral assessment in this study.

5.5 Pharmacokinetic Assessments

Table 5.5-1 lists the pharmacokinetic sampling schedule to be followed for DCV, SOF and its metabolites. The PK data collected will be analyzed using a nonlinear mixed effect modeling approach and may be reported separately from the Clinical Study Report (CSR). The data may be combined with relevant data collected from others studies where DCV and/or SOF were administered. The purpose of the analysis is to explore exposure-response relationship in the target population and to identify factors that may affect the treatment response.

Table 5.5-1: Pharmacokinetic Sampling Schedule

Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	PK Blood Sample for DCV[a]	Blood Sample for Protein Binding of DCV	PK Blood Sample for SOF and its metabolites
Week 1	0 (predose)	00:00	X		X
Week 2	0 (predose)	00:00	X		X
Week 4	0 (predose)	00:00	X		X
	0.5	00:30	X		X
	2	02:00	X	X	X
Week 8	0 (predose)	00:00	X		X
Week 12	0 (predose)	00:00	X		X
Confirmation of Virologic Breakthrough or Treatment Futility[b]	0 (predose)	00:00	X		X

[a] PK samples for DCV will only be collected for subjects who received DCV + SOF treatment

[b] PK blood sample at any time of HCV RNA viral breakthrough or treatment futility

For the intensive PK/viral kinetics (VK) substudy (approximately N = 10 subjects with liver cirrhosis receiving DCV+SOF treatment), additional PK and HCV RNA samples will collected on Days 1 and 2 according to Table 5.5-2.

Table 5.5-2: Additional PK and HCV RNA Sampling Schedule for Intensive PK/VK Substudy in Cirrhotic Subjects

Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	HCV RNA Sample	HCV Resistance Sample	PK Blood Sample for DCV	PK Blood Sample for SOF and its metabolites
Day 1	0 (predose)	00:00	X			
	0.5	00:30	X			X
	1	01:00	X		X	X
	2	02:00	X		X	X
	3	03:00	X			
	4	04:00	X		X	X
	8	08:00	X		X	X
Day 2	0 (predose)	00:00	X	X	X	X

The plasma samples will be analyzed for DCV concentrations by validated LC/MS/MS assay. The plasma samples for SOF and its metabolites concentrations may be analyzed depending on availability of a validated LC/MS/MS assay. After the scheduled analyses are completed, residual plasma samples may be utilized for exploratory metabolite or biomarker analyses. Detailed instructions for the PK blood collection, labeling, processing, storage and shipping will be provided to the site(s) in the procedure manual.

5.6 Biomarker Assessments

Recent studies have identified single nucleotide polymorphisms in the IL28B and IFNL4 regions associated with increased rates of SVR with pegylated interferon alpha-2a (Pegasys®, pegIFNα-2a)/RBV treatment in HCV-infected individuals treatment in HCV-infected individuals.[41,42] IL28B, along with IL28A, IL29 and IFNL4, encode proteins of the IFNλ family. The rs12979860 SNP associated with the IL28B gene has shown the strongest association with SVR in patients treated with pegIFNα-2a/RBV. Analysis of the rs12979860 SNP will be performed at screening, and additional SNPs in IL28B and IFNL4 will be performed at baseline.

5.7 Outcomes Research Assessments

5.7.1 EuroQol (EQ-5D)

The EuroQol[43] (EQ-5D) provides a simple but effective standardized measure of a subject's quality of life and health state classification and will be assessed at Baseline, End of Treatment and Post-Treatment Week 24. It is intended to provide both a compact descriptive profile and a single index value that will be used in the clinical and economic evaluation of health care.

The questionnaire consists of 2 parts, which together are used to build a composite picture of the respondent's health status. In the first part, the "health state classification", the respondent is asked to indicate his/her current health state, by ticking the most appropriate of three statements about each of the 5 quality of life dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each statement represents an increasing level of severity (1 = no problem, 2 = some or moderate problem, 3 = unable, or extreme problem). The second part, "Visual Analogue Scale Thermometer", will evaluate the respondent's current health-related quality of life by means of a 20 cm visual analogue scale (VAS) with endpoints at 100 (best imaginable health state) and 0 (worst imaginable health state).

The score obtained from each of the 5 health state dimensions (first part of the questionnaire) will be combined and converted to a utility score using the mapping program. Only subjects who provide answers to all 5 questions will be assigned a utility score. Otherwise, the utility score will be deemed missing.

5.8 Other Assessments

5.8.1 Virologic Resistance Testing

Stored plasma specimens for possible resistance testing will be collected at study visits indicated in Table 5.1-2 and Table 5.1-3. Resistance testing will be performed by population sequencing on samples from subjects with HCV RNA ≥ 1,000 IU/mL. This includes samples from all subjects experiencing on-treatment failure or relapse, defined as:

- Virologic breakthrough, defined as confirmed ≥ 1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, **or** confirmed increase in HCV RNA ≥ LLOQ if HCV RNA previously declined to < LLOQ (TD/TND);
- Relapse, defined as HCV RNA < LLOQ (TND) at EOT followed by confirmed detectable HCV RNA ≥ LLOQ in any follow-up visit window
- HCV RNA ≥ LLOQ at any time point not meeting the definition of virologic breakthrough or relapse.

For subjects who experience virologic failure, NS5A and NS5B resistance testing will be performed on samples that best approximate the time of failure, when HCV RNA levels are ≥ 1,000 IU/mL. The respective baseline samples from these subjects will also be tested. In addition, NS5A resistance testing will be performed on all baseline samples. Further testing will occur at selected time points if needed using either storage specimens for resistance testing or other available stored specimens. In addition, clonal analysis may be performed on samples for which population sequencing demonstrates only wild-type virus, or if novel viral variants are identified by population sequencing. Exploratory resistance testing to evaluate for low level variants may be performed on subsets of samples depending on patterns of viral load response.

5.8.2 Brief Questionnaire/Interim Phone Contacts

A brief questionnaire will be completed by the subject on Day 1 to include the subject's e-mail address, name of the subject's primary care physician and 2 non-residing contacts in case the

subject cannot be reached for their study assessments. This questionnaire will be reviewed for the confirmation or modification (as applicable) by the subject at the end of treatment visit and all post-treatment follow-up visits.

During the post-treatment follow-up phase, sites will be required to perform an interim telephone contact with the subject on a monthly basis when the subject is not required to come for an in-office visit (ie, Weeks 8, 16, and 20). The purpose of phone contacts is to verify the subjects continuation in the study, verify the results of home pregnancy testing if applicable, and to confirm with the subject the date of his/her next study visit.

5.9 Results of Central Assessments

Not Applicable

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing.

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

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 (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

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.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

If grading of laboratory abnormalities is reported as AE or SAE, the Division of AIDS table for Grading the Severity of Adult and Pediatric Adverse Events should be used (Appendix 2).

6.4 Pregnancy

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 (or designee) Medical Monitor 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 described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, 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.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

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.

6.5 Overdose

- DCV: total daily dose > 200 mg
- SOF: total daily dose > 800 mg;

Alternatively, an overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

6.6 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 (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1. ALT ≥ 5 times baseline or nadir value, whichever is lower, AND ≥ 10 x ULN (upper limit of normal
   AND
2. Total bilirubin ≥ 2 x ULN
   AND
3. 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.

After the initial event, subsequent monitoring should be discussed with the BMS medical monitor.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

No Data Monitoring Committee (DMC) will be used for AI444218. The following key points were considered for this decision:

- DCV and SOF have been established to be safe in a large subject safety database from Phase 2/3 studies.
- DCV/SOF as combination therapy for up to 24 weeks has been shown in Phase 2 studies to be safe and efficacious in more than 200 total subjects. Routine safety monitoring should be sufficient to detect future events.
- Well-defined discontinuation criteria are established in the protocol for individual subjects for both safety and treatment futility (see Section 3.5).
- There is a well-defined duration of treatment for all study participants.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

This is an open label and two-cohort trial evaluating the combination therapy of DCV and SOF for 12 weeks duration in treatment-naive and treatment-experienced HCV GT-3-infected subjects.

The study will include a total of approximately 150 treated subjects, with approximately 100 treatment-naive subjects and approximately 50 treatment-experienced subjects. The subject population will be HCV treatment naive and treatment experienced subjects chronically infected with HCV GT-3 infection with or without cirrhosis (up to 50% cirrhotics will be allowed). Subjects who have been previously treated with PegIFNα/RBV or SOF may also be enrolled in the treatment-experienced group.

The co-primary objectives of this study are to estimate the SVR12 rate in both treatment-naive and treatment-experienced subjects treated with 12 weeks of DCV+SOF therapy.

The target sample sizes of 100 treatment-naive subjects and 50 treatment-experienced subjects provide 95% confidence that the observed SVR12 rate can be estimated to within 9.7% and 14.2% of the estimates respectively when the observed SVR12 rate is 75% or higher.

For the efficacy analysis in treatment-naive subjects, the target sample size of 100 can provide with a 95% confidence that the lower bound of the observed SVR12 rate will exceed 76% with an observed SVR rate of 85%.

For the efficacy analysis in treatment-experienced subjects, the target sample size of 50 can provide with a 95% confidence that the lower bound of the observed SVR12 rate will exceed 73% with an observed SVR rate of 86%.

Table 8.1-1 and Table 8.1-2 present some scenarios of observed SVR12 rates and 95% confidence intervals for treatment naive and treatment experienced subjects.

Table 8.1-1: SVR12 Observed Rates and Exact Binomial 95% Confidence Intervals in Treatment Naive Subjects

Observed SVR12 Rate	Observed Responders	95% CI
75%	75 of 100	(65.3%, 83.1%)
80%	80 of 100	(70.8%, 87.3%)
85%	85 of 100	(76.5%, 91.4%)
90%	90 of 100	(82.4%, 95.1%)
95%	95 of 100	(88.7%, 98.4%)

Table 8.1-2: SVR12 Observed Rates and Exact Binomial 95% Confidence Intervals in Treatment Experienced Subjects

Observed SVR12 Rate	Observed Responders	95% CI
76%	38 of 50	(61.8%, 86.9%)
80%	40 of 50	(66.3%, 90.0%)
84%	42 of 50	(70.9%, 92.8%)
86%	43 of 50	(73.3%, 94.2%)
88%	44 of 50	(75.7%, 95.5%)
92%	46 of 50	(80.8%, 97.8%)
96%	48 of 50	(86.3%, 99.5%)

8.2 Populations for Analyses

- Enrolled subjects are those who signed an informed consent form and were assigned a Subject Identification number (PID).
- Treated subjects are enrolled subjects who received at least 1 dose of study therapy.

8.3 Endpoints

Efficacy analyses will evaluate HCV RNA as measured by the Roche HighPureTaqman v2.0 assay [lower limit of quantification of (LLOQ): 25 IU/mL].

8.3.1 Primary Endpoints

- Proportion of treatment naive subjects with SVR12, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12;
- Proportion of treatment experienced subjects with SVR12, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12.

8.3.2 Secondary Endpoints

- On treatment safety, as measured by frequency of SAEs, discontinuations due to AEs, Grade 3/4 AEs, and Grade 3/4 laboratory abnormalities through the end of treatment plus 7 days;
- The proportion of subjects who achieve HCV RNA < LLOQ-TD/TND at each of the following Weeks: 1, 2, 4, 6, 8, and 12; EOT; post-treatment Weeks 4 and 24 for each cohort;
- The proportion of subjects who achieve HCV RNA < LLOQ TND at each of the following Weeks: 1, 2, 4, 6, 8, and 12; EOT for each cohort;
- The proportion of subjects who achieve SVR12 (HCV RNA < LLOQ-TD/TND at post treatment week 12) by baseline cirrhosis (presence or absence) for each cohort;
- The proportion of subjects with CC or non-CC genotype at the IL28B rs12979860 single nucleotide polymorphisms (SNPs) who achieve SVR12 for each cohort.

8.3.3 Exploratory Endpoints

- Frequency of genotypic substitutions associated with virologic failure for HCV;
- Summary statistics of trough concentrations of DCV and possibly SOF; summary statistics of plasma concentrations of DCV and possibly SOF. In addition unbound fraction of DCV in plasma at Week 4 will be estimated and summarized.
- Exposure-response analyses will explore the relationship between endpoints of safety and/or efficacy and exposure to DCV and/or possibly SOF and its metabolites;
- Summary statistics of the EQ-5D utilities at baseline, EOT and post-treatment Week 24 by cohort.

8.4 Analyses

Results will be presented by cohort for treated subjects. Demographics, baseline characteristics and safety data will also be presented by cohort.

Categorical variables will be summarized using counts and percents. Continuous variables will be summarized with univariate statistics (eg, mean, median, standard deviation).

Longitudinal summaries of safety and efficacy endpoints will use pre-defined visit week windows. Windows around planned measurement times will be constructed based on the midpoint between planned study visits. Laboratory measures will be summarized using standard international values and units, and US units will be provided in the appendix.

On-treatment endpoints will be assessed using measurements from the start of study therapy through the last dose of study therapy plus 7 days. Follow-up endpoints will be assessed with measurements after the last dose of study therapy plus 7 days.

8.4.1 Demographics and Baseline Characteristics

The following will be summarized by cohort for treated subjects:

- Demographics including: gender, age, race and ethnicity;
- Physical measurements at baseline: height, weight, body mass index (BMI);
- Disease characteristics at baseline: HCV RNA level, IL28B SNP genotype, prior medication response (treatment-experienced cohort) and presence of cirrhosis;
- Laboratory tests at baseline;
- Prior medications. Prior medications are those taken before the first dose of study therapy.

8.4.2 Efficacy Analyses

Efficacy endpoints during the on-treatment period will be based on HCV RNA measurements closest to the planned visits within pre-defined visit windows. Efficacy endpoints during the follow-up period will be based on the last HCV RNA measurements in pre-defined visit windows.

The primary analysis for the proportions of patients meeting the efficacy endpoints will be for all treated subjects.

For binary efficacy endpoints including secondary efficacy endpoints, response rates and 2-sided 95% exact Binomial confidence intervals (CIs) will be estimated for each cohort.

8.4.2.1 Primary Efficacy

The primary analysis for the primary endpoint will use all treated subjects, and missing HCV RNA data at follow-up Week 12 will be imputed using the Next Value Carried Backwards (NVCB) approach (See Section 8.3.1).

The following sensitivity analyses on the primary endpoint will also be conducted:

- Sensitivity analysis using all treated subjects: SVR12 rates and two-sided 95% CIs will use all treated subjects. The SVR12 status for subjects with missing follow-up Week 12 HCV RNA will be counted as non-responders;
- Sensitivity analysis using observed values: SVR12 rates and two-sided 95% CIs will use observed values. This sensitivity analysis is based on subjects who have a post-treatment Week 12 HCV RNA measurement.

8.4.2.2 Secondary Efficacy

The following efficacy endpoints will be summarized for treated subjects:

- The proportion of subjects who achieve HCV RNA < LLOQ-TD/TND at each of the following Weeks: 1, 2, 4, 6, 8, and 12; EOT; post-treatment Week 4 and 24 for each cohort;
- The proportion of subjects who achieve HCV RNA < LLOQ TND at each of the following Weeks: 1, 2, 4, 6, 8, and 12; EOT for each cohort;
- The proportion of subjects who achieve SVR12 (HCV RNA < LLOQ-TD/TND at post treatment week 12) by baseline cirrhosis (presence or absence) for each cohort;
- The proportion of subjects with CC or non-CC genotype at the IL28B rs12979860 single nucleotide polymorphisms (SNPs) who achieve SVR12 for each cohort.

8.4.3 Safety Analyses

Safety data will be summarized for treated subjects in each cohort.

Deaths will be listed for enrolled subjects regardless of onset.

The frequencies of the following safety events will be summarized by study period (on treatment and follow-up) for treated subjects:

- SAEs;
- AEs leading to discontinuation of study therapy (regardless of onset);
- AEs by intensity;
- Laboratory abnormalities by toxicity grade.

The investigators should determine the grade of AEs according to the Division of AIDS (DAIDS) of the US National Institutes of Health Table for Grading the Severity of Adult and Pediatric Adverse Events (2004) (Appendix 2). The investigators' terms will be coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in production at BMS. AEs will be presented by system organ class and preferred term. Presentations will include both non-serious and SAEs, unless otherwise specified. If a subject had an AE with different intensities over time, only the worst grade will be reported for a study period.

Laboratory toxicities will be graded according to the Division of AIDS (DAIDS) of the US National Institutes of Health Table for Grading the Severity of Adult and Pediatric Adverse Events (2004) (Appendix 2). The laboratory value during the study period with the worst grade will be reported for each test.

The target sample sizes of approximately 100 treatment-naive and 50 treatment-experienced GT-3 subjects on the 12-week DCV+SOF regimen can provide 90% probability to detect a safety event that occurs at an incidence rate of 2.3% and 4.6% respectively for each cohort.

8.4.4 Pharmacokinetic Analyses

The trough and plasma concentrations of DCV and possibly SOF and its metabolites (pending the assay availability) will be summarized versus time by cohort. In addition, plasma unbound fraction of DCV will be summarized by cohort.

The PK samples collected in this study will be pooled with PK data from other studies to perform an integrated population PK analysis, the results of which will be reported separately.

8.4.5 Biomarker Analyses

Analyses will focus on SNPs in IL28B for treated subjects. For each SNP in each candidate gene, genotype frequencies will be summarized. Minor allele frequencies and departures from Hardy Weinberg equilibrium will be summarized for each SNP.

Efficacy endpoints (eg, SVR12 or SVR24) will also be summarized by treated subjects and by host genotype for each SNP.

8.4.6 Outcomes Research Analyses

The EQ-5D descriptive system has 5 dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression) and 3 levels (no problems, some problems, and extreme problems). Frequency and proportion of subjects with reported problems for each level for each dimension will be presented at baseline, EOT and post-treatment Week 24 by cohort. Summary statistics for the EQ-5D index scores will be summarized at baseline, EOT and post-treatment Week 24 by cohort, and change from baseline will be summarized at EOT and post-treatment Week 24, by cohort.

8.4.7 Other Analyses

Analyses for the frequency of genotypic substitutions at baseline, on treatment, and post-treatment associated with virologic failure for each cohort will be conducted.

8.4.8 Pharmacodynamics

The relationship between safety or antiviral activity endpoints and exposure to DCV or possibly SOF and its metabolites will be explored using regression models. Antiviral activity endpoints may include SVR12, and the change from baseline in HCV RNA. Safety endpoints may include select AEs and change from baseline in laboratory tests.

The exposure-response analyses for selected safety and antiviral activity endpoints may be conducted using integrated population-based modeling, and results of these analyses will be reported separately than the clinical study report.

8.5 Interim Analyses

Schedule of Analyses:

- An interim analysis will be performed after all subjects have completed post-treatment Week 4 (SVR4) (the analysis for the primary endpoint of SVR12 will not be performed at this interim analysis);
- The analysis for the primary endpoint will be performed after all subjects have completed post-treatment Week 12 (SVR12) ;
- The final analysis (SVR24) will be performed at study completion.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects

currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drugs are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers

- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form .For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- External Principal Investigator designated at protocol development
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APRI	aspartate aminotransferase platelet ratio index
AST	aspartate aminotransferase
ASV	asunaprevir
AUC	area under the concentration-time curve
AUC_{TAU}	area under the concentration-time curve in one dosing interval
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 or electronic
CVR	combined virologic response
CYP	cytochrome p-450
D/C	discontinue
DAA	direct acting antiviral
DCV	daclatasvir
DCV/ASV	daclatasvir and asunaprevir combination therapy

Term	Definition
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
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
Eg	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
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HE	hepatic encephalopathy
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
Ie	id est (that is)

Term	Definition
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IUD	intrauterine device
IVRS	Interactive Voice Response System
Kg	kilogram
L	liter
LADR	low acceleration dose regimen
LDV	ledipasvir
LLOQ	lower limit of quantification
LT	liver transplant
Mg	milligram
Min	minute
mITT	modified intent-to-treat
mL	milliliter
µg	microgram
N	number of subjects or observations
N/A	not applicable
NIMP	non-investigational medicinal products
NVCB	Next Value Carried Backwards
OLT	orthotopic liver transplant
pegIFN	pegylated interferon
PI	protease-inhibitor
PID	Patient Identification Number
PK	pharmacokinetics
QD, qd	quaque die, once daily
QUAD	daclatasvir/asunaprevir/pegylated interferon/ribavirin therapy
r	ritonavir

Term	Definition
RBV	ribavirin
RCI	replication complex inhibitor
SAE	serious adverse event
SAR	serious adverse reaction
SmPC	Summary of Product Characteristics
SNP	single nucleotide polymorphism
SOC	standard of care
SOF	sofosbuvir
SOP	Standard Operating Procedures
SSC	Special Search Categories
SVR	sustained virologic response
TD	target detected
TND	target not detected
TVR	telaprevir
USPI	United States Package Insert
VBT	virologic breakthrough
VK	viral kinetics
WBC	white blood cell
WOCBP	women of childbearing potential

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APPENDIX 1 DSM IV: DIAGNOSTIC CRITERIA FOR DRUG AND ALCOHOL ABUSE

Criteria for Alcohol & Substance Abuse

1) A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:
   a) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (eg, repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
   b) recurrent substance use in situations in which it is physically hazardous (eg, driving an automobile or operating a machine when impaired by substance use)
   c) recurrent substance-related legal problems (eg, arrests for substance-related disorderly conduct)
   d) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (eg, arguments with spouse about consequences of intoxication, physical fights)
2) The symptoms have never met the criteria for Substance Dependence for this class of substance.

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APPENDIX 2 DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

This clarification of the DAIDS Table for Grading the Severity of Adult and Pediatric AE's provides additional explanation of the DAIDS AE Grading Table and clarifies some of the parameters.

I. Instructions and Clarifications

Grading Adult and Pediatric AEs

The DAIDS AE Grading Table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the Table. If there is no distinction in the Table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

> **Note:** In the classification of adverse events, the term "**severe**" is not the same as "**serious**." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "**serious**" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

Addenda 1-3 Grading Tables for Microbicide Studies

For protocols involving topical application of products to the female genital tract, male genital area or rectum, strong consideration should be given to using Appendices I-III as the primary grading scales for these areas. The protocol would need to specifically state that one or more of the Appendices would be primary (and thus take precedence over the main Grading Table) for items that are listed in both the Appendix and the main Grading Table.

- Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - PDF

Grade 5

For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

Estimating Severity Grade for Parameters Not Identified in the Table

In order to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on Page 3.

Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1

Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

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Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges
In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local lab LLN.

For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years (Page 20) Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1 – 3.8 mg/dL. A participant's actual lab value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.

II. Definitions of terms used in the Table:

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Correction: in Grade 2 to 160 - 179 from > 160-179 (systolic) and to ≥ 100 -109 from > 100-109 (diastolic) and in Grade 3 to ≥ 180 from > 180 (systolic) and to ≥ 110 from > 110 (diastolic).				
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Comment: Parameter changed from "Infant, < 1 day" to "Infant, ≤1 day"				
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)				
Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab.				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62–5.23 mmol/L*	6.50 – 7.4 g/dL *4.03–4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 - 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL *> 2.79 mmol/L*	< 7.0 g/dL *< 4.34 mmol/L*
Comment: The decrease is a decrease from baseline				
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 - 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant*†, ≤ 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59- 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
Correction: Parameter changed from "Infant < 21 days" to "Infant ≤ 21 days"				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^3 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^3 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Comment: Some laboratories will report this value as Bicarbonate (HCO_3) and others as Total Carbon Dioxide (CO_2). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above.				
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences

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† Use age and sex appropriate values (e.g., bilirubin).

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Comment: Added ULN to Grade 1 parameter				
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*
URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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