Protocol Number: AI444423
IND Number: N/A
EX-US Non-IND
EUDRACT Number: 2017-003338-94
Date: 30-Nov-2017
Revised Date: 18-Dec-2019

Clinical Protocol AI444423

Open-Label, Single-Arm Trial to Evaluate the Pharmacokinetics, Safety and Efficacy of Daclatasvir (DCV) in Combination with Sofosbuvir (SOF) in Children from 3 to less than 18 Years of Age with GT-1 to -6 Chronic Hepatitis C (CHC) Infection

Revised Protocol 01

Study Director
Michelle Treitel, PhD

[redacted]

Medical Monitor

[redacted]

[redacted]

DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Revised Protocol 01	18-Dec-2019	• Early termination of the study • Participants will not be enrolled in Cohorts 2 and 3 • Long-term follow-up period will be reduced from the initially planned 96 week follow-up period after Post-Treatment Week 12. • Limitation of enrollment in Cohort 1 to participants weighing ≥ 45 kg • Removal of the analyses related to the secondary objectives of evaluation of genotypic substitution(s) associated with virologic failure and the assessment of palatability and acceptability of the daclatasvir formulations • [redacted] • Removal of Interim Analysis • Update of Appendix 5 with July 2017 version 2.1 of DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
Original Protocol	30-Nov-2017	Not applicable

[redacted]

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Update with name of new Medical Monitor	
Document History	Added Revised Protocol 01 to the table	[redacted]
Synopsis	Updated to align with changes made in the protocol body as described below	[redacted]
Table 2-2: On Treatment Procedural Outline	Addition of footnote to clarify drug dispensing and dosing at the Treatment Week 12 visit	[redacted]
Table 2-3:Post-Treatment Procedural Outline	Addition of note to indicate that upon approval of Revised Protocol 01, participants should perform an End of Study visit and do not need to complete any other post-treatment visit if not yet conducted	[redacted]
[redacted]	Addition of note: With early termination of this study, only participants 12 to <18 years of age will be enrolled in the study (Cohort 1). Upon approval of the revised protocol, all enrolled participants will be asked to return to the clinic to perform an End of Study (EOS) visit and will not complete the initially planned 96 week LTFU period. No participants 3 to <12 years of age will be enrolled (Cohorts 2 and 3).	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01

Section Number & Title	Description of Change	Brief Rationale
[redacted]	Added note: On 18 October 2019, the PDCO adopted a positive opinion on BMS' PIP request for a full product-specific waiver (EMEA-001191-PIP01-11-M03) on the grounds that clinical studies with DAKLINZA cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subsets. As a result, BMS will terminate Study AI444423 early.	[redacted]
[redacted]	Added note: With regard to paediatric HCV treatment regimens, all-oral, pangenotypic, non-DCV containing regimens, are being developed with the intention to commercialize them in the context of their existing adult MA; these regimens are more advanced in their development than the DCV+SOF regimen, the regimen being investigated in this study. In this context, on 18 October 2019, the PDCO of the EMA adopted a positive opinion on BMS' PIP request for a full product-specific waiver (EMEA-001191-PIP01-11-M03) on the grounds that clinical studies with DAKLINZA cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subsets. As a result, BMS will terminate Study AI444423 early.	[redacted]
Section 4 Objectives and Endpoints	Added note: With the early termination of this study, previously collected data to address PK, SVR, and select safety assessments (e.g. AEs, laboratory tests, end of treatment subject status) will be reported only within adolescent participants 12 to <18 years of age. The secondary objectives related to assessment of genotypic substitutions associated with virologic failure and the acceptability and palatability of the daclatasvir formulations and the exploratory objective regarding durability of response will not be reported.	[redacted]
Section 5.1 Overall Design	Addition of note: Due to the early termination of the study, only participants 12 to <18 years of age were enrolled in the study into Cohort 1; no participants will be enrolled in Cohorts 2 and 3. The duration of the Long-Term Follow-Up period for these participants will be less than the initially planned 96 weeks. Upon approval of this revised protocol, participants will return to the study center to conduct an EOS visit.	[redacted]
Section 5.2 Number of Participants	Addition of note: Although the original protocol provided for a total of 30 participants, only 5 participants, limited to Cohort 1, will have been enrolled in the study, as the result of the early termination of this study.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]	Added note: Due to the early termination of the study, only 5 participants 12 to <18 years of age were enrolled in the study into Cohort 1; the duration of the Long-Term Follow-Up period for these participants will be less than the initially planned 96 weeks. No participants will be enrolled in Cohorts 2 and 3.	[redacted]
Section 6.1 Inclusion Criteria	Added limitation of enrollment to Cohort 1 participants ≥ 45 kg on Day 1	[redacted]
Section 7.1 Treatments Administered	Updated text with the limitation of participants in Cohort 1 to participants ≥ 45 kg on Day 1 Added note: Due to the early termination of the study, participants will only have been enrolled in Cohort 1 and administered the adult formulations of DCV and SOF (60 mg dose of DCV and 400 mg dose of SOF). No paediatric formulations will be administered in the study. Added footnote to Table 7.1-1 to clarify that adult formulation would only be administered to participants in Cohort 1 who were required to be ≥ 45kg	[redacted]
Section 8.1.1 Post Study Treatment Follow Up	Clarified duration of follow up period for participants who discontinue as 'completion of the designated follow up period' versus 'conclusion of study'	[redacted]
Section 8.2 Discontinuation from the Study	Added that follow-up procedures should be completed prior to initiation of alternate HCV therapy	[redacted]
Section 9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Added SOF SmPC as reference safety information	[redacted]
Section 9.4.4 Clinical Safety Laboratory Assessments	Added note: All laboratory assessments scheduled for the Post-Treatment Week 108 visit should be performed at the EOS visit.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01

Section Number & Title	Description of Change	Brief Rationale
Section 9.8.2.1 HCV Virologic Resistance Testing	Added note that resistance testing will not be performed on Baseline samples	[redacted]
Section 9.8.2.3 Brief Questionnaire/Interim Phone Contact	Added note: Due to the early termination of the study, participants will perform an EOS visit and interim telephone contact will not be necessary after the EOS visit.	[redacted]
Section 10.1 Sample Size Determination	Added note: Not Applicable due to the early termination of the study; a total of 5 participants will have been enrolled in the study into Cohort 1.	[redacted]
Section 10.3 Statistical Analyses	Added note: With the early termination of this study, previously collected data to address PK, SVR, and select safety assessments (e.g. AEs, laboratory tests, end of treatment subject status) will be reported only within adolescent participants 12 to <18 years of age. Given the small number of subjects enrolled in the study, no statistical analyses will be performed. Genotypic substitution(s) associated with virologic failure and the acceptability and palatability of the DCV formulations will not be reported. Likewise, an interim analysis will not be performed.	[redacted]
Section 10.3.2 Resistance Analyses	Added note: These data will not be reported because the prevalence of the relevant RAV varies from 4-10% and as such might not be detected at Baseline in a sample size of 5 participants. As of 18 October 2019, all participants had completed at least 41 weeks of post-treatment follow-up and none had experienced viroloogic failure.	[redacted]
Section 10.3.5.1 Acceptability and Palatability Assessments of Daclatasvir Formulations	Added note: These data will not be reported as only the adult formulation was administered in the study and there is no value to perform an analysis of the adult formulation	[redacted]
Section 10.3.6 Interim Analysis	Added note: An interim analysis will not be performed. As only 5 subjects will be enrolled in this study, analyses are not needed to guide dosing for additional participants.	[redacted]
Appendix 5	Updated version of DIADS table from December 2004 to July 2017 version 2.1 of DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events	[redacted]

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: Open-Label, Single-Arm Trial to Evaluate the Pharmacokinetics, Safety and Efficacy of Daclatasvir (DCV) in Combination with Sofosbuvir (SOF) in Children from 3 to less than 18 Years of Age with GT-1 to -6 Chronic Hepatitis C (CHC) Infection

Study Phase: 2

[redacted]

[redacted]

Study Population:

Paediatric patients (3 years to < 18 years of age) monoinfected with Hepatitis C virus (genotypes (GT)-1 to -6) who are non-cirrhotic and either treatment-naive or treatment-experienced.

Note: With the early termination of the study, only adolescent participants 12 to <18 years of age will have been enrolled in the study.

Objectives and Endpoints:

Note: With the early termination of this study, previously collected data to address PK, SVR, and select safety assessments (e.g. Adverse Events (AEs), laboratory tests, end of treatment subject status) will be reported only within adolescent participants 12 to <18 years of age. The secondary objectives related to assessment of genotypic substitutions associated with virologic failure and the acceptability and palatability of the daclatasvir formulations [redacted] will not be reported.

Objectives	Endpoints
Primary • To evaluate the PK profile of DCV in combination with SOF in children and adolescents aged 3 to <18 years of age	• Pharmacokinetic parameters (Cmin, Cmax, Tmax, AUC (TAU), CLT/F) for DCV derived from plasma concentration versus time data on Day 10 (+/-3 days) within a dosing interval. • In Cohort 3 (ages 3 to <6 years of age); PK parameters will be assessed using model-based analyses with 5 samples from each participant.
Secondary • To assess the safety and tolerability of the DCV+SOF regimen in paediatric participants • To determine the proportion of participants with SVR12	• Frequencies of serious adverse events (SAEs), adverse events (AEs) leading to discontinuation of study therapy, AEs by intensity, and laboratory abnormalities by toxicity grade on treatment and during follow-up • Proportion of participants with HCV RNA <LLOQ (TD or TND) at post-treatment follow-up Week 12

Objectives	Endpoints
• To evaluate genotypic substitution(s) associated with virologic failure	• Frequencies of NS5A and NS5B resistance-associated variants (RAVs) emergent at the time of virologic failure on treatment and during follow-up in non-responders
• To assess the acceptability and palatability for the age-appropriate chewable tablet formulation, and acceptability for adult film-coated tablet	• Summary of responses from questionnaire assessing acceptability and palatability at Day 1, Week 4, and Week 12
[redacted]	[redacted]

Overall Design:

The study will be an open-label, single-arm, descending-age cohort trial evaluating the PK profile, safety, tolerability, and efficacy of DCV+SOF administered for 12 weeks to paediatric participants (3 < 18 years of age) with CHC virus infection.

Enrolment will begin with Cohort 1, followed by Cohorts 2 and 3.

- Cohort 1: 12 to < 18 years of age
- Cohort 2: 6 to < 12 years of age
- Cohort 3: 3 to < 6 years of age

Note: Due to the early termination of the study, only participants 12 to <18 years of age were enrolled in the study into Cohort 1; no participants will be enrolled in Cohorts 2 and 3.

Samples for assessment of DCV PK will be collected on Day 10 of the study. In each cohort, DCV PK will be evaluated after the initial 5 participants complete their Day 10 visit in order to determine if the target DCV exposure is achieved.

Enrolment in Cohorts 2 and 3 will be dependent on the availability of the European Commission (EC) approved SOF age appropriate dose and formulation for the corresponding age cohort.

Post treatment, participants will be followed for 12 weeks to assess sustained virologic response at Post-treatment Week 12 (SVR12) and then for an additional 2 years (96 weeks) as long-term follow-up to assess [redacted], durability of response, long-term safety, and the persistence of resistance variants in non-responders.

Note: With the early termination of this study, participants will not complete the initially planned 96 weeks of LTFU. As of 18 October 2019, all participants will have completed their Post Treatment Week 24 visit and approximately 41 to 53 weeks of post-treatment follow-up;

participants will be asked to return to the study site to perform an EOS visit upon approval of the revised protocol.

Number of Participants:

A minimum of 30 participants will be evaluated for the primary endpoint (PK), and assigned to 3 age-descending cohorts (12 to <18 years of age, 6 to < 12 years of age and 3 to < 6 years of age); at least 8 participants will be treated in each age cohort.

Note: Although the original protocol provided for a total of 30 participants, only 5 participants, limited to Cohort 1, will have been enrolled in the study as the result of the early termination of this study.

For further information regarding sample size determination, please refer to Section 10.1.

Treatment Arms and Duration:

This will be a single-arm study in which participants will be administered DCV+SOF QD for 12 weeks.

Study treatment:

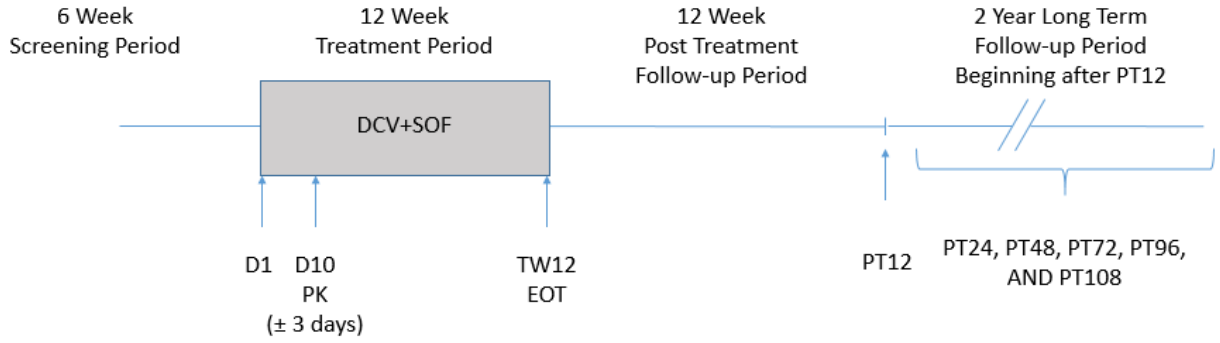
Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Daclatasvir[a] (BMS-790052-05/DCV) Film Coated Tablet	60 mg (as the free base)	IP	Open	Bottle Each tablet is plain, green, biconvex, pentagonal and film-coated.	Store per IP Label.
Daclatasvir Dihydrochloride Chewable Tablet	20 mg	IP	Open	Blister A white to off white, flat, plain oval tablet	Store per IP Label.
Daclatasvir Dihydrochloride Chewable Tablet	10 mg	IP	Open	Blister A white to off white, flat, plain round tablet	Store per IP Label.
Daclatasvir Dihydrochloride Chewable Tablet	5 mg	IP	Open	Blister A white to off white, flat, plain round tablet	Store per IP Label.
Sofosbuvir[b], (SOF) Film Coated Tablet	400 mg	IP	Open	Bottle Yellow, capsule-shaped, film-coated tablets debossed with "GSI" on one side and "7977" on the other side	Store per IP Label
Sofosbuvir (SOF) (paediatric formulation, TBD)	50 mg	IP	Open	TBD	Store per IP Label

[a] Daclatasvir clinical presentation, adult formulation

[b] Sofosbuvir adult formulation

Note: Due to the early termination of the study, participants will only have been enrolled in Cohort 1 and administered the adult formulations of DCV and SOF. The paediatric formulations will not be administered in the study.

Study Schematic:



The total duration of the study for each participant is approximately 2.5 years:

- Screening: 42 days
- Treatment Duration: 12 weeks
- Post-Treatment Follow-up Duration: Upon completion of the Post-treatment Week 12 visit, participants will be followed for an additional 2 years (96 weeks) as long-term follow-up to assess SVR24, durability of response, long term safety, and the persistence of resistance variants in non-responders.

Note: With the early termination of this study, the duration of the study for participants will be less than 2.5 years; participants will not complete the initially planned 96 weeks of long-term follow-up. As of 18 October 2019, all participants will have already completed their Post Treatment Week 24 visit and approximately 43 to 51 weeks of post-treatment follow-up. Upon approval of the revised protocol, participants will be asked to return to the study site to perform an EOS visit.

The dose of DCV will be determined according to the weight of the participant prior to dosing on Day 1; the dose will not be adjusted to weight over the course of the study.

DCV should be administered as the adult film-coated 60-mg tablet formulation to adolescent participants 12 to < 18 years of age (Cohort 1 who are ≥ 45 kg) and as a paediatric chewable-tablet formulation (5, 10, 20 mg) to all participants < 12 years of age (Cohorts 2 and 3) according to Table 7.1-1.

The SOF dose administered will be the dose and formulation approved by the European Commission for the corresponding age cohort. Cohort 1 will receive the 400-mg adult

formulation. Enrollment in Cohorts 2 and 3 will begin following EC approval of the age appropriate dose and formulation for SOF for those respective age groups.

Doses of DCV and SOF assigned on Day 1 cannot be modified but can be interrupted or discontinued to manage adverse events. In the event of interruption or discontinuation, both DCV and SOF must be stopped simultaneously. DCV+SOF treatment can be interrupted for a maximum of 7 days, and if not restored after 7 days, the treatment should be permanently discontinued.

Note: DCV dose modification will only be permissible if PK data from the initial 5 participants in the cohort suggest that the dose administered does not achieve the desired exposure criteria. The sponsor will advise how to modify the dose of DCV being administered, if needed.

Note: With the early termination of this study, only the adult formulations of DCV and SOF will be administered in this study.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (AI444423)

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent and Assent (where applicable)	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	To include route of HCV transmission and prior response to anti-HCV medications, if applicable
HCV Serology	X	
HCV RNA and backup HCV RNA sample	X	
HCV Genotype	X	
HIV, HBV Serology	X	
Alpha fetoprotein (AFP)	X	
Assessment of liver fibrosis status by liver biopsy, Fibroscan or Serologic test (APRI [AST to platelet ratio index])	X	Refer to Section 6.2 for fibrosis determination criteria and timing of assessments
Safety Assessments		
Physical Examination	X	
Physical Measurements	X	Height and weight
Vital Signs	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been at rest
Serious Adverse Events Assessment	X	Report SAEs that occur after consent is obtained
Concomitant and Previous Medication Use	X	Refer to Section 7.7.1 for details
Laboratory Tests	X	Fasting not required, see Section 9.4.4
ECG, Single 12-Lead	X	ECG should be recorded after the participant has been at rest

Table 2-1: Screening Procedural Outline (AI444423)

Procedure	Screening Visit[a]	Notes
Pregnancy Test FOCBP only	X	Urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG); Collect serum sample if urine is positive. Pregnancy test should be repeated within 24 hours prior to first dose of study treatment
Obtain participant number via IRT	X	

[a] All screening procedures, except where noted, must be completed within 42 days of the screening visit

Table 2-2: On Treatment Procedural Outline (AI444423)

Procedure	Day 1 Visit	During Treatment Day 10 (± 3 days)	During Treatment Weeks 4 and 8 (± 3 days)	End of Treatment/ Week 12 (± 3 days)/Early Discontinuation	Notes
Eligibility Assessments					
Inclusion/Exclusion Criteria	X				Review eligibility criteria prior to treatment to ensure requirements are met
Safety Assessments					
Targeted Physical Examination	X		X	X	Should include assessment of heart, lung, and abdomen
Physical Measurements	X	X	X	X	Height and weight
Vital Signs	X	X	X	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate; blood pressure and heart rate should be measured after the participant has been at rest
Serious Adverse Event Assessment	X	X	X	X	
Adverse Events Assessment	X	X	X	X	AE assessment begins after Day 1 study treatment administration
Concomitant Medication Use	X	X	X	X	See Section 7.7.1
Laboratory Tests	X	X	X	X	Fasting not required. See Section 9.4.4
Pregnancy Test FOCBP only	X		X	X	Urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG); results of urine test, performed within 24 hours of first dose, should be negative prior to dosing

Table 2-2: On Treatment Procedural Outline (AI444423)

Procedure	Day 1 Visit	During Treatment Day 10 (± 3 days)	During Treatment Weeks 4 and 8 (± 3 days)	End of Treatment/ Week 12 (± 3 days)/Early Discontinuation	Notes
Efficacy Assessments					
HCV RNA and backup HCV RNA	X	X (primary tube required; backup sample optional)	X	X	Participants with indeterminate HCV RNA testing or with suspected on treatment failure (HCV virologic breakthrough) will be retested for HCV RNA, HCV genotype, and HCV resistance along with PK trough levels at an unscheduled visit as soon as possible before their next regular visit
HCV Resistance and back up HCV Resistance	X	X (primary tube required; backup sample optional)	X	X	
HCV Genotype	HCV Genotype sample to be collected at time of HCV RNA sample collection to confirm suspected virologic breakthrough/other on-treatment failure				
Other Assessments					
[redacted]	X				
Serial Blood PK of DCV and trough levels of SOF and its metabolites (all participants)		X			See Section 9.5
Trough Blood PK: DCV, SOF and its metabolites (all participants)			X	X	See Section 9.5

Table 2-2: On Treatment Procedural Outline (AI444423)

Procedure	Day 1 Visit	During Treatment Day 10 (± 3 days)	During Treatment Weeks 4 and 8 (± 3 days)	End of Treatment/ Week 12 (± 3 days)/Early Discontinuation	Notes
Acceptability and Palatability Questionnaire	X		X	X	Day 1, Week 4, and Week 12/ End of treatment/Early Discontinuation, See Section 9.8.2.2
Brief Questionnaire	X			X	A brief questionnaire will be completed by the participant/guardian to include contact details such as email address, primary care physician, and 2 non-residing contacts in case the participant/guardian cannot be reached for their study assessments unless prohibited by local laws or regulations
Study Treatment					
Register eligible participants for treatment via IRT	X				Day 1 age and weight to be used for determining formulation and dose
Dispense Study Treatment and on-site dosing	X	X	X[a]		Study treatment should be administered in office at all study visits and after trough PK sample collection on all visits after Day 1
Assessment of Study Medication Use/Treatment Compliance		X	X	X	See Section 7.6

[a] If the participant cannot attend the Treatment Week 12 visit as scheduled, the participant should complete treatment on Day 84. Treatment Week 12 assessments should be conducted once the participant returns to the site and no additional dispensing or dosing will occur on this visit. Similarly drug dispensing and dosing will not occur for those participants that discontinue early from the study

Table 2-3: Post-Treatment Long-term Procedural Outline (AI444423)

Procedure	Post-Treatment Week 4 (± 7 days)	Post-Treatment Weeks 12 and 24 (± 7 days)	Post-Treatment Weeks 48, 72, 96 (± 6 weeks)	Post-Treatment Week 108/ End of Study (± 6 weeks)	Notes
Safety Assessments					
Targeted Physical Examination	X			X	Should include assessment of heart, lung, and abdomen
Physical Measurements	X	X	X	X	Height and weight
Vital Signs	X	X	X	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been at rest.
Serious Adverse Events Assessment	X	X	X	X	Only SAEs related to study drug or protocol-specified procedure(s) should be reported after Post-Treatment Week 4.
Adverse Events Assessment	X				
Hepatic disease progression	X	X	X	X	Development of cirrhosis and/or its complications
Laboratory Tests	X	X	X	X	Fasting not required
Pregnancy Test FOCBP only	X				Post-Treatment Week 4 only. Urine pregnancy test; collect serum if urine is positive
Efficacy Assessments					
HCV RNA and backup HCV RNA sample	X	X	X	X	Participants with suspected relapse will have samples collected to retest HCV

Table 2-3: Post-Treatment Long-term Procedural Outline (AI444423)

Procedure	Post-Treatment Week 4 (± 7 days)	Post-Treatment Weeks 12 and 24 (± 7 days)	Post-Treatment Weeks 48, 72, 96 (± 6 weeks)	Post-Treatment Week 108/ End of Study (± 6 weeks)	Notes
HCV Resistance and backup HCV Resistance	X	X	X	X	RNA, HCV genotype, and HCV resistance at an unscheduled visit as soon as possible before their next regular visit
HCV Genotype	HCV Genotype sample to be collected at time of HCV RNA sample collection for suspected relapse to evaluate for possible re-infection/relapse				
Other Assessments					
Confirm Brief Questionnaire Responses[a]	X	X	X	X	
Interim Phone Contacts	Required on a quarterly basis in between office visits (ie, post-treatment Week 36, 60, and 84 (± 2 weeks)). The purpose of the phone contact is to verify the participant's continuation in the study and to confirm the next study visit.				

[a] Applicable where local regulations permit

Note: Upon approval of Revised Protocol 01, participants should perform an End of Study visit and do not need to complete any other post-treatment visits if not yet conducted.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Note: With the early termination of this study, previously collected data to address PK, SVR, and select safety assessments (e.g. AEs, laboratory tests, end of treatment subject status) will be reported only within adolescent participants 12 to <18 years of age. The secondary objectives related to assessment of genotypic substitutions associated with virologic failure and the acceptability and palatability of the daclatasvir formulations and the exploratory objective regarding durability of response will not be reported.

Objectives	Endpoints
Primary	
• To evaluate the PK profile of DCV in combination with SOF in children and adolescents aged 3 to <18 years of age	• Pharmacokinetic parameters (Cmin, Cmax, Tmax, AUC (TAU), CLT/F) for DCV derived from plasma concentration versus time data on Day 10 (± 3 days) within a dosing interval. • In Cohort 3 (ages 3 to < 6 years of age); PK parameters will be assessed using model-based analyses with 5 samples from each participant.
Secondary	
• To assess the safety and tolerability of the DCV+SOF regimen in paediatric participants	• Frequencies of serious adverse events (SAEs), adverse events (AEs) leading to discontinuation of study therapy, AEs by intensity, and laboratory abnormalities by toxicity grade on treatment and during follow-up
• To determine the proportion of participants with SVR12	• Proportion of participants with HCV RNA <LLOQ (TD or TND) at post-treatment follow-up Week 12
• To evaluate genotypic substitution(s) associated with virologic failure	• Frequencies of NS5A and NS5B resistance-associated variants (RAVs) emergent at the time of virologic failure on treatment and during follow-up in non-responders
• To assess the acceptability and palatability for the age-appropriate chewable tablet formulation, and acceptability for adult film-coated tablet	• Summary of responses from questionnaire assessing acceptability and palatability at Day 1, Week 4, and Week 12
[redacted]	[redacted]

5 STUDY DESIGN

5.1 Overall Design

The study will be an open-label, single-arm, descending age cohort trial evaluating the PK profile, safety, tolerability, and efficacy of DCV+SOF, administered for 12 weeks, to paediatric participants (3 years to < 18 years of age), monoinfected with the hepatitis C virus (genotypes (GT) -1 to -6), who are non-cirrhotic and either treatment naive or treatment experienced.

The total duration of the study for each participant is approximately 2.5 years:

- Screening Duration: 42 days
- Treatment Duration: 12 weeks
- Post-Treatment Follow-up Duration: 108 weeks. Upon completion of the Post-treatment Week 12 visit, participants will be followed for an additional 2 years (96 weeks) as long-term follow-up to assess SVR24, durability of response, long term safety, and the persistence of resistance variants in non-responders.

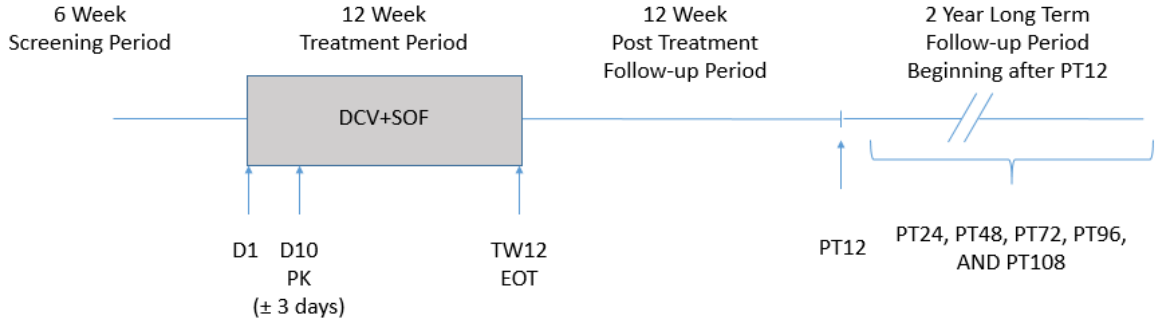
A minimum of 30 participants will be evaluated for the primary endpoint (PK), with at least 8 treated per age cohort:

- Cohort 1: 12 to < 18 years of age
- Cohort 2: 6 to < 12 years of age
- Cohort 3: 3 to < 6 years of age

Enrolment will begin with Cohort 1, followed by Cohorts 2 and 3. Enrolment in Cohorts 2 and 3 will be dependent on the availability of the European Commission approved age-appropriate SOF formulation and dose for the corresponding age cohort.

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



Note: Due to the early termination of the study, only participants 12 to <18 years of age were enrolled in the study into Cohort 1; no participants will be enrolled in Cohorts 2 and 3. The duration of the Long-Term Follow-Up period for these participants will be less than the initially planned 96 weeks. Upon approval of this revised protocol, participants will return to the study center to conduct an EOS visit.

5.1.1 Data Monitoring Committee and Other External Committees

Not applicable.

5.2 Number of Participants

It is expected that approximately 45 participants will be screened. A minimum of 30 participants, evaluable for the primary end point, will be assigned to 3 age descending cohorts (12 to < 18 years of age, 6 to < 12 years of age, and 3 to < 6 years of age); at least 8 participants evaluable for the primary end point will be treated in each age cohort.

For further information regarding sample size determination, please refer to Section 10.1.

> **Note**: Although the original protocol provided for a total of 30 participants, only 5 participants, limited to Cohort 1, will have been enrolled in the study, as the result of the early termination of this study.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. End of trial is defined as the last visit shown in the Schedule of Activities for the last participant. Study completion is defined as the final date on which data for the primary endpoint is expected to be collected, if this is not the same.

[redacted]

[redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant or the participant's legally acceptable representative, parent(s), or legal guardian [and the participant's assent, when applicable,] before any study-specific activity is performed that is not part of normal patient care [unless a waiver of informed consent has been granted by an Institutional Review Board (IRB)/Ethics Committee (EC)]. The investigator will retain the original copy of each participant's signed consent [assent] document;

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study;

c) Should a participant become capable or reach the age of majority, his or her consent should be obtained as soon as possible. The explicit wish of a participant who is a minor or unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

2) Type of Participant and Target Disease Characteristics

a) Participants with chronic HCV infection GT-1 to -6, 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) Documented liver biopsy results consistent with chronic HCV infection

b) HCV RNA ≥ 1,000 IU/mL at Screening

c) Participants who are HCV-treatment naive defined as no previous exposure to any interferon formulation (i.e. IFNα, peg-IFNα) or RBV, or HCV DAAs

OR

d) Participants who are HCV-treatment experienced:

i) All anti-HCV therapies (for example IFNα with or without RBV, cyclophilin inhibitors and inhibitors of microRNA) are permitted with the exception of previous exposure to SOF and/or any NS5A inhibitors

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

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

e) Participants must be non-cirrhotic. Absence of cirrhosis will be defined as any one of the following:

i) Documented liver biopsy results within 3 years before Screening suggestive of absence of cirrhosis (F0-F3 stage of fibrosis by METAVIR or equivalent)

OR

ii) Documented Fibroscan (transient elastography) measurement within 1 year before Day 1 consistent with absence of cirrhosis (< 12.5 kPa)

OR

iii) APRI score at Screening (aspartate aminotransferase to platelet ratio index) consistent with absence of liver cirrhosis (≤ 0.5).

If fibrosis stage data are available by several modalities, then the biopsy takes precedence over Fibroscan results, and Fibroscan measurements supersede APRI test.

f) Participants with body weight ≥ 10 kg at Day 1; participants in Cohort 1 must have a body weight ≥ 45kg at Day 1.

3) Age and Reproductive Status

a) Males and Females, ages, 3 to < 18 years of age on Day 1 of study treatment.

b) Females of childbearing potential (FOCBP) 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 treatment.

c) Females must not be breastfeeding.

d) FOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with DCV+SOF plus 5 half-lives of study treatment plus 30 days (duration of ovulatory cycle) for a total of 5 weeks post-treatment completion.

e) Males who are sexually active with FOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with DCV+SOF plus 5 half-lives of the study treatment plus 90 days (duration of sperm turnover) for a total of 14 weeks post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

f) Azoospermic males are exempt from contraceptive requirements. FOCBP 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 FOCBP, and male participants who are sexually active with FOCBP, 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 (Appendix 4).

6.2 Exclusion Criteria

1) Medical Conditions

a) Mixed genotype HCV infections

b) Evidence of an ongoing medical condition contributing to chronic liver disease other than HCV (such as, but not limited to: autoimmune hepatitis, Wilson disease, inherited metabolic and cholestatic liver diseases, alpha-1 anti-trypsin deficiency, cystic fibrosis, toxin exposures)

c) Evidence of cirrhosis, either compensated or decompensated

d) Positive serological test for chronic HBV-infection (HBsAg+) and/or HIV-infection. Participants with isolated anti-HBcore or in combination with anti-HBs (anti-HBcore positive ± anti-HBs) may participate.

e) 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)

f) Evidence of current or history of pre-malignant lesions and malignancies, including hematological, within 5 years prior to Screening

g) Liver or any other organ transplant (including hematopoietic stem cell transplants)

h) Use of chemotherapy within 2 months prior to Day 1

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

j) Participant with any gastrointestinal disease or surgical procedure that may impact the absorption of study drug including malabsorption syndrome

k) Other serious medical conditions that might preclude completion of this study

l) Clinically relevant alcohol or drug abuse within 12 months of screening; or psychiatric hospitalization, suicide attempt, or disability resulting from psychiatric illness, severe psychiatric disorders (eg. schizophrenia, psychosis, bipolar disorder, post-traumatic stress disorder, mania, etc.) within 5 years prior to Screening

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

n) Inability to tolerate oral medication

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

2) Prior/Concomitant Therapy

a) Medications prohibited and restricted prior to Day 1 visit are described in Section 7.7.1

3) Physical and Laboratory Test Findings

a) Any clinically significant findings on ECG, such as but not limited to QT prolongation.

b) ALT or AST ≥ 10 x the upper limit of normal (ULN)

c) Albumin < 35 g/L

d) Total bilirubin > 1.1 mg/dL unless participant has confirmed Gilbert syndrome

e) Alpha-fetoprotein > 50 ng/mL (> 41.3 IU/mL)

f) Absolute neutrophil count < 1500 x 10^6/L

g) Hb level < 100 g/L

h) Platelets < 100 x 10^9/L

i) Creatinine clearance < 60 ml/min as calculated by the Schwartz formula:

i) CrCl (ml/min/1.73m^2)= [length (cm) x k] / Serum Cr

k =0.55 for children 3 to < 13 years; k=0.55 for adolescent females 13 to < 18 years of age; k = 0.7 for adolescent males 13 to < 18 years of age

4) Allergies and Adverse Drug Reaction

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

b) Any other criteria or known contraindication that would exclude the participant from receiving DCV or SOF (see section 4.3 of DCV and SOF SmPCs)

5) Other Exclusion Criteria

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

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

c) Concurrent enrolment in another interventional clinical study

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently treated in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been treated). If re-enrolled, the participant must be re-consented.

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

The most current result prior to dosing is the value by which study inclusion will be assessed, as it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline, may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation

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

- Daclatasvir dihydrochloride chewable tablet (paediatric formulation)-IP
- Daclatasvir film-coated tablet (adult formulation)-IP
- Sofosbuvir (paediatric formulation)-IP
- Sofosbuvir film-coated tablet (adult formulation)-IP

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

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. Not applicable for this study.

Study treatments are summarized in Table 7-1.

Table 7-1: Study treatments for AI444423

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/DCV) Film Coated Tablet	60 mg (as the free base)	IP	Open	Bottle Each tablet is plain, green, biconvex, pentagonal and film-coated.	Store per IP Label.
Daclatasvir Dihydrochloride Chewable Tablet	20 mg	IP	Open	Blister A white to off white, flat, plain oval tablet	Store per IP Label.
Daclatasvir Dihydrochloride Chewable Tablet	10 mg	IP	Open	Blister A white to off white, flat, plain round tablet	Store per IP Label.
Daclatasvir Dihydrochloride Chewable Tablet	5 mg	IP	Open	Blister A white to off white, flat, plain round tablet	Store per IP Label.
Sofosbuvir[b], (SOF) Film Coated Tablet	400 mg	IP	Open	Bottle Yellow, capsule-shaped, film-coated tablets debossed with “GSI” on one side and “7977” on the other side	Store per IP Label
Sofosbuvir (SOF) (paediatric formulation, TBD)	50 mg	IP	Open	TBD	Store per IP Label

[a] Daclatasvir clinical presentation, adult formulation

[b] Sofosbuvir adult formulation

7.1 Treatments Administered

DCV+SOF will be administered QD for 12 weeks as outlined in Table 7.1-1 and Table 7.1-2.

The dose of DCV will be determined according to the weight of the participant prior to dosing on Day 1; the dose will not be adjusted to weight over the course of the study.

DCV should be administered as the adult film-coated 60 mg tablet formulation to adolescent participants 12 to < 18 years of age (Cohort 1 who are ≥ 45 kg) or as a paediatric chewable tablet formulation to all participants < 12 years of age (Cohorts 2 and 3) according to Table 7.1-1 below.

The SOF dose administered (refer to Table 7.1-2) will be the dose and formulation approved by the European Commission for the corresponding age cohort[8]. Cohort 1 (12 to < 18) will receive the 400 mg SOF tablet. Enrollment in Cohorts 2 and 3 will begin following European Commission approval of the age appropriate dose and formulation for SOF for those respective age groups.

On study visit days, DCV+SOF should be administered at the site after the trough PK sample is collected.

Table 7.1-1: Selection and Timing of DCV Dose

Weight on Day 1 (kg)	Study Treatment DCV (mg)[a]	Dosage formulation Frequency of Administration	Route of Administration
≥-10 --< 30	20 mg	QD	PO
≥ 30 - < 45	40 mg	QD	PO
≥ 45	60 mg[b]	QD	PO

[a] DCV strength and formulation (approved or under investigation): 5, 10, 20 mg chewable tablet; 60 mg film coated adult tablet; the DCV dose may be adjusted if PK data suggest that the dose did not meet the targeted exposure criteria.

[b] Adult formulation (60 mg) only used for Cohort 1

Table 7.1-2: Selection and Timing of SOF Dose

Cohort (Age range)	Study Treatment SOF (mg)[a]	Dosage formulation Frequency of Administration	Route of Administration
Cohort 1 (12 to <18)	400 mg	QD	PO
Cohort 2 (6 to <12)	TBD[b]	TBD[b]	PO
Cohort 3 (3 to <6)	TBD[b]	TBD[b]	PO

[a] SOF strength and formulation (approved or under investigation): European Commission approved paediatric formulation; 400 mg film coated tablet

[b] SOF dose will be the European Commission approved dose and formulation for the age range in the cohort. Refer to most current SOF SmPC for dosing guidance.

Note: Due to the early termination of the study, participants will only have been enrolled in Cohort 1 and administered the adult formulations of DCV and SOF (60 mg dose of DCV and 400 mg dose of SOF). No paediatric formulations will be administered in the study.

7.2 Method of Treatment Assignment

All participants will be assigned to treatment using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT.

During the screening visit, the investigative site will call into the enrollment option of the Interactive Response Technology (IRT) designated by BMS for assignment of a 5-digit participant number that will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (eg, 00001, 00002, 00003.... 00010). The participant identification number (PID) will ultimately be comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1, will have a PID of 0001 00001. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT, prior to the start of study treatment administration, to assign the participant into a cohort and to receive DCV and SOF treatment assignment. The site will record the treatment assignment on the applicable case report form.

Participants without evaluable Day 10 PK data may be replaced.

Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

7.3 Blinding

This is an open-label study, blinding procedures are not applicable.

7.4 Dosage Modification

Doses of DCV and SOF assigned on Day 1 cannot be modified but can be interrupted or discontinued to manage adverse events (See Section 8.1). In the event of interruption or discontinuation, both DCV and SOF must be stopped simultaneously. DCV+SOF treatment can be interrupted for a maximum of 7 days, and if not restored after 7 days, the treatment should be permanently discontinued.

Note: DCV dose modification will only be permissible if PK data from the initial 5 participants in a cohort suggest that the dose administered does not achieve the desired exposure criteria. The sponsor will advise how to modify the dose of DCV being administered, if needed.

7.5 Preparation/Handling/Storage/Accountability

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

The product storage manager should ensure that the study treatment 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 treatment arise, the study treatment should not be dispensed and the site should contact BMS immediately.

Study treatment 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).

- Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not Applicable

7.6 Treatment Compliance

Study treatment compliance will be assessed at all on-treatment study visits through review of the participant's dosing diary and drug accountability (review of used/unused study medication).

Participants [or the participant's legally acceptable representative, parent(s), or legal guardian] will be instructed to record dosing in a dosing diary and to bring unused study medication containers to each visit as well as any empty containers. The diaries will be reviewed at each visit in combination with drug accountability, and the sites should discuss any discrepancies noted.

Study drugs will be collected at all visits and new study drug may be dispensed; unused SOF will be redispensed. The dates and number of DCV tablets and SOF tablets/European Commission approved paediatric formulation dispensed and returned must be recorded on the drug accountability form maintained on-site.

On Day 10, when the serial PK sampling will be performed, treatment should be administered at the clinic and not taken at home. Likewise, on visits when trough PK samples are collected, Week 4, Week 8 and Week 12, treatment should be administered at the clinic after collection of the PK sample. The timing of the dose prior to PK sample collection should be recorded in the diary.

[redacted]

[redacted]

7.8 Treatment After the End of the Study

At the end of the study, BMS will not continue to provide BMS supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of DCV or SOF is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's [or the participant's legally acceptable representative, parent(s), or legal guardian] request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant [or the participant's legally acceptable representative, parent(s), or legal guardian] specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- 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 participant
- 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. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Laboratory or Clinical Criteria: If any of the following laboratory or clinical criteria is obtained for any participant, the test must be repeated/confirmed within 72 hours and the BMS medical

monitor should be informed. If the results are confirmed, the participant 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 x baseline and 5 x ULN and either total bilirubin > 2 x ULN or INR > 2
- Any Grade 4 AE or clinically significant laboratory abnormality considered study drug related
- Virologic Breakthrough (confirmatory results must be obtained 2 weeks from original result) defined as:
  - Confirmed increase in HCV RNA ≥ 1 $\log_{10}$ IU/mL on-treatment from nadir
  - Confirmed increase in HCV RNA ≥ LLOQ after HCV RNA declined to < LLOQ TD/TND while on treatment

In the event of interruption or discontinuation, both DCV and SOF must be stopped simultaneously. DCV+SOF treatment can be interrupted for a maximum of 7 days, and if not restored by 7 days, the treatment should be permanently discontinued.

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

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a normal healthy female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

8.1.1 Post Study Treatment Study Follow-up

In this study, PK is the primary endpoint while safety and tolerability, efficacy, long term safety and evolution of resistance variants in virologic failures are key endpoints of the study. Post study

follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of follow-up data as required and in line with Section 5 until death or completion of the designated follow up period.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant [or the participant's legally acceptable representative, parent(s), or legal guardian] specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants [or the participant's legally acceptable representative, parent(s), or legal guardian] 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 treatment 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 participant 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.
- If the participant [or the participant's legally acceptable representative, parent(s), or legal guardian] withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant initiates alternate anti-HCV therapy, the participant should complete the procedures specified for Post-treatment Week 4 (Table 2-3) prior to study discontinuation and prior to the initiation of any alternate therapy.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant [or the participant's legally acceptable representative, parent(s), or legal guardian].
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain 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 participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant'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 participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria prior to dosing. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (Section 2).

9.1 Efficacy Assessments

HCV RNA collected on treatment, at Post-treatment Week 12, and at other post-treatment visits will be used for antiviral efficacy assessments.

- The Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test (LLOQ = 15 IU/mL) will be used to measure HCV RNA levels.

Samples will be collected to perform phylogenetic analyses at baseline and in the event of virologic failure.

- 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.

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment and at the time-points specified in the Schedule of Activities (Section 2). 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 participants.

Section 4.8 of the DCV SmPC[13] and/or SOF SmPC[8] represent the reference safety information for the DCV+SOF regimen to determine expectedness of serious adverse events for expedited reporting. Following the participant'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 that is believed to be related to study drug, protocol-specified procedure or hepatic disease progression (i.e. development of liver cirrhosis and/or its complications).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant [or the participant's legally acceptable representative, parent(s), or legal guardian]. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment 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.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/European Commission and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant 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 Appendix 3.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

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.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or electronic SAE Report Form, 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 participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant 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).

9.2.7 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 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

1) ALT ≥ 5x baseline or nadir value, whichever is lower, AND ≥ 10 times upper limit of normal (ULN)

AND

2) Total bilirubin ≥ 2 times ULN

AND

3) No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including but not limited to, acute viral hepatitis, cholestasis, pre-existing hepatic disease excluding HCV or the administration of other drug(s), herbal medications, or substances known to be hepatotoxic.

After the initial event, subsequent monitoring should be discussed with the BMS Medical Monitor.

9.2.8 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.

9.3 Overdose

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 9.2).

An overdose of DCV is defined as follows:

- for participants assigned to a 60mg dose of DCV, any total daily dose of DCV ≥ 200 mg;
- for participants assigned to a 40 mg dose, any daily dose ≥ 120 mg
- for participants assigned to a 20 mg dose, any daily dose ≥ 60 mg

An overdose of SOF for participants assigned a 400 mg dose is any daily dose greater than 800 mg. For paediatric formulations, refer to the SmPC[8] for guidance on overdose.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2).

9.4.1 Physical Examinations

A full physical examination will be performed at the screening visit. A targeted physical exam should be performed during the on-treatment visits (except Day 10). A targeted physical examination may be performed by a qualified professional guided by the examiner's observations and/or participant complaints on new or changed conditions, symptoms or concerns. Targeted physical exam should include assessment of heart, lung and abdomen.

Refer to Schedule of Activities.

9.4.2 Vital signs

Refer to Schedule of Activities.

9.4.3 Electrocardiograms

Refer to Schedule of Activities.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- The following assessments, listed in Table 9.4.4-1, will be analyzed by a central laboratory or other BMS specified laboratory.
- Participants are not required to be fasting prior to any laboratory assessments.

Table 9.4.4-1: Laboratory Assessments

	Screening (Table 2-1)	Study Visits On Treatment (Table 2-2)	Study Visit Post-Treatment Week 4 (Table 2-3)	Study Visits Post-Treatment Weeks 12 to 108 (Table 2-3)
Hematology				
Hemoglobin	X	X	X	-
Hematocrit	X	X	X	-
White Blood Cell (WBC) Count with Differential	X	X	X	-
ANC (neutrophils plus band)	X	X	X	-
Platelets	X	X	X	X
Coagulation				
INR	X	X Not required Day 10	X	X
Chemistry				
Albumin	X	X	X	X
Total Protein	X	X	X	-
Aspartate aminotransferase (AST)	X	X	X	X
Alanine aminotransferase (ALT)	X	X	X	X
Total bilirubin	X	X	X	X
Direct Bilirubin	X	X	X	X
Alkaline Phosphatase	X	X	X	X
Lactate dehydrogenase (LDH)	X	X	X	X
Creatinine	X	X	X	X
Creatinine Clearance	X	X	X	X

Table 9.4.4-1: Laboratory Assessments				
	Screening (Table 2-1)	**Study Visits On Treatment (Table 2-2)**	**Study Visit Post-Treatment Week 4 (Table 2-3)**	**Study Visits Post-Treatment Weeks 12 to 108 (Table 2-3)**
Creatinine phosphokinase (CPK)	-	For AST elevation ≥ Grade 1 without ALT elevation		
Creatine Kinase MB Isoenzyme (CK-MB)	-	Reflex if CPK is elevated > 5xULN		
Lipase	X	X	X	-
Gamma-Glutamyl Transferase (GGT)	X	X	X	X
Electrolytes (sodium, bicarbonate, potassium,choloride	X	-	X	-
Blood Urea Nitrogen (BUN)	X	-	X	-
Glucose	X	-	X	-
HbA1c	X Only in participant with elevated plasma glucose level ≥ 200 mg/dL (11.1 mmol/L)	-	X	-
Calcium	X	-	X	-
Phosphate	X	-	X	-
Uric Acid	X	-	X	-
Alfa fetoprotein (AFP)	X	-	X	-
APRI	X	-	X	X Week 108 only
Other				
Urine pregnancy test (reflex to serum if positive)	X 24 hours prior to dosing in FOCBP	X Every 4 weeks	X	-
HCV RNA (and back up HCV RNA sample)	X	X	X	X
HCV resistance specimen for storage	-	X	X	X

Table 9.4.4-1: Laboratory Assessments				
	Screening (Table 2-1)	**Study Visits On Treatment (Table 2-2)**	**Study Visit Post-Treatment Week 4 (Table 2-3)**	**Study Visits Post-Treatment Weeks 12 to 108 (Table 2-3)**
HCV genotype	X	Participants with suspected virologic breakthrough or relapse will have samples collected to retest HCV RNA, HCV resistance and HCV Genotype at an unscheduled visit as soon as possible before their next regular visit.		
Anti-HCV	X	-	-	-
HIV-1 and -2 antibody	X	-	-	-
HBsAg, anti-HBcore	X	-	-	-
[redacted]	-	X (Day 1 only)	-	-
PK Samples DCV, SOF and its metabolites	-	Day 10; Weeks 4, 8 and 12; and virologic breakthrough See Section 9.5	-	-
Total approx. blood volume per visit, mL	18	17 (Day 1); 19-20 (Day 10); 16 (Week 4, 8 and 12)	14	14

For all participants, local standards for volumes of blood based on body weight that may be drawn within a specific time period should be followed. Blood volumes will be minimized as best as possible. If, despite the use of these measures, the blood volumes required in the Schedule of Activities (Section 2) for a time point will exceed those recommended for the participant, then the Sponsor should be contacted for instructions on which blood tests can be omitted or modified to meet volume requirements. These will likely be back up samples, since all required laboratory assessments should be performed. The volume of blood required will be detailed in the Informed Consent as well as in the Procedure Manual.

> **Note:** All laboratory assessments scheduled for the Post-Treatment Week 108 visit should be performed at the EOS visit.

9.4.5 Imaging Safety Assessment

Not applicable.

9.5 Pharmacokinetics

Pharmacokinetic parameters (Cmin, Cmax, Tmax, AUC (TAU), CLT/F) for DCV will be derived from plasma concentration versus time data on Day 10 (± 3 days). The observed trough plasma concentrations of DCV and SOF/metabolites (Ctrough) will be assessed.

Table 9.5-1 lists the pharmacokinetic sampling schedule to be followed for the assessment of DCV and SOF/metabolites pharmacokinetics. On Day 10, when the serial PK sampling will be performed, treatment should be administered at the clinic and not taken at home. Likewise, on visits when trough PK samples are collected, treatment should be administered at the clinic after collection of the PK sample. The timing of the dose prior to the PK sample collection should be recorded. There is no restriction on food consumption with regard to dosing and PK sample collection. Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

Table 9.5-1: Pharmacokinetic Sampling Schedule for DCV and SOF

Study Day of Sample Collection	Cohort	Time (Relative To Dosing) Hour	PK Blood Sample for DCV	PK Blood Sample for SOF/metabolites
Day 10 +/- 3 days	All Cohorts	0 (Predose)	X	X
	All Cohorts	00:30	X	-
	Cohorts 1, 2 only	01:00	X	-
	All Cohorts	02:00	X	-
	All Cohorts	04:00	X	-
	All Cohorts	08:00	X	-
Week 4	All Cohorts	0 (Predose)	X	X
Week 8	All Cohorts	0 (Predose)	X	X
Week 12 (EOT)	All Cohorts	0 (Predose)	X	X
Virologic Breakthrough[a]	All Cohorts	0 (Predose)	X	X

[a] When confirming on-treatment virologic breakthrough, PK samples should be collected along with the HCV RNA samples

In addition, plasma samples will be archived for potential metabolite analysis, if the need arises and to the extent possible.

[redacted]

9.8.1 Additional Research Collection

This protocol will not include sample collection and/or residual sample storage for additional research (AR).

9.8.2 Other Assessments

9.8.2.1 HCV Virologic Resistance Testing

Plasma specimens for possible resistance testing will be collected at study visits indicated in Table 2-1, Table 2-2, and Table 2-3.

Phylogenetic analyses will be performed on all available baseline NS5A sequences to confirm/determine the HCV genotype and subtype of each treated participant. NS5A resistance testing will be performed on all baseline samples. Resistance testing will be performed using population-based sequencing and may be performed by next-generation sequencing on samples from participants with HCV RNA ≥ 1,000 IU/mL. This includes samples from all participants experiencing on-treatment failure or relapse, defined as:

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

For participants who experience virologic failure, NS5A and NS5B resistance testing will be performed on samples that best approximate the time of failure, when HCV RNA levels are ≥ 1,000 IU/mL. The respective baseline samples from these participants will also be tested. Genotype testing will also be performed on virologic failure samples collected close to the time of failure.

Further testing will occur at selected time points, if needed, using either storage specimens for resistance testing or other available stored specimens. Exploratory resistance testing to evaluate low frequency variants may be performed on subsets of samples depending on patterns of viral load response.

> **Note:** With this revised protocol, resistance testing will not be performed on Baseline samples

9.8.2.2 Acceptability and Palatability Assessments of Daclatasvir Formulations

Participants/caregivers will be asked to complete a questionnaire regarding the acceptability and palatability (including a hedonic scale) of the DCV formulations in conjunction with the dose of DCV administered on Day 1, Treatment Week 4, and Treatment Week 12 (10 seconds, 1 minute,

and 5 minutes after taking the tablet(s)); DCV will be administered at the site on the visits. Specific instructions for the assessment tool and documentation of results will be provided to the sites.

After the participant has been dosed with DCV, any issue associated with the palatability of the investigational product should be reported as an adverse event (ie, spitting up).

9.8.2.3 Brief Questionnaire/Interim Phone Contacts

A brief questionnaire will be completed by the participant [or the participant's legally acceptable representative, parent(s), or legal guardian] on Day 1 to include the participant's e-mail address, name of the participant's primary care physician and 2 non-residing contacts in case the participant cannot be reached for their study assessments. This questionnaire, unless prohibited by local laws or regulations, will be reviewed for the confirmation or modification (as applicable) by the participant [or the participant's legally acceptable representative, parent(s), or legal guardian] 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 participant [or the participant's legally acceptable representative, parent(s), or legal guardian] on a quarterly basis when the participant is not required to come for an in-office visit (ie, post-treatment Week 36, 60, and 84). The purpose of phone contacts is to verify the participant's continuation in the study and to confirm the date of the next study visit.

> **Note**: Due to the early termination of the study, participants will perform an EOS visit and interim telephone contact will not be necessary after the EOS visit.

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

> **Note**: Not Applicable due to the early termination of the study; a total of 5 participants will have been enrolled in the study into Cohort 1.

A minimum of 30 participants, assigned to 3 age descending cohorts, will be evaluated for the primary endpoint (PK) with at least 8 participants assessed in each age cohort.

The primary objective of this study is to evaluate the PK of DCV. The PK profile of DCV has been well characterized in the clinical development program and it has been noted that DCV is associated with predictable pharmacokinetics. The intra-participant variability for DCV Cmax and AUC (INF) was assessed from clinical studies where single oral doses of DCV were administered with or without food and were estimated to be low with a % CV of 18% for Cmax and 10% for AUC (INF). Similarly, the inter-participant variability in DCV Cmax and AUC were assessed from clinical studies where single and multiple oral doses of DCV administered alone, and with or without food in some cases, was identified to be modest with % CV values of 37.5% for Cmax

and 35% for AUC. PK will be assessed in all participants, however, due to the low observed variability in DCV exposure, assessment of the PK in the initial 5 participants per age cohort will provide the necessary information to match DCV exposures between adults and paediatric participants and either allow enrolment to be initiated in the next descending age cohort(s) or indicate that additional participants need to be enrolled in the cohort with a modified dose. Enrolment will continue in each cohort, after the initial 5 participants have completed their Day 10 assessments, to have a minimum of 8 evaluable participants in each cohort.

Descriptive summary statistics will be provided for the secondary endpoints in this study.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled Participants	All participants who sign informed consent and are assigned a Participant Identification Number
Treated Participants	All enrolled participants who take at least 1 dose of study treatment.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

A description of the participant population will be included in the statistical output reported, including subgroups of age, gender and race.

> **Note:** With the early termination of this study, previously collected data to address PK, SVR, and select safety assessments (e.g. AEs, laboratory tests, end of treatment subject status) will be reported only within adolescent participants 12 to <18 years of age. Given the small number of subjects enrolled in the study, no statistical analyses will be performed. Genotypic substitution(s) associated with virologic failure and the acceptability and palatability of the DCV formulations will not be reported. Likewise, an interim analysis will not be performed.

10.3.1 Efficacy Analyses

Efficacy endpoints will be assessed for treated participants by age cohort and total.

The proportion of participants achieving SVR12 (HCV RNA <LLOQ, TND or TD at Post-treatment Week 12) will be presented along with the corresponding 95% exact binomial confidence interval (CI). The principal analysis method will compute SVR12 on all treated participants, and missing HCV RNA data at post-treatment Week 12 will be imputed using the Next Value Carried Backwards (NVCB) approach, i.e., missing HCV RNA data in the post-

treatment 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. A sensitivity analysis will compute SVR12 on treated participants with observed HCV RNA at follow-up Week 12.

10.3.2 Resistance Analyses

The frequencies of NS5A RAVs at baseline will be presented by genotype, and if applicable, by subtype, for responders (SVR12) and virologic failures with genotypable isolates.

The frequencies of newly emergent NS5A RAVs detected at virologic failure on treatment or during follow-up will be presented for virologic failures with genotypable isolates. Newly emergent substitutions are substitutions that were not detected at baseline.

> **Note**: These data will not be reported because the prevalence of the relevant RAV varies from 4-10% and as such might not be detected at Baseline in a sample size of 5 participants. As of 18 October 2019, all participants had completed at least 41 weeks of post-treatment follow-up and none had experienced viroloogic failure.

10.3.3 Safety Analyses

The frequencies of the following safety endpoints will be presented separately for each study period (on treatment and follow-up) for treated participants by age cohort and total: SAEs; AEs leading to discontinuation of study therapy; AEs by intensity; laboratory abnormalities by toxicity grade.

The Investigators will determine the intensity of AEs. 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. AEs will be presented by system organ class and preferred term. Presentations will include both non-serious and SAEs, unless specified otherwise. If a participant had an AE with different intensities over time, then only the greatest intensity 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 adverse experiences ([December 2004; clarification August 2009]) (Appendix 5). The laboratory value during the study period with the highest toxicity grade will be reported for each test.

10.3.4 Pharmacokinetic Analyses

Individual pharmacokinetic parameter values for DCV will be derived from plasma concentration versus time using non-compartmental methods or model based approaches as needed on Day 10 (± 3 days). Values will be summarized with descriptive statistics (n, arithmetic mean, standard deviation, geometric mean, coefficient of variation, median, minimum, maximum) by age cohort. Parameters will include: Cmin, Cmax, Tmax, AUC (TAU), and CLT/F.

10.3.5 Other Analyses

10.3.5.1 Acceptability and Palatability Assessments of Daclatasvir Formulations

The acceptability and palatability questionnaire results from Day 1, Week 4, and Week 12 will be summarized and assessed by age cohort and total for participants treated with DCV chewable and

adult tablets. The age-appropriate chewable tablet formulation and adult film-coated tablet will be assessed separately.

> **Note**: These data will not be reported as only the adult formulation was administered in the study and there is no value to performing an analysis of the adult formulation.

10.3.6 Interim Analyses

The timing of interim analyses will depend on the availability of Day 10 PK results. An interim analysis will be performed when the first 5 participants in each age cohort complete the Day 10 PK sample collection.

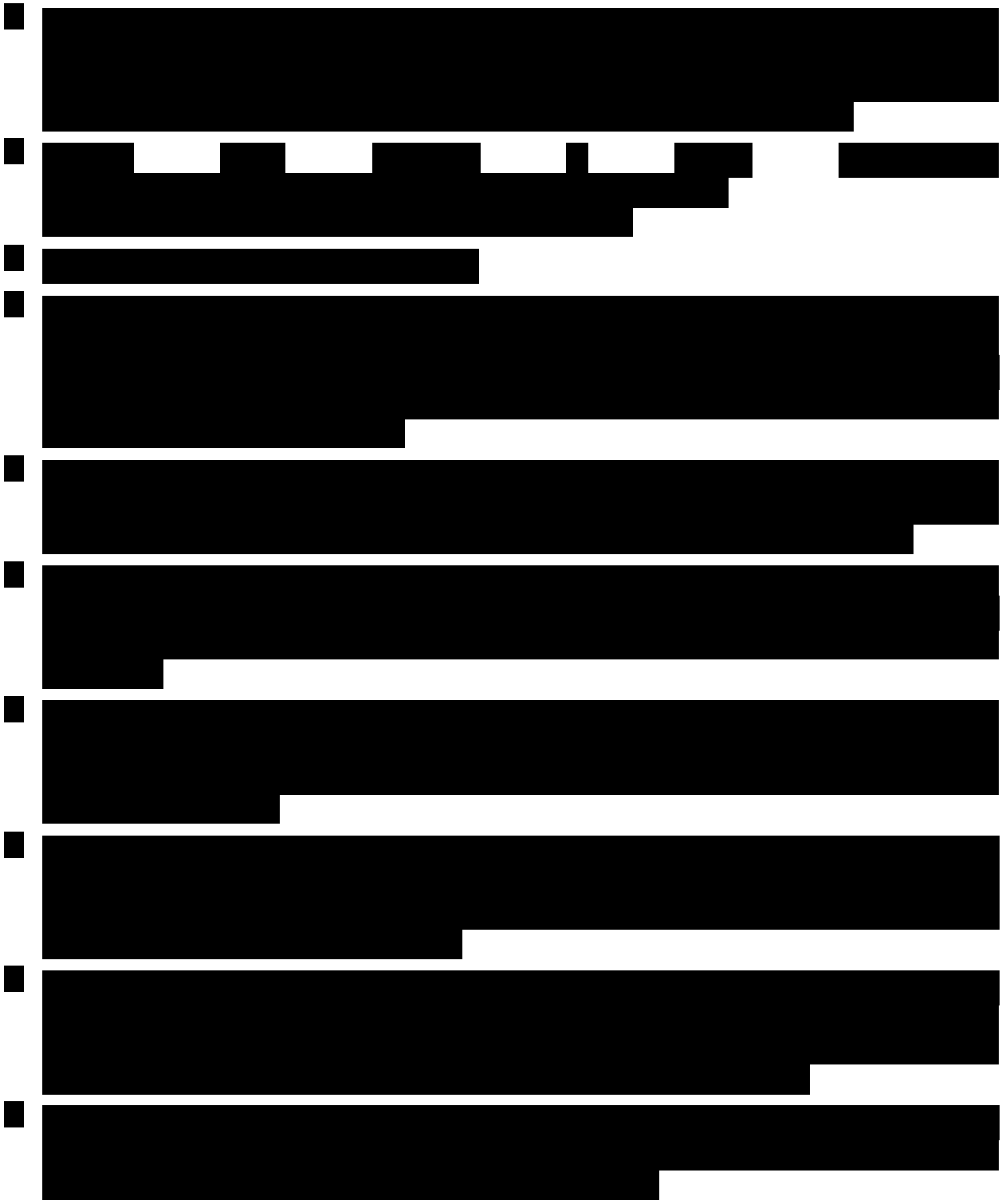
If the median plasma exposure in a cohort is outside the predefined therapeutic range, then dose modification will be performed using paediatric formulations of DCV, and an additional 5 participants will be enrolled. Another interim analysis will be performed when these additional participants complete the Day 10 PK sample collection in order to confirm the exposure at the modified dose. All Day 10 PK interim analyses will focus on PK and select safety listings (eg, AEs, laboratory abnormalities, participant disposition). In each cohort, enrollment will continue in order to achieve at least 8 evaluable participants per cohort.

Additional interim analyses will be performed when all participants in an age cohort complete the Post-Treatment Week 12 visit and when all participants complete the follow-up Week 12 visit in order to assess the primary and secondary endpoints.

The final analysis will be conducted when all participants complete long-term follow-up to assess long-term efficacy [redacted]), safety, and evolution of resistance variants in virologic failures.

The Statistical Analysis Plan will further describe the planned interim analyses.

> **Note**: An interim analysis will not be performed. As only 5 subjects will be enrolled in this study, analyses are not needed to guide dosing for additional participants.



12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	Adverse event
AFP	Alpha fetoprotein
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APRI	Aspartate aminotransferase platelet ratio index
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC(TAU)	area under the concentration-time curve in one dosing interval
BMS	Bristol-Myers Squibb
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CHC	Chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CK-MB	Creatine Kinase MB Isoenzyme
CLTF	Apparent total body clearance
CPK	Creatinine phosphokinase
Cmax, CMAX	Maximum observed concentration
Cmin, CMIN	Trough observed concentration
CrCl	Creatinine clearance
CRF	Case Report Form, paper or electronic
CSR	Clinical study report
CYP	Cytochrome p-450
DAA	Direct acting antiviral
DAIDS	Division of AIDS
DCV	Daclatasvir
DCV+SOF	Daclatasvir and sofosbuvir combination therapy
DC	Discontinue
DILI	Drug-induced liver injury

Term	Definition
dL	Deciliter
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	End of treatment
EPA	Early Patient Access
FDA	Food and Drug Administration
FDC	Fixed dose combination
FOCBP	Female of childbearing potential
G	Gram
GGT	Gamma-Glutamyl Transferase
GT	Genotype
H	Hour
Hb	Hemoglobin
HbA1C	Glycated hemoglobin
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCG	Human chorionic gonadotrophin
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
Ie	id est (that is)
IEC	Independent Ethics Committee
IFN	Interferon
IMP	Investigational medicinal products
INR	International normalized ratio

Term	Definition
IP	Investigational products
IRB	Institutional Review Board
IRT	Interactive Response Technology
IST/ISR	Investigator-sponsored -trials/research
IU	International Unit
Kg	Kilogram
L	Liter
LC/MS/MS	Liquid Chromotography - tandem mass spectrometry
LDH	Lactate dehydrogenase
LDV	Ledipasvir
LLOQ	Lower limit of quantification
LTFU	Long term follow up
Medra	Medical Dictionary for Regulatory Activities
mg	Milligram
Min	Minute
mL	Milliliter
µg	microgram
N	number of participants or observations
NS5A	Nonstructural protein 5A
NS5B	Nonstructural protein 5B
NVCB	Next Value Carried Backwards
PIP	Pediatric Investigational Plan
PDCO	Paediatric Committee
pegIFN	Pegylated interferon
PID	Patient/Participant Identification Number
PK	Pharmacokinetics
PO	Per os
PT	Post treatment
QD,	Quaque die, once daily
RAV	Resistance-associated variants

Term	Definition
RBV	ribavirin
RNA	Ribonucleic acid
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SNP	single nucleotide polymorphism
SOF	Sofosbuvir
SUSAR	Suspected, Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
TBD	To be determined
TD	Target detected
Tmax	Time taken to reach maximum concentration
TND	Target not detected
ULN	Upper limit of normal
VBT	Virologic breakthrough
WBC	White blood cell

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee 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).

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, participant 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, Sponsor or designee 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.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) 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 relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (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).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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 participant volunteers to participate.

Sponsor or designee 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 participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant'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 participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant'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 participant records.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

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

SOURCE DOCUMENTS

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.

STUDY TREATMENT RECORDS

Records for study treatments DCV and SOF (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	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 participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., 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.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

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 Sponsor or designee 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 Sponsor or designee.

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. Subinvestigators in Japan may not be delegated the CRF approval task 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 Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

Sponsor or designee 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 .Certain CRF pages and/or electronic files may serve as the source documents:

In addition, the study may be evaluated by Sponsor or designee 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 Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) 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 or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) 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, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor or sourced by the investigator) such as partially used study treatment containers, vials and syringes may be destroyed on site.

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, 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. The following minimal standards must be 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.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

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:

- Participant recruitment (eg, among the top quartile of enrollers)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment 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 treatment, whether or not considered related to the study treatment.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant 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) 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 (e.g., 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
Results in persistent or significant disability/incapacity

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
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 participant or may require intervention [e.g., 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 9.2.7 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study treatment 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 9.2.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Causality
The causal relationship to study treatment 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 treatment administration and the AE. Not related: There is not a reasonable causal relationship between study treatment administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Follow-up of AEs and SAEs
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 treatment 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.

Follow-up of AEs and SAEs
All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, 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

APPENDIX 4 FEMALE OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Female of Childbearing Potential (FOCBP)

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Female in the following categories are not considered FOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 Days after the end of study treatment, plus 30 days.

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion

• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the FOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • FOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the FOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. Refer to DCV SmPC. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 5 Days (5 half lives of the study drug) after the end of treatment plus an additional 90 days.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 5 Days after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 5 Days after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and until 5 Days after the end of treatment plus an additional 90 days.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 5 DIVISION OF AIDS (DAIDS) TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: JULY, 2017

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Corrected Version 2.1
July 2017

Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
US Department of Health and Human Services

Table of Contents

Glossary and Acronyms

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (*serum glutamic pyruvic transaminase)*
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (*serum glutamic-oxaloacetic transaminase)*
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: <u>Adults</u> Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. <u>Young Children</u> Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

Introduction

The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS grading table.

Instructions for Use

General Considerations

The *Division of AIDS* (*DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

Instructions for Use

When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric AEs
When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes
In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades
If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Laboratory Values
General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory

Instructions for Use

value. For example, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Appendix Usage
Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates.

Using Addenda 1-3: Grading Tables Used in Microbicide Studies
In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1-3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (i.e., the *Division of AIDS (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies- *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

[redacted]

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	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
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms 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	No symptoms AND Abnormal laboratory value	Symptoms 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[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	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
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, 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 *≥ 1 year of age*	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 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	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	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with 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)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes 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)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	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	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
Myalgia (generalized)	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
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[redacted]

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	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	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	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
Developmental Delay *< 18 years of age* *Specify type, if applicable*	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 OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	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
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	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
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
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
Visual Changes (assessed 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)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of 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
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	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 symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	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 indicated

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Systemic

Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

[redacted]

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	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

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

*Laboratory Values**
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; *mmol/L*)				
≥ *7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 ≥ *3.38*
< *7 days of age*	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 ≥ *3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 ≥ *1.8*
Calcium, Low (mg/dL; *mmol/L*)				
≥ *7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< *7 days of age*	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] **or eGFR, Low** **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 ≥ *27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 ≥ *27.75*

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, Low (mg/dL; *mmol/L*)				
≥ 1 month of age	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 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
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High				
≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High				
≥ 18 years of age	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17]				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Appendix A.
Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18]**, High** (mg/dL; *µmol/L*)[19]				
Term Neonate[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171* to < *290.7*	≥ 17 ≥ *290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2* to < *324.9*	≥ 19 ≥ *324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5* to < *376.2*	≥ 22 ≥ *376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8* to < *410.4*	≥ 24 ≥ *410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 ≥ *239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 ≥ *171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 ≥ *136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.