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Clinical Protocol AI444379

A Phase 3 Evaluation of Daclatasvir and Sofosbuvir with Ribavirin in Cirrhotic Subjects with Genotype 3 Chronic Hepatitis C Infection

[redacted]

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol	14-Dec-2015	Not applicable

SYNOPSIS

Clinical Protocol AI444379

Protocol Title: A Phase 3 Evaluation of Daclatasvir and Sofosbuvir with Ribavirin in Cirrhotic 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 of 60 mg (unless otherwise dictated by concomitant cART) once daily, by mouth for 24 weeks
- Sofosbuvir (SOF): in tablet form at the dose of 400 mg once daily, by mouth for 24 weeks
- Ribavirin (RBV): in tablet form at the dose of 1000-1200 mg per day, weight based twice daily by mouth for 24 weeks
  - For subjects weighing < 75 kg at Day1, the total dose is 1000 mg/day. Subjects should take 400 mg (2 x 200 mg tablets) in the morning with a meal, and 600 mg (3 x 200 mg tablets) in the evening with a meal
  - For subjects weighing ≥ 75 kg at Day 1, the total dose is 1200 mg/day. Subjects should take 600 mg (3 x 200 mg tablets) in the morning and in the evening with a meal

Study Phase: 3

Research Hypothesis:

Combination therapy with DCV and SOF plus RBV for 24 weeks is safe and demonstrates an SVR12 rate greater than the threshold SVR rate in chronically infected subjects with HCV GT-3 and cirrhosis.

Objectives:

Primary Objective

- To demonstrate the SVR12 rate, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) at follow-up Week 12 in subjects treated with 24 weeks of DCV+SOF+RBV therapy is greater than the historical threshold SVR rate

Key Secondary Objective

- To assess the impact of baseline NS5A resistance-associated polymorphisms on the SVR12 rate

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 laboratory abnormalities;
- To assess antiviral activity, as measured by:
  - The proportion of subjects who achieve HCV RNA < LLOQ, TD or TND at each of the following Weeks: 1, 2, 4, 8, 12, 16, 20, 24, 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, 8, 12, 16, 20, 24, and EOT

Study Design:

AI444379 is an open-label trial evaluating the combination therapy of DCV+ SOF with RBV for 24 weeks in subjects infected with HCV GT-3 with compensated cirrhosis. The study will include approximately 75 subjects.

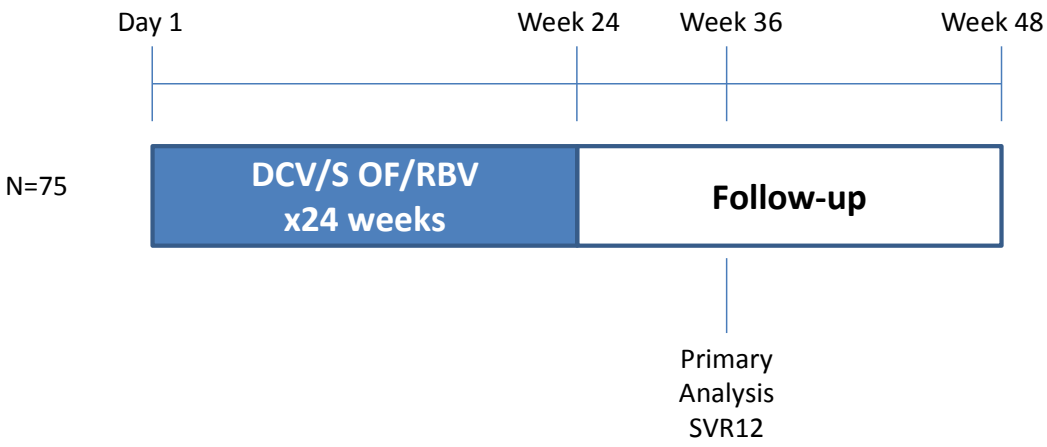
Subjects will receive the combination of DCV 60 mg QD (unless concomitant HIV regimen dictates otherwise) + SOF 400 mg QD + RBV (weight based 1000 mg-1200 mg daily) for 24 weeks. HCV RNA will be available for review by the clinical site personnel. After treatment is completed subjects will be followed for 24 weeks. Subjects who discontinue early should be followed for 24 weeks post-treatment.

The primary analysis is SVR12 and the final analysis is SVR24.

Duration of study:

The screening/enrollment period is anticipated to be approximately 8 weeks from FPFV to LPFV. Study duration will be 52 weeks (4 week screening period, 24 weeks of therapy, and 24 weeks of follow-up).

Study Design
Subjects with GT-3 Infection with Cirrhosis



Study Population:

The key subject population will be subjects chronically infected with HCV GT-3 with compensated cirrhosis. Subjects with cirrhosis who are mono-infected with HCV genotype 3 or coinfected with HCV genotype 3 and HIV-1 will be permitted to enroll.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for AI444379		
Medication	**Potency**	**IP/Non-IP**
Daclatasvir, BMS-790052	60 mg	IP
Daclatasvir, BMS-790052	30 mg	IP
Sofosbuvir	400 mg	IP
Ribavirin	200 mg	IP

Study Assessments:

On treatment visits will occur at Weeks, 1, 2, 4, 8, 12, 16, 20, and 24/EOT. Following discontinuation or completion of therapy, safety will be assessed through post-treatment Week 4, while efficacy and/or resistance will be assessed through post-treatment Week 24.

Statistical Considerations:

Sample Size:

This is an open-label trial evaluating the combination therapy of DCV+ SOF with RBV for 24 weeks in subjects infected with HCV GT-3 with compensated cirrhosis. The study will include approximately 75 subjects.

For the efficacy analysis, the target sample size of 75 can provide with a 95% confidence that the lower bound of the observed SVR12 rate will exceed 82% with an observed SVR rate of 91%. The primary objective is to determine whether the SVR12 rate, is higher than the historical threshold. The threshold rate is estimated at 79% and is based on the upper bound of the SVR rate from GT3 Cirrhotic subjects in the ALLY 3 study, where SVR12 rate is 63% with a confidence interval of (43.7%, 78.9%).

The lower bound of the two-sided 95% confidence interval (CI) of the SVR12 from this study will be used to compare to the historical threshold (79%). For the primary objective, with 75 subjects it would take a minimum of an observed SVR12 rate of 91% (68/75; 95% CI: 81.7%, 96.2%) for the lower bound of the 95% CI to exceed the threshold, and conclude the SVR12 rate of 24-week DCV/SOF/RBV treatment is higher than the historical threshold

Endpoints:

Primary Endpoint

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

Key Secondary Endpoint

- The proportion of subjects who achieve SVR12 in the presence and absence of NS5A resistance-associated polymorphisms.

Secondary Endpoint(s)

- On treatment safety, as measured by frequency of deaths, serious adverse events (SAE)s, discontinuation due to adverse events (AE)s, Grade 3/4 AEs and Grade 3/4 laboratory abnormalities
- The proportion of subjects who achieve HCV RNA < LLOQ, TD or TND at each of the following Weeks: 1, 2, 4, 8, 12, 16, 20, 24, 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, 8, 12, 16, 20, 24, and EOT

Analyses:

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

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:

The primary analysis will be performed after all subjects have completed post-treatment Week 12 (SVR12). A final analysis (SVR24) will be performed at study completion. Additional interim efficacy analyses may be performed prior to post-treatment 12 to support external data presentations or correspondences with health authorities.

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1.2 Research Hypothesis

Combination therapy with DCV and SOF plus RBV for 24 weeks is safe and demonstrates an SVR12 rate greater than the threshold SVR rate in chronically infected subjects with HCV GT-3 and cirrhosis.

1.3 Objectives(s)

1.3.1 Primary Objective

To demonstrate the SVR12 rate, defined as HCV RNA < LLOQ target detected (TD) or target not detected (TND) as follow-up Week 12 in subjects treated with 24 weeks of DCV+SOF+RBV therapy is greater than the historical threshold SVR rate.

1.3.2 Key Secondary Objective

- To assess the relationship between efficacy and NS5A resistance-associated polymorphisms.

1.3.3 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 laboratory abnormalities
- To assess antiviral activity, as measured by:
  - The proportion of subjects who achieve HCV RNA < LLOQ, TD or TND at each of the following Weeks: 1, 2, 4, 8, 12, 16, 20, 24, 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, 8, 12, 16, 20, 24, and EOT

1.3.4 Exploratory Objectives

[redacted]

[redacted]

1.4 Product Development Background

[redacted]

[redacted]

[redacted]

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 (as per country guidelines) 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:

- 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.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- 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.
- 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.

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.

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.

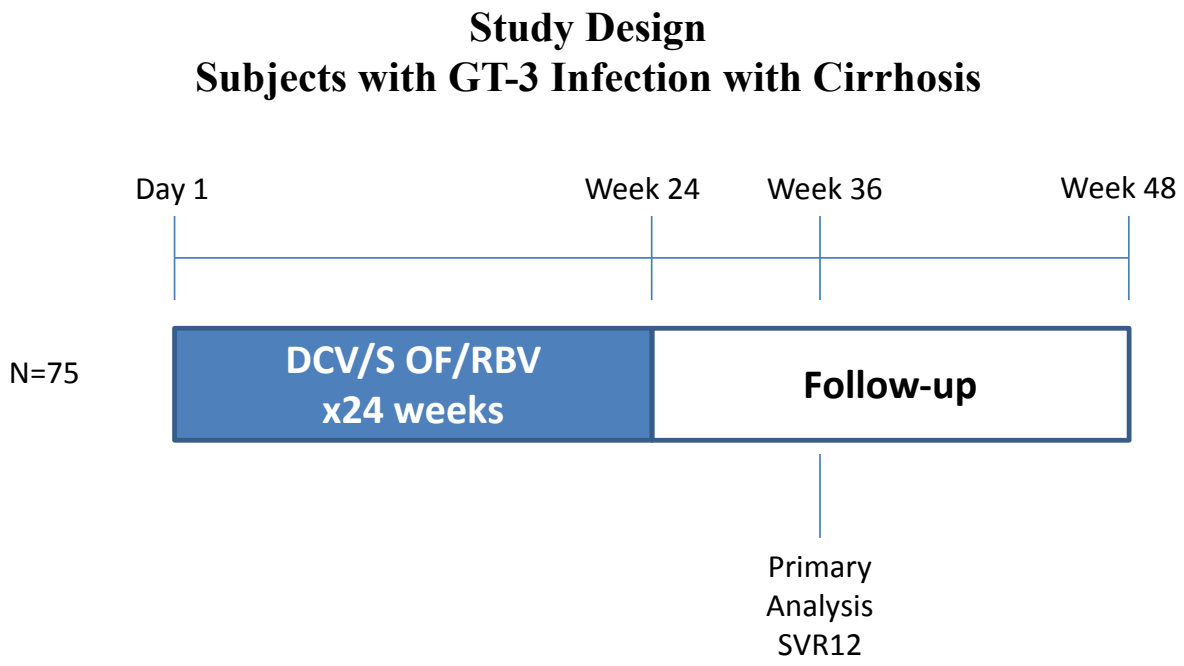
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Subjects with GT-3 Infection with Cirrhosis



AI444379 is an open-label trial evaluating the combination therapy of DCV + SOF with RBV for 24 weeks in subjects infected with HCV GT-3 with compensated cirrhosis. Subjects with cirrhosis who are mono-infected with HCV genotype 3 or coinfected with HCV genotype 3 and HIV-1 infection will be permitted to enroll. The study will include approximately 75 subjects.

Subjects will receive the combination of DCV 60 mg QD (unless otherwise dictated by concomitant combination anti-retroviral therapy [cART] therapy) + SOF 400 mg QD + RBV (weight based 1000 mg-1200 mg daily) for 24 weeks. HCV RNA will be available for review by the clinical site personnel. After treatment is completed, subjects will be followed for 24 weeks. Subjects who discontinue early should be followed for 24 weeks post-treatment.

The primary analysis is SVR12 and the final analysis is SVR24.

Duration of study:

The screening/enrollment period is anticipated to be approximately 8 weeks from FPFV to LPFV. Study duration will be 52 weeks (4 week screening period, 24 weeks of therapy, and 24 weeks of follow-up).

Virologic Failure:

Virologic breakthrough is defined as:

1. Any confirmed ≥ 1 log10 increase in HCV RNA from nadir, OR;
2. Any confirmed HCV RNA ≥ LLOQ after HCV RNA <LLOQ, TD or TND while on treatment

Subjects who meet a definition of viral breakthrough will discontinue therapy. If discontinuation of therapy is required, this must occur no later than the next study visit following confirmation of breakthrough.

Viral relapse is defined as:

> Confirmed HCV RNA ≥ LLOQ in post-treatment follow-up after HCV RNA < LLOQ, TND at EOT

Long-term follow-up study: Following completion of the follow-up period of the study, select subjects at selected sites may be asked to enroll into a separate long term observational 3 year follow-up study to evaluate durability of response (if SVR is achieved) or persistence of possible drug-resistant virus (if treatment failure occurs). 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 provide BMS supplied 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.

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) Freely given informed consent must be obtained from subjects prior to clinical trial participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

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 at screening (or a liver biopsy performed within 36 months prior to enrollment with evidence of chronic Hepatitis C such as the presence of fibrosis).

c) HCV RNA ≥ 10,000 IU/mL at Screening

d) Subjects who are HCV-treatment naive with no previous exposure to any:

i. Interferon formulation (ie IFNα, peg-IFNα) or RBV
ii. HCV direct acting antivirals (DAAs)

OR

e) Subjects who are HCV-treatment experienced:
   i. All anti-HCV therapies (for example, IFNα with or without RBV, SOF/RBV, cyclophilin inhibitors and inhibitors of microRNA) are permitted with the exception of previous exposure to NS5A inhibitors.
   ii. All permitted prior anti-HCV therapies must be discontinued or completed ≥ 12 weeks prior to screening.

   Documentation of prior virologic response to treatment is desirable but not strictly required.

f) Subjects with compensated cirrhosis. Determination of cirrhosis status is required prior to randomization. A biopsy is not needed for participation. Cirrhosis will be defined as any one of the following:
   i. Liver biopsy at any time prior to Screening showing cirrhosis (Metavir > F3, Ishak > 4, or equivalent), OR
   ii. Most recent Fibroscan with a result of ≥ 14.6 kPa within ≤ 1 year of Baseline/Day 1, OR
   iii. FibroTest score of ≥ 0.75 AND an APRI of ≥ 2 at Screening

   In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy is required. Liver biopsy supersedes Fibroscan which supersedes FibroTest.

g) Body Mass Index (BMI) of 18 to 40 kg/m^2, inclusive at Screening.

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) up to one time. If re-enrolled, the subject must be re-consented.

i) Subjects with HCV monoinfection or HCV/HIV-1 coinfection.
   i. Subjects with HCV/HIV-1 coinfection must currently be receiving cART (See section 3.4.2 for permitted cART), have CD4 cell count >200 cells/μL at screening, HIV RNA < 40 copies/mL at screening and must be <200 copies/mL within 8 weeks prior to screening.

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 the duration of treatment and for a total of 6 months post-treatment completion or time specified by country-specific RBV label, whichever is longer.

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

   i. For the duration of treatment with RBV and for 6 months post-treatment completion, or per local guidelines, whichever is longer. In addition, male subjects must be willing to refrain from sperm donation during this time

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

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 on the use of highly effective methods of contraception, which have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to use two methods of contraception. This would include:

1) Any 2 Highly Effective Methods indicated below, or
2) 1 Highly Effective method and one Less Effective Method.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use at least one of the highly effective methods of contraception listed below in addition to another highly effective method or less effective method. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1) Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®**.**
2) Nonhormonal IUDs, such as ParaGard®
3) Bilateral tubal occlusion
4) Vasectomised partner with documented azoospermia 90 days after procedure
   - ♦ Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

5) Intrauterine hormone-releasing system (IUS).
6) Complete abstinence
    - ♦ Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms)
    - ♦ Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment plus the following:
        - o For both WOCBP and men receiving RBV: 6 months post-treatment completion or time specified by country-specific RBV label, whichever is longer.
    - ♦ It is not necessary to use any other method of contraception when complete abstinence is elected.
    - ♦ Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 6.4.
    - ♦ Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
    - ♦ The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Less Effective Methods of Contraception (Can only be utilized in combination with one highly effective method):

- Male or female condom with or without spermicide *
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide
- For **female partner**, who is a WOCBP, of a male subject participating in the study may use Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action **(Note: Progestogen only hormonal contraception is NOT an acceptable method of contraception for WOCBP female subjects).**

*A male and a 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.

UNACCEPTABLE METHODS OF CONTRACEPTION

1) Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2) Withdrawal (coitus interruptus)
3) Spermicide only
4) Lactation amenorrhea method (LAM)

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

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

b) Absence of cirrhosis (subject must meet inclusion criteria of compensated cirrhosis).

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 an ongoing 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) 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);

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

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

j) Confirmed, uncontrolled hypertension (any screening systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg should be excluded);

k) 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

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

m) Inability to tolerate oral medication;

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

o) Prior NS5A treatment failures;

p) Discontinuations of prior SOF/RBV treatment due to intolerance and/or exacerbations of anemia;

q) Subjects infected with HIV-2;

r) Presence of AIDS-defining opportunistic infections or any AIDS diagnosis within 12 weeks prior to study entry (AIDS-defining opportunistic infections as defined by the CDC);

s) The following conditions are exclusion criteria for the use of RBV, based on the label:

i. History of hemoglobinopathies (eg, thalassemia major or sickle cell anemia), diagnoses associated with an increased baseline risk for anemia (eg, spherocytosis), hemolytic anemia, or diseases in which anemia would be medically problematic;

ii. History of cardiomyopathy, active unstable coronary artery disease (including angina), ventricular arrhythmia, congestive heart failure (other than fluid overload due to hepatic insufficiency), pulmonary hypertension or other clinically significant cardiac disease;

iii. Historical or current electrocardiogram (ECG) finding indicative of cardiovascular instability, including but not limited to evidence of myocardial ischemia, unstable re-entry phenomena, other significant dysrhythmias, and/or uncontrolled hypertension

iv. History of hypersensitivity to drugs with a similar biochemical structure to RBV;

v. Any other criteria that would exclude the subject from receiving RBV, per the local label

3) Physical and Laboratory Test Findings

a) Alanine aminotransferase (ALT) ≥ 10x ULN

b) Total bilirubin ≥ 2 mg/dL (≥ 34 μmol/L), unless due to Atazanavir/Ritonavir treatment or subject has a documented history of Gilbert's disease

c) Albumin < 3.0 g/dL (30 g/L);

d) Platelets < 50 x 103 cells/μL;

e) ANC < 0.75 x 103 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, SOF, and RBV

b) Any other criteria or known contraindication that would exclude the subject from receiving DCV, SOF, and RBV

5) Prohibited Treatments and/or Therapies

a) Exposure to any investigational drug or placebo within 4 weeks of study drug administration

b) Use of amiodarone for 60 day time period prior to start of treatment

Refer to Section 3.4.1 for prohibited and/or restricted treatments during treatment, re-treatment and post-treatment

6) Sex and Reproductive Status

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

b) Male subjects must confirm that their female sexual partners are not pregnant at the time of screening

7) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required).

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

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

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

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, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

*Females 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.

- 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. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

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 use of amiodarone is prohibited and must be discontinued 60 days prior to the start of treatment.

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, 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)

3.4.1.2 Prohibited and/or Restricted Treatments for Subjects on RBV

The use of erythropoiesis-stimulating agents (ESAs) is discouraged. The risks and benefits of the use of ESAs for the management of HCV treatment-related anemia has not been standardized nor established in well controlled clinical trials. Although the use of ESA for the treatment of HCV treatment-related anemia is at the investigator's discretion, the following guidelines are recommended (please refer to the ESAs product information for additional information):

- ESAs should not be initiated until the hemoglobin (Hb) falls below 10g/dL
- Iron assessments should be obtained prior to and during treatment with ESA
- Iron supplementation should be initiated for deficient subjects and to maintain transferrin saturation at a level that will support erythropoiesis
- Once an ESA is initiated, Hb levels and blood pressure must be monitored weekly until Hb level stabilizes
- Treatment should target a Hb level sufficient to avoid transfusion
- ESA dose should be titrated to treatment response
- ESA dose should be reduced if the Hb increases by more than 1 g/dL in a 2-week period
- ESA dose should not exceed those recommended for currently approved indications
- ESAs should not be used in subjects at increased risk for thromboembolic events, cardiovascular events, including those with inadequately controlled hypertension, and in subjects diagnosed with malignancies

The cost of ESAs or granulocyte colony-stimulating factors will not be reimbursed by the Sponsor because of the rationale above.

[redacted]

[redacted]

[redacted]

3.4.2.1 Prohibited and/or Restricted Treatments for Subjects on cART regimens

Most of the commonly used ART will be allowed as outlined in Table 3.4.2-1. Alternative cART medications not listed may be considered only after review with the BMS medical monitor.

Use of any other cART therapy within one month prior to Day 1 of study drug dosing and throughout the treatment period of the trial is prohibited.

Co-administration of a non-nucleoside reverse transcriptase inhibitor (NNRTI) (excluding rilpivirine) with a boosted protease inhibitor (PI) **is prohibited**.

3.4.3 Change of cART regimens

For subjects receiving cART and requiring a change in therapy, the choice of antiretrovirals will be determined by the investigator on the basis of the HIV viral resistance profile and the subject's HIV treatment history. Refer to Table 3.4.2-1 and local country label for guidance.

cART should remain unchanged throughout the duration of the study unless changes are required in the opinion of the investigator (ie, confirmed on-treatment HIV RNA ≥ 400 copies/mL, treatment-limiting antiretroviral toxicity, etc) in consultation with the BMS medical monitor. The choice of permitted antiretroviral regimen will be determined by the investigator on the basis of prior treatment history (including HIV viral resistance profile for the subject), local HIV treatment guidelines, and expert opinion.

3.4.4 Definitions for HIV management

This section provides definitions for the clinical management of subjects with regard to HIV viral rebound and virologic failure during the study.

HIV Virologic Failure is defined as:

Confirmed HIV RNA value ≥ 400 copies/mL. Measurements are confirmed by a second plasma HIV RNA level ≥ 400 copies/mL redrawn within 2 to 4 weeks from original sample.

HIV Viral rebound is defined as:

A confirmed plasma HIV RNA level ≥ 200 copies/mL. Confirmation should be within 2-4 weeks after the original rebound sample.

HIV Viral blip is defined as:

- An isolated detectable HIV RNA (≥ 40 copies/mL) level that is followed by a return to virologic suppression.

Subjects meeting the criteria for viral rebound or virologic failure at any time during the study will be managed as follows:

- Those with a confirmatory HIV RNA of < 200 copies/mL may continue on their assigned HIV treatment
- Those subjects with a confirmed HIV RNA of ≥ 200 copies/mL may remain on assigned HCV and HIV treatment at the discretion of the investigator, in consultation with the BMS Medical Monitor
- An HIV viral resistance test will be conducted automatically in subjects with confirmed HIV RNA ≥ 400 copies/mL and the result forwarded to the study site
- Subjects with Genotypic and/or Phenotypic resistance to one or more assigned antiretroviral treatment may be allowed to switch to a different antiretroviral therapy. The choice of the new antiretroviral therapy will be those permitted by the protocol and determined by the investigator on the basis of the HIV viral resistance profile for the subject and local guidelines for treatment of HIV infected subjects
- Further management will be at the discretion of the investigator in consultation with the BMS Medical Monitor

Subjects who require discontinuation due to HIV virologic failure should comply with protocol specified follow-up procedures

3.4.5 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
- 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 following any Treatment with Study Drug

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
- 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
- Pregnancy
- 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 (confirmatory results must be obtained 2 weeks from the original result) 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.

Any subject who receives anti-HCV therapy in the post-treatment period prior to Post-Treatment 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 investigator must notify the BMS Medical Monitor/designee in the event that a female subject becomes pregnant within 24 hours and submit information to WWS on the pregnancy form within 24 hours. The study drug should be discontinued after pregnancy has been confirmed.

All subjects who discontinue study drug 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).

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.

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 Study Drug Study Follow up

In this study, Post-Treatment Follow up Week 12 is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug 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 drug 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 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

Table 4-1: Study Drugs for AI444379

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Daclatasvir[a] (BMS-790052-05), HCV NS5A inhibitor, Film Coated Tablet	60 mg (as the free base)	IP	Open Label	33 tablets per bottle. 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.
Daclatasvir[a] (BMS-790052-05), HCV NS5A inhibitor, Film Coated Tablet	30 mg (as the free base)	IP	Open Label	33 tablets per bottle. 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)[b] nucleotide NS5B polymerase inhibitor, Film Coated Tablet	400 mg	IP	Open Label	28 tablets per bottle. Yellow, capsule-shaped, film-coated tablet debossed with "GSI" on one side and "7977" on the other side.	Store at 15°C-25°C (59°F-77°F). Store in original container.
Ribavirin (RBV)[b], nucleoside analogue, Film Coated Tablet	200 mg	IP	Open Label	168 tablets per bottle. Capsule-shaped, light blue color, film-coated tablet debossed with "200"on one side and logo "3RP" on the other side.	Store at 25 °C (77 °F). Excursions permitted between 15 °C and 30 °C (59 °F to 86 °F). Keep bottle tightly closed.

[a] Daclatasvir will be provided as the Phase 3 clinical presentation for 30 mg and 60 mg film-coated tablets.

[b] Commercially available Sofosbuvir (Sovaldi®) and Ribavirin (Ribasphere®) will be procured and distributed by BMS. Storage for SOF should be in accordance with the SmPC. Storage for RBV should be in accordance with the package insert. SOF and RBV will be supplied by BMS, but may be sourced locally if necessary.

4.1 Investigational Product

4.2 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.

Additionally, in this protocol, cART medications are considered non-investigational study drug and will not be provided by the sponsor. HIV medications will be obtained by the investigating sites standard prescribing procedures. Marketed product will be utilized for this study and should be stored in accordance with the package insert or summary of product characteristics (SmPC).

4.3 Storage 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.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) 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).

[redacted]

[redacted]

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Assessment of study medication will be performed at each study visit. The subject 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) and RBV 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.

Subjects 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 subject if there are discrepancies between the diary and the drug log to reconcile actual dosing at each visit

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) 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 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 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.

4.9 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 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.

4.10 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

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 IRT manual. Dosing diaries may 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 assessment listed in Table 5.3.1-1 will be analyzed by a central laboratory or other BMS specified laboratory. Subjects are not required to be fasting prior to any laboratory assessments.

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 monthly during post-treatment (Weeks 4, 8, 12, 16, 20, and 24) for WOCBP receiving RBV (see Table 5.1-3). 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.

The Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test (LLOQ = 15 IU/mL) will be used to measure HCV RNA levels. The Versant HCV genotype 2.0 assay (LIPA) will be used for all genotype/subtype assessments. For samples where HCV genotype or subtype results are unavailable or inconclusive, the Abbott RealTime HCV Genotype II assay or viral sequence analysis may be used for genotype/subtype assessments. HCV RNA and HCV genotype will be analyzed by the central laboratory.

5.3.2 Imaging Assessment for the Study

Not Applicable.

5.3.3 Adverse Events Assessment

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.

5.3.4 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.

5.3.5 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, for subjects treated with DCV + SOF + RBV for 24 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, 8, 12, 16, 20 and 24 (EOT); post-treatment Weeks 4 and 24 will be used for the secondary antiviral assessment in this study.

5.5 Pharmacokinetic Assessments

[redacted]

[redacted]

5.7 Outcomes Research Assessments

Not Applicable

5.8 Other Assessments

5.8.1 HCV Virologic Resistance Testing

[redacted]

5.8.2 HIV Resistance Testing

Plasma samples for HIV resistance testing will be collected at Baseline and all on-treatment, post-treatment, visits and are tested upon rebound or virologic failure. An HIV viral resistance test will be automatically conducted following confirmation of HIV RNA levels of ≥ 400 copies/mL and the result will be forwarded to the study site. Results should be confirmed within 2-4 weeks after the visit where HIV RNA was ≥ 400 copies/mL. The investigators may request a resistance test if HIV RNA levels are lower (between 200 – 400 copies/mL) based upon clinical experience.

5.8.3 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.

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 study drug 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 study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal 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.)

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

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).

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).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited 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 must 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 must 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 must 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 of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system

is not functioning. In this case, the paper forms 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. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. 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 must 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, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must 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 electronic) as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- 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 study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

The study drug should be permanently discontinued after pregnancy has been confirmed.

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 of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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

All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

- DCV: total daily dose > 200 mg
- SOF: total daily dose > 800 mg
- RBV: total daily dose > 20 mg/kg/day

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:

- ALT ≥ 5 times baseline or nadir value, whichever is lower, AND ≥ 10 x ULN (upper limit of normal
  AND
- Total bilirubin ≥ 2 x ULN
  AND
- No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, acute viral hepatitis, cholestasis, pre-existing hepatic disease excluding HCV or the administration of other drug(s), herbal medications or substances known to be hepatotoxic

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

Not applicable

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

[redacted]

8.2 Populations for Analyses

- Enrolled subjects are those who signed an informed consent form and are assigned a Subject Identification number (PID)
- Randomized subjects are enrolled subjects who received a treatment assignment from the central randomization center
- Treated subjects are randomized subjects who received at least 1 dose of study therapy
- Follow-up subjects are treated subjects who continue into the follow-up period, as indicated on the end of treatment subject status Case Report Form (CRF).

8.3 Endpoints

Efficacy analyses will evaluate HCV RNA as measured by the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test (LLOQ = 15 IU/mL)

8.3.1 Primary Endpoint

Proportion of subjects with SVR_{12}, defined as HCV RNA < LLOQ, target detected (TD) or target not detected (TND) at follow-up Week 12 in all treated subjects. Missing HCV RNA data at follow-up Week 12 will be imputed using the Next Value Carried Backwards (NVCB) approach, i.e., missing HCV RNA data in the follow-up Week 12 window

will be imputed using the next and closest available HCV RNA measurement after the follow-up Week 12 HCV RNA window.

8.3.2 Key Secondary Endpoint

- The proportion of subjects who achieve SVR_{12} in the presence and absence of baseline NS5A resistance-associated polymorphisms.

8.3.3 Secondary Endpoints

- On treatment safety, as measured by frequency of deaths, serious adverse events (SAE)s, discontinuation due to adverse events (AE)s, Grade 3/4 AEs and Grade 3/4 laboratory abnormalities;
- The proportion of subjects who achieve HCV RNA < LLOQ, TD or TND at each of the following Weeks: 1, 2, 4, 8, 12, 16, 20, 24, 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, 8, 12, 16, 20, 24, and EOT

8.3.4 Exploratory Endpoint(s)

[redacted]

8.4 Analyses

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

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 treatment 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, HIV positive, and fibrosis stage
- 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 treatment arm.

8.4.2.1 Primary Efficacy

The primary analysis will be performed after all subjects have completed post-treatment Week 12 (SVR12). A final analysis (SVR24) will be performed at study completion.

The primary analysis for the primary endpoint SVR12 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, ie, missing HCV RNA data in the follow-up Week 12 window will be imputed using the next and closest available HCV RNA measurement after the follow-up Week 12 HCV RNA visit window.

The lower bound of the SVR12 95% confidence interval (CI) will be used to compare to the historical threshold of 79%. If it exceeds 79%, it can be concluded that the primary objective is achieved.

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

- Sensitivity analysis using mITT: 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. The numerator is based on subject meeting the response criteria. However, the denominator is based on treated subjects with HCV RNA at post-treatment Week 12

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, 8, 12,16, 20, 24 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, 8,12, 16, 20, 24 and EOT

8.4.3 Safety Analyses

Safety data will be summarized for treated subjects.

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.

8.4.4 Pharmacokinetic Analyses

[redacted]

[redacted]

8.4.6 Outcomes Research Analyses

Not Applicable

8.4.7 Pharmacodynamics

[redacted]

8.4.8 Other Analyses

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

8.5 Interim Analyses

The primary analysis will be performed after all subjects have completed post-treatment Week 12 (SVR12). A final analysis (SVR24) will be performed at study completion. Additional interim efficacy analyses may be performed prior to post-treatment Week 12 to support external data presentations or for correspondences with health authorities.

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

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

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 study drug (inventoried and dispensed) is maintained at the study site to include investigational products. 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 electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. 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, 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 as appropriate based on 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 must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AFP	Alpha fetoprotein
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APRI	aspartate aminotransferase platelet ratio index
ART	Anti-retroviral therapy
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
cART	Combination anti-retroviral therapy
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
CTA	Clinical Trial Agreement
CVR	combined virologic response
CYP	cytochrome p-450

Term	Definition
D/C	discontinue
DAA	direct acting antiviral
DAIDS	Division of AIDS
DCV	daclatasvir
DCV/ASV	daclatasvir and asunaprevir combination therapy
DCV+SOF	daclatasvir and sofosbuvir combination therapy
DILI	drug-induced liver injury
dL	Deciliter
DMC	Data Monitoring Committee
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
DUAL	daclatasvir/asunaprevir therapy
EAP	Expanded Access Program
ED50	50% effective concentration
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
Eg	exempli gratia (for example)
EOT	End of Treatment
E-R	Exposure-response
ERCP	endoscopic retrograde cholangiopancreatography
ESAs	erythropoiesis-stimulating agents
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
Hb	hemoglobin
HBsAg	hepatitis B surface antigen

Term	Definition
HBV	hepatitis B virus
HCC	heptaocellular carcinoma
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HE	hepatic encephalopathy
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICH	International Conference on Harmonisation
Ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IUD	intrauterine device
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

Term	Definition
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
PPK	Population pharmacokinetics
QD, qd	quaque die, once daily
QUAD	daclatasvir/asunaprevir/pegylated interferon/ribavirin therapy
RBV	ribavirin
RCI	replication complex inhibitor
SAE	serious adverse event
SAR	serious adverse reaction
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
TN	Treatment-Naïve
TVR	telaprevir
ULN	Upper limit of normal
USPI	United States Package Insert
VBT	virologic breakthrough

Term	Definition
VK	viral kinetics
WBC	white blood cell
WOCBP	women of childbearing potential

12 REFERENCES

REFERENCES FOR THE USE OF CONDOMS WITH SPERMICIDE.

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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.

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
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

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.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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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.

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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.).

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

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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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
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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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
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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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
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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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
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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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
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.).

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
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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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
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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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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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 x 10^9/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 10^9 – 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 10^9 – 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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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**
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

* 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

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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