CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Pharmacokinetics, Safety and Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir Fixed Dose Combination in Adolescents and Children with Chronic HCV Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
IND Number:	Not Applicable
EudraCT Number:	2018-000480-87
Clinical Trials.gov Identifier:	Not Applicable
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-367-1175
Gilead Study Director and Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404, USA

Study Title:	A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Pharmacokinetics, Safety and Efficacy of Sofosbuvir/ Velpatasvir/Voxilaprevir Fixed-Dose Combination in Adolescents and Children with Chronic HCV Infection
IND Number:	Not Applicable
EudraCT Number:	2018-000480-87
Clinical Trials.gov Identifier:	Not Applicable
Study Centers Planned:	Approximately 20 sites in Europe.
Objectives:	The primary objective of this study is as follows: • To evaluate the steady-state pharmacokinetics (PK) and confirm the age-appropriate dose of Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX) FDC in pediatric subjects with chronic hepatitis C virus (HCV) infection The secondary objectives of this study are: • To evaluate the safety and tolerability of SOF/VEL/VOX FDC in pediatric subjects with chronic HCV infection • To evaluate the antiviral efficacy of SOF/VEL/VOX FDC treatment in pediatric subjects with chronic HCV infection, as assessed by the proportion of pediatric subjects with sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12) • To evaluate the antiviral efficacy of SOF/VEL/VOX FDC treatment in pediatric subjects with chronic HCV infection, as assessed by the proportion of pediatric subjects with SVR 4 and 24 weeks after cessation of treatment (SVR4 and SVR24) • To evaluate the proportion of pediatric subjects with virologic failure, including on-treatment virologic failure and relapse • To evaluate the kinetics of circulating HCV ribonucleic acid (RNA) during treatment and after cessation of treatment • To evaluate the emergence of viral resistance to SOF, VEL, and VOX during treatment and after cessation of treatment

- To evaluate the effect of SOF/VEL/VOX FDC on growth and development of pediatric subjects during and after treatment
- To evaluate acceptability, including palatability, and swallowability, of formulations (as applicable) used in the study
- To assess the effect of treatment with SOF/VEL/VOX FDC on quality of life as measured by PedsQL™ Pediatric Quality of Life survey

CCI [redacted]

Study Design:

Open-label, multi-cohort study evaluating the PK, safety, and antiviral activity of SOF/VEL/VOX FDC in pediatric subjects with chronic HCV infection.

Pediatric subjects with chronic HCV infection of any HCV genotype, including indeterminate or mixed genotypes, will be enrolled. Both direct-acting antiviral (DAA)-naive and DAA-experienced subjects will be enrolled. DAA-experienced subjects are defined as subjects who have been exposed to a regimen including any DAAs (eg, NS3/4A protease inhibitors, NS5A inhibitor, or NS5B nucleotide/nucleoside inhibitor).

Three sequential age-based cohorts will be enrolled:

- Cohort 1: at least 20 subjects 12 to < 18 years old
- Cohort 2: at least 20 subjects 6 to < 12 years old
- Cohort 3: at least 20 subjects 3 to < 6 years old

CCI [redacted] For all subjects sparse PK samples will also be collected at various timepoints (Weeks 1, 2, 4, 8, and 12) dependent on treatment duration CCI [redacted]

PK and safety data from at least 20 evaluable subjects in each cohort will be reviewed to confirm the appropriateness of the SOF/VEL/VOX FDC dose used in each cohort and to determine the dose to be evaluated in the next cohort.

[redacted] CCI [redacted]

Number of Subjects Planned:	At least 60
Target Population:	DAA-naive and DAA-experienced adolescents and children who are 3 to <18 years old with HCV infection
Duration of Treatment:	8 weeks (DAA-naive subjects without cirrhosis), or 12 weeks (DAA-naive subjects with cirrhosis or DAA-experienced subjects with or without cirrhosis)
Diagnosis and Main Eligibility Criteria:	DAA-naive and DAA-experienced subjects, who are 3 to < 18 years old as determined at Day 1. Refer to Section 4.2 and 4.3 for detailed Inclusion and Exclusion Criteria.
Study Procedures/ Frequency:	Screening assessments will be completed within 28 days of the Day 1 visit. The screening window can be extended to 42 days for extenuating circumstances with sponsor approval. DAA-naive subjects without cirrhosis will complete the following study visits: Screening, Day 1, Weeks 1, 2, 4, and Week 8/End of Treatment. DAA-naive subjects with cirrhosis or DAA-experienced subjects with or without cirrhosis will complete the following study visits: Screening, Day 1, Weeks 1, 2, 4, 8, and Week 12/End of Treatment. All subjects will complete posttreatment visits at Weeks 4, 12, and 24 weeks after discontinuation of study drug.

Screening assessments will include: informed consent, medical history, determine eligibility, complete physical examination, vital signs, height and weight, adverse events (AEs), concomitant medications, SOF/VEL/VOX FDC swallowability assessment (may be performed at Screening up to Day 1), transient elastography test (FibroScan® if available; may be performed at Screening up to Day 1), safety laboratory tests (including hematology, chemistry, and coagulation tests), hemoglobin A1c (HbA1c), alpha-1 anti-trypsin (AAT), thyroid stimulating hormone (TSH), serology (hepatitis A virus [HAV], HCV, and hepatitis B virus [HBV]), serology and/or antigen testing for HIV, HCV RNA, HCV genotyping, serum β-human chorionic gonadotropin (β-hCG - females of childbearing potential only), IL28B (may be performed at Screening up to Day 1), Fibrotest®, AST to Platelet Ratio Index (APRI), urinalysis, and urine drug screen.

On-Treatment assessments include: complete or symptom-directed physical examinations (as applicable), parental height (if available), vital signs, height and weight (with calculation of BMI), AEs and serious adverse events (SAEs), concomitant medications, pregnancy prevention counseling (all subjects ≥ 12 years of age and subjects < 12 years of age at the discretion of the Investigator based on subject's pubertal status), medication compliance, transient elastography test (FibroScan® if available; may be performed at Day 1 if not performed at Screening), safety laboratory tests (including hematology, chemistry, and coagulation tests), TSH, bone age biomarkers, HBV DNA for subjects hepatitis B core antibody (HBcAb) positive at Screening, HCV RNA, CCI [redacted] IL28B (may be performed at Day 1 if not performed at Screening), urinalysis, urine pregnancy tests (females of childbearing potential only), a quality of life survey, Tanner Pubertal Stage assessment, and radiographic bone age assessment.

SOF/VEL/VOX FDC swallowability assessment may be performed at Day 1 if not performed at Screening. Acceptability questionnaire, including palatability assessment, will be completed by the subject and parent/legal guardian at Day1 and End of Treatment.

CCI [redacted]

On-Treatment PK assessments include the following:

CCI

2) For all enrolled subjects, the following sparse PK samples will be collected, as applicable:

   - For subjects receiving 8 weeks of treatment: a single sparse PK sample will be collected at any time at Weeks 1 and 8; Unscheduled and Early Termination visits as applicable.
   - For subjects receiving 12 weeks of treatment: a single sparse PK sample will be collected at any time at Weeks 1, 8, and 12; Unscheduled and Early Termination visits as applicable.
   - For all subjects 2 sparse PK samples will be collected at Week 2 and Week 4 at the following timepoints: pre-dose and between 15 minutes to 4 hours postdose CCI

Posttreatment assessments will include: vital signs, height and weight (with calculation of BMI), symptom-directed physical examination, AEs, SAEs, concomitant medications, safety laboratory tests (including hematology and chemistry tests), bone age biomarkers, HBV DNA for subjects HBcAb positive at Screening, HCV RNA, CCI urine pregnancy tests (females of childbearing potential only), pregnancy prevention counseling for females of childbearing potential, a quality of life survey, and Tanner Pubertal Stage assessment.

An external Data Monitoring committee (DMC) will meet at an interval of approximately every 6 months from the first subject enrolled.

Test Product, Dose, and Mode of Administration:	SOF/VEL/VOX FDC is manufactured as a tablet, consisting of: • 400 mg SOF, 100 mg VEL, and 100 mg VOX (adult tablet) for oral administration SOF/VEL/VOX FDC tablets will be administered once daily with food. Smaller tablets of lower dose and a non-tablet pediatric formulation for oral use will be developed. Cohort 1: DAA-naive subjects without cirrhosis who are 12 to < 18 years old will receive SOF/VEL/VOX FDC (400/100/100 mg) adult tablet for 8 weeks. DAA-naive subjects with cirrhosis and DAA-experienced subjects with or without cirrhosis will receive SOF/VEL/VOX FDC (400/100/100 mg) treatment for 12 weeks. Subjects unable to swallow the SOF/VEL/VOX FDC (400/100/100 mg) adult tablet (as determined by SOF/VEL/VOX FDC swallowability assessment at Screening or at Day 1) will be re-assigned to a smaller tablet of lower dose or a non-tablet formulation of SOF/VEL/VOX FDC when available. The smaller tablet dose and non-tablet formulation will be included in a protocol amendment, when available.
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	AEs, SAEs, laboratory tests, physical examinations, and vital sign measurements will be collected throughout the study.
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using COBAS® AmpliPrep/COBAS® TaqMan® HCV Test.
Pharmacokinetics:	For all subjects, the steady-state PK of SOF, and its major metabolite (GS-331007), VEL and VOX will be assessed. Plasma PK parameters such as C_{max}, C_{tau}, AUC_{tau}, CLss/F, and Vz/F will be estimated, as appropriate.

Statistical Methods:

The primary endpoint for determining steady-state PK is AUC_{tau} of SOF, GS-331007, VEL and VOX in each cohort. The following plasma PK parameters will be estimated and summarized: AUC_{tau}, C_{max}, C_{tau}, volume of distribution and clearance, as appropriate. The effect of age and SOF/VEL/VOX FDC dose on PK will be explored.

The main secondary safety endpoint is review of any AEs with a focus on AEs that lead to discontinuation of study drug. In addition, neuropsychiatric examinations as measured by PedsQL™ Pediatric Quality of Life survey, growth and development endpoints (eg, height and weight percentiles, Tanner Pubertal Stage assessment, radiographic bone age assessment and bone age biomarkers) will be assessed.

The key efficacy endpoint is SVR12 in all enrolled and treated subjects.

Other secondary efficacy endpoints include SVR4, SVR24, antiviral activity (on-treatment HCV RNA), on-treatment virologic failure, and relapse.

Acceptability, including palatability, and swallowability assessments are secondary endpoints of the study.

All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and maximum). All categorical endpoints will be summarized by number and percentage of subjects who meet the endpoint definition. Safety endpoints will be analyzed by the number and percentage of subjects with events or abnormalities for categorical values or by the 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum maximum) for continuous data.

Assuming similar variability for SOF, GS-331007, VEL, or VOX AUC_{tau} in the pediatric population compared to adults, a sample size of 20 pediatric subjects per cohort will provide at least 80% power to target a 90% confidence interval of the geometric mean ratio (GMR) within the bounds of 50% to 200% when comparing with the adult population.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
AAT	alpha-1 anti-trypsin
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
ANOVA	analysis of variance
APRI	AST: platelet ratio index
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
AUC	area under the curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BCRP	breast cancer resistance protein
BLQ	below the lower limit of quantification
BMI	body mass index
CatA	Cathepsin A
CES1	carboxylesterase
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CLss/F	apparent clearance at steady state
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval (tau)
CRO	contract (or clinical) research organization
CYP2B6	Cytochrome P450 2B6
CYP2C8	Cytochrome P450 2C8
CYP3A4	Cytochrome P450 3A4
CTX	C-type collagen sequence
DAA	Direct-acting antiviral
dL	deciliter
DNA	deoxyribonucleic acid
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form(s)
EMA	European Medicines Agency
E_{max}	maximum effect
ESA	erythropoiesis stimulating agent

eSAE	electronic serious adverse event
EU	European Union
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination
FEV1	forced expiratory volume in one second
GCP	Good Clinical Practice (Guidelines)
GCSF	granulocyte colony stimulating factor
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GMR	geometric mean ratio
GSI	Gilead Sciences, Inc.
GT	genotype (viral)
HAV	hepatitis A virus
Hb	hemoglobin
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBsAb	hepatitis B surface antibody
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HLGT	High-Level Group Term
HLT	High-Level Term
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN	Interferon
IL28B	IL28B gene
IMP	investigational medicinal product
INR	International Normalized Ratio
IU	International Units
IUD	intrauterine device
IWRS	interactive web response system
kg	Kilogram
L	Liter
LDV	ledipasvir
LiPA	line probe assay
LLN	Lower limit of the normal range
LLOQ	Lower limit of quantification

LLT	Lower-Level Term
MedDRA	Medical Dictionary for Regulatory Activities
MCV	mean corpuscular volume
Mg	Milligram
mL	Milliliter
Mmol	millimole
Min	Minute
mmHg	millimeters mercury
n	number
NS (3/4A/5A/5B)	Non-structural Protein
OATP	Organic Anion-Transporting Polypeptide
PBMC	peripheral blood mononuclear cell(s)
PCR	Polymerase Chain Reaction
PEG	peginterferon alfa-2a
CCI	[redacted]
P-gp	P-glycoprotein
PI	Protease inhibitor
PK	Pharmacokinetic
PPI	Proton pump inhibitors
PT	Prothrombin time or Preferred Term
PVE	Pharmacovigilance & Epidemiology
P1NP	Procollagen type 1 N-terminal propeptide
Q1	first quartile
Q3	third quartile
RBC	Red blood cell count
RBV	ribavirin
RNA	ribonucleic acid
SADR	Serious adverse drug reaction
SAE	serious adverse event
S_{cr}	serum creatinine (mg/dL)
SD	Standard deviation
SNP	single nucleotide polymorphism
SOC	System Organ Class or Standard of Care
SOF	Sofosbuvir
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Virologic Response
t_{max}	The time (observed time point) of C_{max}
TND	Target not detected
TSH	Thyroid stimulating hormone

$t^{1/2}$	An estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λz)
ULN	Upper limit of the normal range
US	United States
VEL	Velpatasvir
Vz/F	apparent volume of distribution
VOX	Voxilaprevir
WBC	white blood cells counts

1. INTRODUCTION

1.1. Background

Hepatitis C virus (HCV) is responsible for a large proportion of chronic liver disease worldwide and accounts for 70% of cases of chronic hepatitis in industrialized countries. Based on recent modeling studies, the global prevalence of chronic hepatitis C is estimated to average 1% in 2015, for a total of 71.1 million {The Polaris Observatory HCV Collaborators 2017}. Although data on the global prevalence of HCV in children are limited, there are estimated to be 5 to 6.6 million viremic infections in children 15 years of age or younger {El-Sayed 2015, Sokal 2017}. The prevalence varies by geographic location. The estimated prevalence of HCV infection in children is up to 0.4% in Europe and the United States (US); and up to 6% in resource-limited countries {El-Shabrawi 2013, Khaderi 2014}.

The natural history of children with chronic HCV infection differs from that in adults since HCV infection in children is relatively benign. Most children chronically infected with HCV are asymptomatic or have mild nonspecific symptoms. Clinical symptoms are present in approximately 20% of children in the first 4 years of life, with hepatomegaly being the most frequent sign (10%). Many, but not all, perinatally infected children will have intermittently or persistently abnormal alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, particularly in the first 2 years of life. In children with vertical HCV infection who have undergone liver biopsy, the histological spectrum is usually mild, although severe liver disease is encountered {Mohan 2010}. Despite the overall more favorable prognosis compared to adults, approximately 4% to 6% of children with chronic HCV infection have evidence of advanced fibrosis or cirrhosis and some children eventually require liver transplantation for end-stage liver disease as a consequence of HCV infection {Hu 2010}.

Recently, in the United States (US) and European Union (EU), sofosbuvir (Sovaldi®) and ledipasvir/sofosbuvir (Harvoni®) were approved for use in treatment-naive or interferon (IFN)-experienced patients who are 12 years old and older or weighing at least 35 kg (US only). For patients younger than 12 years or weighing less than 35 kg the only currently available HCV treatment is pegylated-interferon (Peg-IFN) and weight-based ribavirin (RBV) for 24 or 48 weeks depending on HCV genotype. The option of Peg-IFN+RBV therapy remains inadequate in regard to both efficacy and safety {Jonas 2012, Wirth 2012}.

Sofosbuvir (SOF) in combination with RBV is indicated in patients 12 to < 18 years old with genotype 2 or genotype 3 HCV infection for 12 or 24 weeks, respectively, based on the results of study GS-US-334-1112. In study GS-US-334-1112, this treatment was demonstrated to be safe, well tolerated and highly effective resulting in SVR12 rates of 100% and 97% in genotype 2 and genotype 3 subjects 12 to < 18 years old, respectively. No subject experienced on-treatment virologic failure or relapse; one genotype 3 subject was lost to follow up {Wirth 2017}. The study is ongoing in 3 to < 12 years old subjects.

Ledipasvir/sofosbuvir (LDV/SOF) is indicated in patients 12 to < 18 years old with genotype 1, 4, 5 or 6 HCV infection, for 12 or 24 weeks depending on the HCV genotype and cirrhosis status, based on the results of study GS-US-337-1116. In addition, in some countries, ledipasvir/sofosbuvir plus ribavirin for 24 weeks is indicated in patients with genotype 3. In study GS-US-337-1116, treatment with LDV/SOF for 12 weeks was safe, well tolerated and highly effective in subjects 12 to < 18 years old with genotype 1 chronic hepatitis C infection resulting in SVR12 rates of 98%. No subject experienced on-treatment virologic failure or relapse; two subjects were lost to follow-up {Balistreri 2017}. The study is ongoing in 3 to < 12 year-old subjects infected with genotypes 1, 3, 4, 5, or 6.

The availability of the first oral direct-acting antiviral (DAA) therapies for HCV infected pediatric patients represents a major therapeutic advance, by eliminating the need for weekly Peg-IFN injections and incidence of systemic side effects associated with its use. However, the treatment combination of SOF with RBV may remain less attractive to patients due to the significant toxicities associated with RBV, including hematologic, constitutional and teratogenic side effects. In addition, treatment duration of 12 or 24 weeks with either SOF or LDV/SOF depending on the HCV genotype and the cirrhosis status may represent a limiting factor for some pediatric patients. Therefore, treatment options that do not include RBV, with shorter fixed duration, and are effective across all HCV genotypes would be beneficial in the pediatric setting by decreasing the frequency of monitoring, blood tests, and increasing patient adherence. Moreover, the availability of a pangenotypic regimen is anticipated to be especially beneficial in areas where HCV genotype diversity is high and genotyping may not be readily available or routinely performed.

It is anticipated that as more pediatric patients are treated for HCV with DAA-based therapies, patients who fail those treatments will increase. Currently, there are no approved treatment options for pediatric patients who fail treatment with DAAs. Therefore, there is an unmet medical need for a pediatric salvage therapy with highly potent DAAs that are active against resistant associated variants.

1.2. Sofosbuvir/Velpatasvir/Voxilaprevir Fixed-Dose Combination

Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX) fixed dose combination (FDC) is a coformulation of SOF 400 mg, VEL 100 mg, and VOX 100 mg into a single tablet for the treatment of chronic HCV infection. This fixed dose combination combines three unique mechanisms of action into a single tablet:

- Sofosbuvir, a nucleotide analog HCV NS5B polymerase inhibitor, which is currently approved in the US, and other regions for the treatment of HCV infection as a component of an antiviral treatment regimen.

- Velpatasvir, an HCV NS5A inhibitor that has potent in vitro anti-HCV activity across all genotypes, which is currently approved in the US, EU, and other regions for the treatment of HCV infection in combination with SOF.

- Voxilaprevir, a macrocyclic HCV NS3/4A protease inhibitor (PI) with potent in vitro antiviral activity against genotypes 1 to 6 HCV, and an improved resistance profile compared to previously developed PIs which is currently approved in the US and other regions for the treatment of HCV infection in combination with SOF and VEL.

1.2.1. General Information

Please refer to the SOF/VEL/VOX FDC Investigator Brochure (IB) for additional information on SOF/VEL/VOX FDC.

Information in the IB includes:

- In Vitro Anti-Hepatitis C Virus Activity
- Nonclinical Pharmacokinetics and In Vitro Metabolism
  - Interactions with other medicinal products and other forms of interaction
- Nonclinical Pharmacology and Toxicology
- Clinical Experience

1.3. Rationale for This Study

This clinical study is designed to evaluate the PK, safety and efficacy of treatment with SOF/VEL/VOX FDC in adolescents and children with chronic HCV infection who are either DAA-naive or DAA-experienced with or without cirrhosis.

Recently in the US and EU, treatment with SOF+RBV and LDV/SOF for 12 or 24 weeks was approved for use in treatment naive or IFN-experienced pediatric patients who are ≥ 12 years old or who weigh at least 35 kg (US only). For all other pediatric patients treatment with Peg-IFN and weight-based RBV is considered the standard of care (SOC). Therefore, for patients younger than 12 years old, there is a need for new treatments that combine potent and sustained efficacy with improved tolerability and safety. In addition for all pediatric patients of any age, oral, RBV-free, highly effective and well-tolerated shorter courses of therapy would require less frequent medical monitoring and blood tests. This represents an advantage enhancing convenience and patient adherence.

Furthermore, it can be anticipated that as more pediatric patients are treated for their HCV infection with DAA-based therapies, the unmet medical need for effective retreatment options for patients who fail these treatments will increase. Currently, there are no approved treatment options for pediatric patients who fail DAA treatments. Therefore, there is a need for development of a salvage therapy with a combination of highly potent DAAs that have enhanced activity against common NS5A and NS5B resistant associated variants.

Data from the Phase 3 study POLARIS-2 (GS-US-367-1172) in adult DAA-naive subjects demonstrated that SOF/VEL/VOX FDC for 8 weeks was safe, generally well tolerated and highly efficacious, with SVR12 rates of 96% in subjects without cirrhosis and 91% in subjects with cirrhosis. Data from the Phase 3 studies POLARIS-1 (GS-US-367-1171) and POLARIS-4 (GS-US-367-1170) in adult DAA-experienced subjects demonstrated that SOF/VEL/VOX FDC for 12 weeks was safe, generally well tolerated and resulted in SVR > 95%, representing an effective retreatment option for subjects who have previously failed treatment with multiple DAAs. Furthermore, in these studies, the SVR12 rate in cirrhotic DAA-experienced subjects treated for 12 weeks was 99%.

In summary, GS-US-367-1175, will evaluate the efficacy of an 8 week treatment of SOF/VEL/VOX FDC in DAA-naive pediatric subjects who do not have cirrhosis and a 12 week treatment in DAA-naive pediatric subjects who have cirrhosis or DAA-experienced pediatric subjects with or without cirrhosis.

1.4. Rationale for Dose Selection of SOF/VEL/VOX FDC

SOF/VEL (400/100 mg) once daily is the approved marketed dose and, as such, was selected for co-formulation with VOX into a fixed dose combination tablet. The VOX 100 mg dose was selected based on the anti-HCV activity of VOX established in the Phase 1b proof-of-concept study GS-US-338-1121 and Phase 2 studies in subjects with HCV infection (GS-US-367-1169 and GS-US-367-1168). These studies indicated that the voxilaprevir exposures achieved following administration of VOX 100 mg + SOF/VEL (400/100 mg) with food are associated with > 90% of the maximum antiviral response across all HCV genotypes.

The combination of SOF 400 mg, VEL 100 mg, and VOX 100 mg has been administered in Phase 2 and Phase 3 studies to over 1900 subjects. SOF/VEL/VOX FDC (400/100/100 mg) tablet was evaluated in the registrational Phase 3 POLARIS program and these doses represent the marketed dose of SOF/VEL/VOX FDC tablet for the treatment of HCV-infection in adults.

Sofosbuvir is a substrate for efflux drug transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). SOF is extensively metabolized to the pharmacologically active nucleoside analog phosphate. The activation pathway involves hydrolysis by intestinal and hepatically expressed carboxylesterase (CES1) and Cathepsin A (CatA) enzymes {Yang 2009, Zhu 2009}. SOF is also converted to GS-331007, an inactive circulating metabolite, which is eliminated renally by active tubular secretion and glomerular filtration.

Velpatasvir is also a substrate for P-gp and BCRP. VEL has low systemic clearance in nonclinical species and low metabolic turnover by Cytochrome P450 2B6 (CYP2B6), Cytochrome P450 2C8 (CYP2C8) and Cytochrome P450 3A4 (CYP3A4). It is eliminated through biliary excretion as unchanged parent drug and metabolites (76.6% of the administered dose is recovered as VEL in feces).

Voxilaprevir is a substrate for P-gp, BCRP, and Organic Anion-Transporting Polypeptide (OATP) 1B1/3. VOX has low in vitro turnover, primarily by CYP3A4. It is eliminated through biliary excretion as unchanged parent drug and metabolites (40% of the administered dose is recovered as VOX in feces).

Selection of doses of SOF/VEL/VOX FDC for adolescents and younger age groups will target systemic exposures similar to those observed in adults at the proposed marketed dose. Body weight/surface area, the potential ontogenic changes in transporters and metabolic enzymes that govern the disposition of SOF, VEL and VOX and the results obtained in older age groups will be taken into consideration. For younger age groups, allometric scaling and observed exposures in the previous age groups will be used to inform dose selection. Available data suggest comparable hepatic expression of CYP2B6 and CES1 in adolescents and adults with modestly decreased expression in children, and comparable levels of CYP2C8, CYP3A4 and OATP1B1/3 to adults from a young age (~3-6 years of age) {Brouwer 2015, Johnson 2006, Prasad 2016}, however, little is known about the developmental regulation of OATP, Pgp, CES, and CatA.

The adult clinical doses of SOF/VEL/VOX FDC (400/100/100 mg) will be evaluated in adolescents (12 to <18 years old). Safety and PK data in the adolescent group (Cohort 1), in addition to considerations of body weight/body surface area, will inform dose selection for the younger age groups.

Age-appropriate formulations of SOF/VEL/VOX FDC (a smaller tablet of lower dose and a non-tablet formulation currently under development) that offer an important option in the treatment of HCV infection in the pediatric population are planned for evaluation in children below 12 years of age or children who are unable to swallow the adult dose tablet formulation. The smaller tablet and non-tablet formulation of SOF/VEL/VOX FDC will be included in a protocol amendment, when available.

1.5. Rationale for Study Design

This open-label, multi-cohort study is designed to collect safety, efficacy, and PK data to determine the appropriate dose for each age group. The treatment durations of 8 weeks for DAA-naive subjects without cirrhosis and 12 weeks for DAA-naive subjects with cirrhosis and DAA-experienced subjects with or without cirrhosis, are based on the Phase 3 POLARIS program. The choice of no comparator or active control group is in line with international guidelines that support single-arm pediatric studies when safety and efficacy have been demonstrated in adults. The minimum number of subjects planned to be enrolled in each age group is considered acceptable to collect PK data to determine the appropriate dose for each age group.

1.6. Risk/Benefit Assessment for the Study

Although the majority of pediatric patients infected with HCV exhibit minimal hepatic sequelae despite active viral replication and inflammation, a subset of children and adolescents will require treatment. Studies suggest that 3 major categories of disease can occur within 10 years after putative HCV exposure: (1) undetectable viremia and normal ALT, (2) persistent yet uncomplicated mild liver disease, and (3) progression to end-stage liver disease {Bortolotti 2008}. It is the last two groups of children in whom therapy may be indicated to prevent end-stage disease, either during childhood/adolescence or in early adulthood.

Recently in the US and EU, treatment with SOF+RBV and LDV/SOF for 12 or 24 weeks were approved for use in treatment naive or IFN-experienced patients who are 12 years old and older or weighing at least 35 kg (US only). For all other pediatric patients treatment with Peg-IFN and weight-based RBV is still considered the SOC. Therefore, for patients younger than 12 years there is a need for new treatments that combine potent and sustained efficacy with improved tolerability and safety. In addition, for all pediatric patients of any age there continues to be a need for new pangenotypic HCV treatments free of RBV and of shorter duration, requiring less frequent medical monitoring and a lower amount of blood tests to ensure greater convenience and patient adherence. Moreover, there are no approved treatment options for pediatric patients who fail treatment with DAAs. Therefore, there is also a need for development of a salvage therapy with combination of highly potent DAAs.

If high rates of SVR can be obtained with short, pangenotypic, well-tolerated regimen, the anticipated improvements in safety and tolerability would offer a favorable risk-benefit determination for individuals with chronic HCV infection.

1.7. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the steady-state pharmacokinetics (PK) and confirm age-appropriate dose of SOF/VEL/VOX FDC in pediatric subjects with chronic HCV infection

The secondary objectives of this study are:

- To evaluate the safety and tolerability of SOF/VEL/VOX FDC in pediatric subjects with chronic HCV infection
- To evaluate the antiviral efficacy of SOF/VEL/VOX FDC treatment in pediatric subjects with chronic HCV infection, as assessed by the proportion of pediatric subjects with sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12)
- To evaluate the antiviral efficacy SOF/VEL/VOX FDC treatment in pediatric subjects with chronic HCV infection, as assessed by the proportion of pediatric subjects with SVR 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of pediatric subjects with virologic failure, including on-treatment virologic failure and relapse
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF, VEL, and VOX during treatment and after cessation of treatment
- To evaluate the effect of SOF/VEL/VOX FDC on growth and development of pediatric subjects during and after treatment
- To evaluate acceptability, including palatability, and swallowability of formulations (as applicable) used in the study
- To assess the effect of treatment with SOF/VEL/VOX FDC on quality of life as measured by PedsQL™ Pediatric Quality of Life survey

CCI [redacted]

3. STUDY DESIGN

3.1. Study Design

This is an open-label, multi-cohort study evaluating the PK, safety, and antiviral activity of SOF/VEL/VOX FDC in pediatric subjects with chronic HCV infection.

Pediatric subjects with chronic HCV infection of any HCV genotype, including indeterminate or mixed genotypes, will be enrolled. Both DAA-naïve and DAA-experienced subjects will be eligible. DAA-experienced subjects are defined as subjects who have been exposed to treatment with DAAs including NS3/4A protease inhibitors, NS5A inhibitor or NS5B nucleotide/nucleoside inhibitor.

3.2. Study Treatments

Three sequential age-based cohorts will be enrolled:

- Cohort 1: at least 20 subjects 12 to < 18 years old
- Cohort 2: at least 20 subjects 6 to < 12 years old
- Cohort 3: at least 20 subjects 3 to < 6 years old

CCI [redacted] For all subjects, sparse PK samples will also be collected at various timepoints (Weeks 1, 2, 4, 8, and 12) dependent on treatment duration CCI [redacted]

The study will start with Cohort 1. DAA-naive subjects without cirrhosis will receive SOF/VEL/VOX FDC (400/100/100 mg) adult tablet for 8 weeks. DAA-naive subjects with cirrhosis and DAA-experienced subjects with or without cirrhosis will receive treatment for 12 weeks.

Subjects unable to swallow the SOF/VEL/VOX FDC (400/100/100 mg) adult tablet (as determined by SOF/VEL/VOX FDC swallowability assessment at Screening or at Day 1) will be re-assigned to a smaller tablet of lower dose and/or a non-tablet formulation of SOF/VEL/VOX FDC when available.

PK and safety data from at least 20 evaluable subjects in each cohort will be reviewed to confirm the appropriateness of the SOF/VEL/VOX FDC dose used in each cohort and to determine the dose to be evaluated in the next cohort.

3.3. Duration of Treatment

DAA-naive subjects without cirrhosis will receive treatment for 8 weeks and will then return for follow-up visits at 4, 12, and 24 weeks after discontinuation of study drug.

DAA-naive subjects with cirrhosis and DAA-experienced subjects with or without cirrhosis will receive treatment for 12 weeks and will then return for follow-up visits at 4, 12, and 24 weeks after discontinuation of study drug.

3.4. Virologic Response-Based Stopping Criteria

The following on-treatment virologic response-based treatment stopping criteria will be utilized:

- Confirmed HCV RNA ≥LLOQ after 2 consecutive HCV RNA <LLOQ
- Confirmed >1 $\log_{10}$ increase on-treatment nadir

Confirmation should be performed as soon as possible and must occur no later than 2 weeks after an initial observation indicating virologic failure during the on-treatment phase.

3.5. Discontinuation Criteria

The medical monitor should be consulted prior to subject discontinuation when medically feasible. Study medication must be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator
- Unacceptable toxicity (as defined in Section 7.5 of the protocol) or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Pregnancy of female subject or female partner of male subject
- Efficacy failure as defined in Section 3.4
- Significant protocol violation including non-compliance with study assessments
- Subject or parent/legal guardian request to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy, or other reason
- Discontinuation of the study at the request of Gilead, regulatory agency, or an Independent Ethics Committee (IEC)

Subjects who meet any of the following criteria must stop treatment with SOF/VEL/VOX FDC:

- Elevation of ALT and/or AST above the upper limit of normal and > 5x Day 1 or nadir, confirmed by immediate repeat testing
- Elevation of ALT >3x Day 1 and total bilirubin >2x ULN, confirmed by immediate repeat testing
- Any Grade 3 or greater rash associated with constitutional symptoms (see Appendix 3)
- Any Grade 4 adverse event assessed as related to administration of SOF/VEL/VOX FDC (see Appendix 3)

3.6. End of Study

The end of study is defined as when the last subject has completed their final visit in the study.

Discontinuation from study drug dosing and discontinuation from the overall study, including the posttreatment period, will be collected as two separate events.

The end of study will occur at the posttreatment Week 24 visit.

3.7. Reconsent

When a subject reaches the age of consent in their country/region, they will be invited to consent with an age-appropriate consent to continue participating in the clinical trial.

CCI [redacted]

[redacted]

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[redacted]

CCI

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

At least 60 subjects will be enrolled in this study.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) Subject or parent/ legal guardian able to provide written informed consent prior to any screening evaluations. Willing to comply with study requirements in accordance with IEC/local requirements and the Investigator's discretion. Subject will provide assent, if possible.

2) 3 to < 18 years of age as determined at Day 1

3) Chronic HCV infection (≥ 6 months) as documented by prior medical history or liver biopsy

4) HCV RNA ≥ 1000 IU/mL at Screening

5) Subjects must have a determination of prior treatment status:

   a) DAA-naive is defined as either:

      i) Treatment naive with no prior exposure to any IFN, RBV, or approved or experimental HCV-specific DAA

      ii) Treatment experienced with an IFN-based regimen and no prior exposure to an approved or experimental HCV-specific DAA

   b) DAA-experienced is defined as prior exposure to a regimen including any DAA (eg, NS3/4A protease inhibitor, NS5A inhibitor, or NS5B nucleotide/nucleoside inhibitor)

6) A negative serum pregnancy test is required at Screening and a negative urine test is required at Day 1 for female subjects of childbearing potential (as defined in Appendix 5).

7) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5.

8) Lactating females must agree to discontinue nursing before the study drug is administered

9) Subject must be able to comply with the dosing instructions for study drug administration and be able to complete the study schedule of assessments.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Current or prior history of clinical hepatic decompensation (eg, clinical ascites, encephalopathy, and/or variceal hemorrhage)

2) Any of the following laboratory parameters at Screening:

   a) INR >1.2 x ULN

   b) Platelets < 50,000/mm^3

   c) Albumin < 3.5 g/dL

   d) ALT> 10 x ULN

   e) AST > 10 x ULN

   f) Direct bilirubin > 1.5 x ULN

   g) Estimated glomerular filtration rate < 90 mL/min/1.73m^2, as calculated by the Schwartz formula

3) Chronic liver disease of a non-HCV etiology (eg, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency)

4) Evidence of hepatocellular carcinoma or other malignancy (with exception of certain resolved skin cancers)

5) Co-infection with human immunodeficiency virus (HIV), acute hepatitis A virus (HAV) or hepatitis B virus (HBV) (hepatitis B surface antigen [HBsAg] positive at Screening)

6) Current or prior history of any of the following:

   a) Clinically significant illness (other than HCV) or any other major medical disorder that may have interfered with subject treatment, assessment, or compliance with the protocol; subjects currently under evaluation for a potentially clinically significant illness (other than HCV) are also excluded

   b) Significant cardiac disease

   c) Gastrointestinal malabsorption syndrome that may interfere with absorption of orally administered medications

   d) History of solid organ or bone marrow transplantation

e) Psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 5 years. Subjects with psychiatric illness (without the prior mentioned conditions) that is well controlled on a stable treatment regimen for at least 6 months prior to enrollment or has not required medication in the last 12 months may be included

7) Clinically relevant alcohol or drug abuse within 12 months of Screening. A positive drug screen will exclude subjects unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator

8) Use of any prohibited concomitant medications as described in Section 5.3.

9) Investigational agents taken within the past 28 days (except with the approval of the sponsor)

10) Known hypersensitivity to the study drug, the metabolites, or formulation excipients

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Description and Handling of SOF/VEL/VOX FDC

5.1.1. Formulation

SOF/VEL/VOX FDC (400/100/100 mg) tablets, with dimensions of approximately 10 × 20mm, are available as beige, capsule-shaped film-coated tablets debossed with "GSI" on one side and a "square" containing the number "3" on the other side. In addition to the active ingredients, SOF/VEL/VOX FDC (400/100/100 mg) tablets also contain copovidone, microcrystalline cellulose, lactose monohydrate, silicon dioxide, croscarmellose sodium, and magnesium stearate. The active tablet film coating material contains polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc, iron oxide yellow, iron oxide red, and ferrosoferric oxide.

Placebo tablets to assess swallowability of SOF/VEL/VOX FDC (400/100/100 mg) tablets, are of similar size and shape. The placebo tablets are available as beige, capsule-shaped film-coated tablets debossed with "GSI" on one side and a "square" containing the number "3" on the other side. The tablets contain copovidone, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The placebo tablet film coating material contains polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc, iron oxide yellow, iron oxide red, and ferrosoferric oxide.

5.1.2. Packaging and Labeling

SOF/VEL/VOX FDC (400/100/100 mg) tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 28 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap fitted with an induction-sealed, aluminum-faced liner.

Placebo tablets to assess swallowability of SOF/VEL/VOX FDC (400/100/100 mg) tablets, are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 28 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap fitted with an induction-sealed, aluminum-faced liner.

SOF/VEL/VOX FDC (400/100/100 mg) tablet bottles and placebo tablets to be distributed to study centers in the participating countries shall be labeled to meet all applicable requirements of the United States Food and Drug Administration (FDA), and EU Guideline to Good Manufacturing Practice-Annex 13 (Investigational Medicinal Products) and/or local regulations as applicable.

Sufficient quantities of SOF/VEL/VOX FDC (400/100/100 mg) tablets will be shipped to the investigator or qualified designee from Gilead Sciences Clinical Supply Management (or its designee).

5.1.3. Storage and Handling

SOF/VEL/VOX FDC (400/100/100 mg) bottles should be stored below 30°C (86°F).

Placebo to match SOF/VEL/VOX FDC (400/100/100 mg) tablets for Swallowability Assessment should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).

All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling SOF/VEL/VOX FDC (400/100/100 mg).

5.2. Dosage and Administration of SOF/VEL/VOX FDC

Cohort 1 (12 to < 18 years): SOF/VEL/VOX FDC (400/100/100 mg) tablets will be administered once daily with food. Enrollment of subjects unable to swallow the placebo to match the SOF/VEL/VOX FDC (400/100/100 mg) tablet will be deferred until small tablet of lower dose and/or non-tablet formulations are available.

DAA-naive subjects without cirrhosis will receive SOF/VEL/VOX FDC (400/100/100 mg) treatment for 8 weeks. DAA-naive subjects with cirrhosis or all DAA-experienced subjects with or without cirrhosis will receive treatment for 12 weeks.

Subjects should be instructed that if vomiting occurs within 4 hours of dosing an additional tablet of SOF/VEL/VOX FDC (400/100/100 mg) should be taken. If vomiting occurs more than 4 hours after dosing, no further dose is needed.

If a dose is missed and it is within 18 hours of the regularly scheduled time, subjects should be instructed to take the tablet as soon as possible and then follow with the next dose at the usual scheduled time.

If a dose is missed after 18 hours of the regularly scheduled time, then it is a missed dose. Subjects should be instructed to take the next dose at the usual next scheduled time. Subjects should be instructed not to take a double dose.

5.3. Prior and Concomitant Medications

Concomitant medications taken within 30 days prior to Screening, through 30 days after the last dose of study drug need to be recorded in the source documents and electronic case report form(s) (eCRFs).

The following medications are prohibited during the screening period and for a minimum of 28 days prior to the Day 1 visit through the end of treatment:

- Hematologic stimulating agents (eg, erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics)

- Chronic use of systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (eg, infliximab)

- Investigational agents or devices for any indication

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters, ie, OATP and P-gp) with study drug(s) may result in PK interactions resulting in increases or decreases in exposure of study drug(s). In addition, study drug(s) may have an impact on pharmacokinetics of other concomitant medicinal products that are substrates of P-gp, BCRP, OATP1B1, OAT1B3, or OATP2B1 as described in the Investigator's Brochure. The use of amiodarone is prohibited from **60 days prior to Day 1** through the end of treatment. Other examples of representative medications which are prohibited or are to be used with caution from 21 days prior to Day 1 through the end of treatment are listed below; this list is not exhaustive. For all co-medications, consult label for pediatric-specific recommendations.

Table 5-1. Disallowed Medications and Concomitant Medications to be used with Caution

Drug Class	Agents Disallowed	Use with Caution
Acid Reducing Agents[a]		Proton-Pump Inhibitors, H2-Receptor Antagonists, Antacids
Anticonvulsants[b]	Carbamazepine, Phenobarbital, Phenytoin, Oxcarbazepine	
Antimycobacterials[b]	Rifabutin, Rifapentine, Rifampin	
Cardiac Medications	Amiodarone[c], Dabigatran Etexilate[d]	Digoxin[d], Vitamin K antagonists[e]
Herbal/Natural Supplements[bf]	St. John's Wort, Echinacea, Milk thistle (ie, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[f]	Rosuvastatin, Atorvastatin[f], Pravastatin[f]	
Other	Modafinil[b], Sulfasalazine[d], Methotrexate [d], Ethinylestradiol-containing products [g], Cyclosporine[h]	

a Proton pump inhibitors (PPIs) comparable to omeprazole 20 mg once-daily may be taken. H2 receptor antagonists must not exceed the equivalent of 40 mg famotidine taken twice daily. Antacids that directly neutralize stomach acid (eg, Tums, Maalox) are permitted, but may not be taken within 4 hours (before or after) study drug administration.
b May result in a decrease in the concentrations of study drugs.
c The use of amiodarone is prohibited from 60 days prior to Day 1 through the end of treatment
d May result in an increase in the concentration of study drugs and/or concomitant medications
e Close monitoring of International Normalized Ratio (INR) is recommended as liver function may improve during treatment with study drug
f Use with study drugs may result in an increase in the concentration of the HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis. Pravastatin and atorvastatin should initiate dosing at the lowest dose, and a gradual dose increase may be tailored to clinical response. Pravastatin may be administered with SOF/VEL/VOX FDC at a dose that does not exceed pravastatin 40 mg, and atorvastatin may be administered with SOF/VEL/VOX FDC at a dose that does not exceed 20 mg.
g May increase the risk of ALT elevations
h May increase the exposure of VOX

Medications for disease conditions **excluded** from the protocol (eg, transplantation) are not listed under this Concomitant Medication section, but are disallowed in the study.

Should subjects have a need to initiate treatment with any disallowed concomitant medication, the medical monitor must be consulted prior to initiation of the new medication. In instances where disallowed medication is initiated prior to discussion with the sponsor, the investigator must notify Gilead as soon as he/she is aware of the use of the medication.

5.4. Accountability for SOF/VEL/VOX FDC

The investigator is responsible for ensuring adequate accountability of all used and unused investigational medicinal product (IMP) bottles. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused IMP bottles dispensed to subjects must be returned to the site.

SOF/VEL/VOX FDC accountability records will be provided to each study site to:

- Record the date received and quantity of IMP kits
- Record the date, subject number, subject initials, the IMP kit number dispensed
- Record the date, quantity of used and unused IMP kits returned, along with the initials of the person recording the information.

5.4.1. Investigational Medicinal Product Return or Disposal

Refer to Section 9.1.7 for information on return and disposal of study drugs.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. Additional information is provided in the study procedures manual.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total trial enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or trial-wide at any time.

6.1.1. Screening Visit

Subjects will be screened within 28 days prior to enrollment to determine eligibility for participation in the study. The screening window can be extended to 42 days with sponsor approval for subjects with extenuating circumstances. In cohort 2 and Cohort 3, for subjects weighing ≤ 25 kg the screening visit samples will be collected in two different days (please see Appendix 2 Table 1). If the subject's weight is > 25 kg, the screening visit blood draw can be completed in one day. The following will be performed and documented at Screening:

- Obtain written informed consent/assent
- Determine eligibility
- Obtain medical history
- Perform complete physical examination
- Vital signs
- Body weight and height
- Assessments of AEs and concomitant medications
- SOF/VEL/VOX FDC swallowability assessment (may be performed at Screening up to Day 1)
- Transient elastography test (FibroScan® if available; may be performed at Screening up to Day 1)

- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - HCV Genotyping
  - Serum β-hCG pregnancy test for females of childbearing potential only
  - IL28B genotyping (may be performed at Screening up to Day 1)
  - HIV testing, HAV antibody, HCV antibody, HBsAg, HBV surface antibody (HBsAb), HBV core antibody (HBcAb)
  - HbA1c
  - TSH
  - Alpha-1 anti-trypsin (ATT)
  - Fibrotest®
  - APRI
- Obtain urine samples for:
  - Urinalysis
  - Urine Drug Screen

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 28 days after Screening for enrollment into the study.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all SAEs, as well as any AEs related to protocol-mandated procedures on the adverse events eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.1.2. Day 1 Assessments

Subjects returning to the clinic for enrollment at Day 1 should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the Day 1 visit to ensure an approximate 8-hour fast prior to the blood sample collection the next morning.

After confirmation of eligibility has been evaluated, the following tests and procedures must be completed prior to enrollment and dosing/dispensing on Day 1:

- Parental height, if known
- Complete physical examination
- Tanner Pubertal Stage assessment
- Vital signs
- Body weight and height (with calculation of BMI)
- A single X-ray of the left wrist, hand, and fingers for radiographic bone age assessment
- Assessment of AEs and concomitant medications
- Transient elastography test (FibroScan® if available and if not completed at Screening)
- Pregnancy prevention counseling including partner pregnancy prevention for male participants (all subjects ≥ 12 years of age and subjects < 12 years of age at the discretion of the investigator based on subject's pubertal status)
- Quality of life survey: Subject is to review questionnaire and write/mark answers directly onto the questionnaire. Parent/guardian completes the parent/guardian questionnaire.
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - CCI [redacted]
  - IL28B genotyping (may be performed at Screening, up to Day 1)

— Bone age biomarkers: CTX and P1NP

— HBV DNA testing for subjects HBcAb positive at Screening

CCI [redacted]

- Obtain urine samples for:

  — Urinalysis

  — Urine pregnancy test for females of childbearing potential only

6.1.2.1. Drug Administration

- Perform SOF/VEL/VOX FDC swallowability assessment (if not previously performed at Screening).
- Dispense study drug as directed by the Interactive Web Response System (IWRS)
- Instruct the subject on the packaging, storage, and administration of the study drug
- Observe the subject taking the first dose of study drug with food and record the time of first dose.
- Subject or parent/legal guardian (if needed) will complete the relevant acceptability questionnaires.

6.2. Enrollment

An IWRS will be employed to manage subject enrollment and treatment assignment. The study will not be randomized; subjects will be enrolled in the appropriate age-based cohort.

6.3. Treatment Assessments

6.3.1. Week 1 (± 3 days)

The following procedures/assessments are to be completed at this visit:

- Perform symptom-directed physical examination
- Vital signs
- Body weight and height

- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - — Hematology
  - — Chemistry
  - — HBV DNA testing for subjects HBcAb positive at Screening
  - — HCV RNA
  - CCI [redacted]
  - — Single sparse PK sample collected anytime
  - CCI [redacted]

6.3.2. Week 2 (± 3 days)

CCI [redacted]

The following procedures/assessments are to be completed at this visit:

- Perform symptom-directed physical examination
- Vital signs
- Body weight and height
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - — Hematology
  - — Chemistry
  - — HCV RNA
  - CCI [redacted]

— HBV DNA testing for subjects HBcAb positive at Screening

— Two sparse PK samples collected pre-dose and between 15 minutes and 4 hours postdose

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6.3.3. Week 4 (± 3 days)

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The following procedures/assessments are to be completed at this visit:

- Perform symptom-directed physical examination
- Vital signs
- Body weight and height
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling including partner pregnancy prevention for male participants (all subjects ≥ 12 years of age and subjects < 12 years of age at the discretion of the investigator based on subject's pubertal status)
- Obtain blood samples for:

  — Hematology

  — Chemistry

  — HCV RNA

  CCI

  — HBV DNA testing for subjects HBcAb positive at Screening

  — Two sparse PK samples collected pre-dose and between 15 minutes and 4 hours postdose

  CCI

  CCI

- Obtain urine sample for:
  - Urine pregnancy test for females of childbearing potential only
- Review medication compliance with subject and/or parent/guardian (subject should return all study drug at these visits)
- Dispense study drug as directed by the IWRS

6.3.4. Week 8 (± 3 days)

The Week 8 Visit will only be completed for subjects that are DAA-naive with cirrhosis or DAA-experienced with or without cirrhosis completing 12 weeks of treatment. The following procedures/assessments are to be completed at this visit:

- Perform symptom-directed physical examination
- Vital signs
- Body weight and height
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling including partner pregnancy prevention for male participants (all subjects ≥ 12 years of age and subjects < 12 years of age at the discretion of the investigator based on subject's pubertal status)
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - CCI [redacted]
  - HBV DNA testing for subjects HBcAb positive at Screening
  - Single sparse PK sample collected anytime
  - CCI [redacted]

- Obtain urine sample for:

  — Urine pregnancy test for females of childbearing potential only

- Review medication compliance with subject and/or parent/guardian (subject should return all study drug at these visits)

- Dispense study drug as directed by the IWRS

6.3.5. End of Treatment (± 3 days) or Early Termination

For subjects that are DAA-naive without cirrhosis, the End of Treatment visit will occur at Week 8. For subjects that are DAA-naive with cirrhosis or DAA-experienced with or without cirrhosis the End of Treatment Visit will occur at Week 12.

Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the Early Termination visit **only** to ensure an approximate 8-hour fast prior to the blood sample collection the next morning. The following procedures/assessments are to be completed at this visit:

- Complete physical examination

- Tanner Pubertal Stage assessment

- A single X-ray of the left wrist, hand, and fingers for radiographic bone age assessment

- Vital signs

- Body weight and height

- Assessment of AEs and concomitant medications

- Pregnancy prevention counseling including partner pregnancy prevention for male participants (all subjects ≥ 12 years of age and subjects < 12 years of age at the discretion of the investigator based on subject's pubertal status)

- Subject and parent/legal guardian will complete the relevant acceptability questionnaires.

- Quality of life survey: Subject is to review questionnaire and write/mark answers directly onto the questionnaire. Parent/guardian completes the parent/guardian questionnaire.

- Obtain blood samples for:

  — Hematology

  — Chemistry

— Coagulation tests

— HCV RNA

CCI [redacted]

— TSH

— Single sparse PK sample collected anytime

— HBV DNA testing for subjects HBcAb positive at Screening

— Bone age biomarkers: CTX and P1NP (**will only be collected at Early Termination**)

CCI [redacted]

- Obtain urine sample for:

  — Urine pregnancy test for females of childbearing potential only

- Review medication compliance with subject and/or parent/guardian.

Subjects should return all bottles of study drug at the End of Treatment (Week 8 for DAA-naive subjects without cirrhosis or Week 12 for DAA-naive subjects with cirrhosis and DAA-experienced subjects with or without cirrhosis) or Early Termination Visit

6.4. Posttreatment Assessments

6.4.1. 4-Week Posttreatment Visit (± 5 days)

The following procedures/assessments are to be completed at this visit:

- Vital signs
- Body weight and height
- Perform symptom-directed physical examination
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling including partner pregnancy prevention for male participants (all subjects ≥ 12 years of age and subjects < 12 years of age at the discretion of the investigator based on subject's pubertal status)

- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - CCI [redacted]
  - HBV DNA testing for subjects HBcAb positive at Screening
  - CCI [redacted]
- Obtain urine sample for:
  - Urine pregnancy test for females of childbearing potential only

6.4.2. 12-Week Posttreatment Visit (± 5 days)

The following procedures/assessments are to be completed at this visit:

- Vital signs
- Body weight and height
- Perform symptom-directed physical examination
- Assessment of SAEs
- Quality of life survey: Subject is to review questionnaire and write/mark answers directly onto the questionnaire. Parent/guardian completes the parent/guardian questionnaire.
- Tanner Pubertal Stage assessment (do not complete if Tanner Pubertal Stage is 5 at Screening)
- Obtain blood samples for:
  - HCV RNA
  - CCI [redacted]
  - HBV DNA testing for subjects HBcAb positive at Screening
  - CCI [redacted]

6.4.3. 24-Week Posttreatment Visit (±5 days)

Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the 24-Week Posttreatment visit to ensure an approximate 8-hour fast prior to the blood sample collection the next morning.

The following procedures/assessments are to be completed at this visit:

- Vital signs
- Body weight and height measurements
- Perform symptom-directed physical examination
- Assessment of SAEs
- Quality of life survey: Subject is to review questionnaire and write/mark answers directly onto the questionnaire. Parent/guardian completes the parent/guardian questionnaire.
- Tanner Pubertal Stage assessment
- Obtain blood samples for:
  - — HCV RNA
  - CCI [redacted]
  - — HBV DNA testing for subjects HBcAb positive at Screening
  - — Bone age biomarkers: CTX and P1NP
  - CCI [redacted]

CCI [redacted]

CCI

[redacted]

[redacted]

6.6. Unscheduled Visit

A subject should attend an unscheduled visit if requested by the sponsor or the investigator. The assessments are at the investigator's discretion as clinically indicated, but the investigator should at a minimum collect AE and concomitant medication information. At all unscheduled visits initiated for the purpose of confirming virologic failure, a sample for a viral RNA sequencing/phenotyping must be collected. Unscheduled visits can be initiated to collect the sparse PK sample if not collected during the treatment visits.

6.7. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 3.5, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.8. Procedures and Specifications

6.8.1. Clinical Laboratory Analytes

Hematology: Hematocrit, hemoglobin (Hb), platelet count, red blood cell count (RBC), white blood cell count (WBC) with differential (absolute and percentage) including lymphocytes, monocytes, neutrophils, eosinophils, basophils, reticulocyte count and mean corpuscular volume (MCV).

Coagulation: INR, Prothrombin time (PT), Activated partial thromboplastin time (APTT)

Chemistry: Alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), albumin, alkaline phosphatase, creatinine, total and direct bilirubin, glucose, lipase, potassium, sodium, gamma-glutamyl transferase (GGT) and creatine kinase (CK).

Urinalysis: Appearance, blood, color, glucose, leukocyte esterase, pH, protein, urobilinogen. Reflex to microscopic urinalysis if dipstick result is abnormal.

Virological Tests: Serologies for HAV, HCV, HBV (HBsAg, HBsAb, HBcAb). HBV DNA testing will be performed in subjects HBcAb positive at Screening. Serology and/or antigen testing for HIV (including reflex testing as necessary).

HCV RNA will be measured using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 for Use with the High Pure System.

HCV GT and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay. Gilead reserves the right to use alternate assays for HCV RNA and HCV GT should the above assays become unavailable.

IL28B genotype will be determined by polymerase chain reaction (PCR) amplification of the single nucleotide polymorphism (SNP), rs12979860, with sequence specific forward and reverse primers and allele specific fluorescently labeled TaqMan® minor groove binder (MGB) probes. Gilead reserves the rights to use alternate assays for IL28B determination should the above assay become unavailable.

Pregnancy Tests: Serum β-hCG, Urine β-hCG (if positive, requires immediate confirmation with Serum β-hCG)

Additional Tests: Urine drug screen (for amphetamines, cocaine, methadone, opiates), hemoglobin A1c (HbA1c), TSH (reflex Free T4), AAT, bone biomarker (CTX and P1NP), Fibrotest®, and APRI.

6.8.2. Medical History

Medical history including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, and medication history will be collected on all subjects during Screening.

6.8.3. Physical Examination

A complete physical examination must include source documentation of general appearance, and the following body systems: Head, neck and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; neurological.

The focus of a symptom directed physical examination will be determined by the investigator based on subject complaint. For example, if a subject complains of a cough, a lung exam should be performed. If consistent with pneumonia (rales/crackles on exam) then an AE would be documented.

6.8.4. Tanner Pubertal Stage Assessment

The Tanner Stage scale is available in Appendix 4. All subjects will receive a baseline Tanner Pubertal Stage assessment. If the assessment determines that the subject is at a Tanner 5 at Day 1, no further Tanner Pubertal Stage Assessments are to be completed.

6.8.5. Height & Weight Measurement

Height and weight measurement will be collected at each study visit. The difference in body weight and height measurements between Day 1 and End of Treatment (Week 8 for DAA-naive subjects without cirrhosis or Week 12 for DAA-naive with cirrhosis and DAA-experienced subjects with or without cirrhosis), posttreatment Week 12, and posttreatment Week 24 will be calculated. Parental heights will be recorded at Day 1 as available.

6.8.6. Radiographic Bone Age Assessment

A single X-ray of the left wrist, hand, and fingers will be performed at Day 1 and End of Treatment (Week 8 for DAA-naive subjects without cirrhosis or Week 12 for DAA-naive subjects with cirrhosis and DAA-experienced subjects with or without cirrhosis). A local radiologist will determine radiographic bone age from X-ray.

6.8.7. Bone Age Biomarkers

Fasting blood samples for bone age biomarkers (CTX and P1NP), will be collected at Day 1, Early Termination (if applicable) and posttreatment Week 24.

6.8.8. Acceptability and Swallowability Assessment

A SOF/VEL/VOX FDC swallowability assessment will be performed at Screening up to Day 1. Subjects who have indicated that they can take pills will be observed taking a placebo to match the SOF/VEL/VOX FDC (400/100/100 mg) adult tablet. This will confirm the swallowability of the (400/100/100 mg) adult tablet formulation size. Subjects unable to swallow the SOF/VEL/VOX FDC (400/100/100 mg) adult tablet will be re-assigned to a smaller tablet of lower dose and/or to a non-tablet formulation of SOF/VEL/VOX FDC is available.

A questionnaire will be administered to subjects to assess acceptability, including palatability, of the formulation they received on Day 1 and End of Treatment (Week 8 for DAA-naive subjects without cirrhosis or Week 12 for DAA-naive subjects with cirrhosis and DAA-experienced subjects with or without cirrhosis) or Early Termination. If the subject is unable to complete the questionnaires, the parent/legal guardian will assist to complete the questionnaire. The subject's parent/legal guardian will also complete a questionnaire at End of Treatment (Week 8 for DAA-naive subjects without cirrhosis or Week 12 for DAA-naive subjects with cirrhosis and DAA-experienced subjects with or without cirrhosis) or Early Termination for their assessment of acceptability of the formulation the subject received.

6.8.9. Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, and temperature.

Blood pressure will be measured using the following standardized process:

- Subject should sit for ≥ 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;
- Measure and record the blood pressure to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

6.8.10. Body Mass Index (BMI)

BMI is calculated by the following equation.

$$\text{BMI} = \frac{\text{weight (pounds)} \times 703}{(\text{height in inches})^2} \quad \text{or} \quad \frac{\text{weight in kilograms}}{(\text{height in meters})^2}$$

6.8.11. Estimated Glomerular Filtration Rate (GFR)

Estimated Glomerular Filtration Rate (GFR) using Schwartz Formula (mL/min/1.73m^2) = k × L/Scr [(k is a proportionality constant, for adolescent females ≥ 12 years old is 0.55; and for adolescent males ≥ 12 years old is 0.70); L is height in centimeters (cm); and S_{cr} is serum creatinine (mg/dL)]

CCI [redacted]

[redacted]

6.8.13. Pharmacokinetic (PK) Sample

CCI [redacted] Sparse PK samples will be collected at various timepoints (Weeks 1, 2, 4, 8, and 12) dependent on treatment duration CCI [redacted]. Collected samples will be used for PK analysis of SOF, its major metabolite GS-331007, VEL, and VOX.

6.8.14. HBV DNA

HBV DNA will only be tested in subjects HBcAb positive at Screening. HBV DNA testing will occur at Day 1, Weeks 1, 2, 4, 8, and End of Treatment (Week 8 for DAA-naive subjects without cirrhosis or Week 12 for DAA-naive subjects with cirrhosis and DAA-experienced subjects with or without cirrhosis), or Early Termination and all posttreatment visits.

6.8.15. Pregnancy Testing

All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 and every 4 weeks during the dosing period and for a minimum of 30 days following the last dose of SOF/VEL/VOX FDC. If required by local regulations, additional pregnancy tests beyond 30 days may be added. In the event of a positive urine pregnancy result, subjects will be instructed to stop study drugs immediately (if applicable) and return to the clinic as soon as possible for a serum pregnancy test.

6.8.16. Quality of Life Survey (PedsQL™)

The PedsQL™ Pediatric Quality of Life Inventory V4.0 Short Form (SF15) will be completed by the subject and the parent/guardian at Day 1, End of Treatment (Week 8 for DAA-naive subjects without cirrhosis or Week 12 for DAA- naive subjects with cirrhosis and DAA-experienced subjects with or without cirrhosis), Early Termination (if applicable), 12-Week Posttreatment, and 24-Week Posttreatment visits.

The PedsQL™ has separate survey instruments administered by age group, including the Teen Report (ages 13-18), Child Report (ages 8-12), Young Child Report (ages 5-7), and Toddlers (ages 2-4). Surveys will be administered for the corresponding age group of the subject at the time of survey administration.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre or posttreatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the Screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (eg., venipuncture)

7.2.2. Assessment of Severity

The severity grading of AEs will be assessed as Grade 1, 2, 3, or 4 using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 3). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the eCRF: all SAEs and adverse events related to protocol mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study IMP and report to the eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required posttreatment follow-up period, must be reported to the eCRF database and Gilead Pharmacovigilance and Epidemiology (PVE) as instructed. This also includes any SAEs resulting from protocol associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead PVE.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead Sciences, Pharmacovigilance and Epidemiology:	Fax:	PPD
	E-mail:	PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

To minimize the possibility of exposing study subjects to unusual risk, the safety information from this study will also be reviewed periodically by an independent DMC. The DMC will make recommendations regarding the study according to the DMC charter.

7.5. Toxicity Management

7.5.1. Subject Stopping Rules

See Section 3.5 for Subject Stopping Rules.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, occupational exposure with an AE, pregnancy reports regardless of an associated AE, and AE in an infant following exposure from breastfeeding.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure with an AE is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the poststudy drug follow-up period, to Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome poststudy must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows:

Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should

continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate the steady-state PK and confirm age-appropriate dose of SOF/VEL/VOX FDC in pediatric subjects with chronic HCV infection

The secondary objectives of this study are:

- To evaluate the safety and tolerability of SOF/VEL/VOX FDC in pediatric subjects with chronic HCV infection
- To evaluate the antiviral efficacy of SOF/VEL/VOX FDC treatment in pediatric subjects with chronic HCV infection, as assessed by the proportion of pediatric subjects with sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12)
- To evaluate the antiviral efficacy of SOF/VEL/VOX FDC treatment in pediatric subjects with chronic HCV infection, as assessed by the proportion of pediatric subjects with SVR 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of pediatric subjects with virologic failure, including on-treatment virologic failure and relapse
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF, VEL, and VOX during treatment and after cessation of treatment
- To evaluate the effect of SOF/VEL/VOX FDC on growth and development of pediatric subjects during and after treatment
- To evaluate acceptability, including palatability, and swallowability, of formulations (as applicable) used in the study
- To assess the effect of treatment with SOF/VEL/VOX FDC on quality of life as measured by PedsQL™ Pediatric Quality of Life survey

CCI [redacted]

8.1.2. Primary Endpoint

The appropriateness of the SOF/VEL/VOX FDC dose will be assessed by evaluating its steady-state PK. The primary PK endpoint is AUC_{tau} of SOF, its major metabolite (GS-331007), VEL and VOX.

8.1.3. Secondary Endpoint

The secondary endpoints are:

- Any AE leading to permanent discontinuation of study drug
- The proportion of subjects with sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12) is the key efficacy endpoint
- The proportion of subjects with HCV RNA < LLOQ at 4 or 24 weeks after cessation of treatment (SVR4 and SVR24)
- The proportion of subjects with virologic failure, including on-treatment virologic failure and relapse
- The proportion of subjects with HCV RNA < LLOQ on treatment
- Emergence of viral resistance to SOF, VEL, and VOX during treatment and treatment is discontinued
- HCV RNA change from Day 1
- Growth and development measurements including height and weight percentiles, Tanner Stage, radiographic bone age and two bone turn-over biochemical markers (CTX and P1NP)
- Acceptability, including palatability, and swallowability assessments
- Neuropsychiatric assessments as measured by PedsQL™ Pediatric Quality of Life survey

8.1.4. Other Endpoints of Interest

Other endpoint of interest may include ALT normalization.

8.2. Analysis Conventions

All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

The study drug in this study is SOF/VEL/VOX FDC. Last dose of study drug will be used in the definition of treatment emergent AEs and laboratory abnormalities as well as the efficacy endpoints of SVR at various posttreatment time points.

8.2.1. Analysis Sets

8.2.1.1. Pharmacokinetics

The primary analysis set for PK analysis set will include all enrolled subjects who took at least one dose of study drug and for whom at least one non-missing concentration data SOF, its primary metabolite(s), VEL or VOX, are available.

8.2.1.2. Safety

The primary analysis set for safety analyses will include all subjects who took at least 1 dose of the study drug.

Treatment-emergent data will be analyzed and defined as data collected from the first dose of the study drug through the last dose date of the study drug plus 30 days.

8.2.1.3. Efficacy

The primary analysis set for efficacy analyses will be the Full Analysis Set (FAS), which includes all enrolled subjects who received at least 1 dose of the study drug.

8.3. Data Handling Conventions

Missing data can have an impact upon the interpretation of the trial data. Other than the endpoints discussed below, values for missing data will not be imputed.

For the analyses of categorical HCV RNA data, missing posttreatment HCV RNA data will have the missing data imputed. Missing on-treatment HCV RNA will have the missing data imputed up to the time of the last dose.

If a data point is missing and is preceded and followed in time by values that are "< LLOQ target not detected (TND)," then the missing data point will be set to "< LLOQ TND." If a data point is missing and preceded and followed by values that are "< LLOQ detected," or preceded by "< LLOQ detected" and followed by "< LLOQ TND," or preceded by "< LLOQ TND" and followed by "< LLOQ detected," then the missing value will be set to "< LLOQ detected." In these situations the data point will be termed a bracketed success; otherwise, the data point will be termed a bracketed failure (ie, ≥ LLOQ detected). If a data point is missing and is not bracketed, the missing data point will also be termed a failure (ie, ≥ LLOQ detected) except for

SVR24, which will be imputed according to the SVR12 status. Success for SVR12 who have no further HCV RNA measurements collected will be counted as a success for SVR24 due to the high correlation between these 2 endpoints.

Where appropriate, safety data for subjects who did not complete the study will be included in summary statistics. For example,

- If a subject took at least 1 dose of study drug, the subject will be included in a summary of adverse events according to the treatment received; otherwise, if the subject is not dosed, then they will be excluded from the summary.

- If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of the summary statistics for that time point. If the subject is missing a predose value, then the subject will be excluded from the calculation of the summary statistics for the predose value and the change from predose values.

Values for missing safety laboratory data will not be imputed; however, a missing Day 1 result will be replaced with a screening result, if available. If no pretreatment laboratory value is available, the Day 1 value will be assumed to be normal (ie, no grade [Grade 0]) for the summary of graded laboratory abnormalities.

Values for missing vital signs data will not be imputed; however, a missing Day 1 result will be replaced with a screening result, if available.

HCV RNA values below the LLOQ for the assay will be set to the lower limit minus 1 for the calculation of summary statistics for the actual HCV RNA values and the change from baseline values by study visit. The reported values will be provided in the HCV RNA listing.

For selected analyses of early time point data, HCV RNA data (IU/mL) may be transformed to the logarithmic (base 10) scale ($\log_{10}$ IU/mL).

For PK plasma concentrations and analysis of PK parameters natural logarithmic transformation will be used. Plasma concentration values that are below the lower limit of quantitation (BLQ) will be presented as “BLQ” in the concentration data listing.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods by age cohort (as described in Section 3.2) and treatment duration (8 weeks vs 12 weeks).

Demographic data will include sex, self-identified race/ethnicity and age.

Baseline characteristics data will include body mass index, HCV RNA level ($\log_{10}$ IU/mL), genotype of HCV infection, IL28B genotype, and additional endpoints as necessary.

8.5. Pharmacokinetic Analysis

Pharmacokinetic parameters (eg, AUC_{tau}, C_{max}, C_{tau}, volume of distribution and clearance) will be listed and summarized for, SOF, its primary metabolite(s), VEL and VOX using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum).

To evaluate if the exposures of SOF, GS-331007, VEL and VOX achieved in pediatric subjects of this study are similar to the exposures observed in adult subjects, SOF, GS-331007, VEL and VOX exposure data from this study will be compared to the integrated adult data. The primary endpoint of this analysis will be evaluated by carrying out an analysis of variance (ANOVA) for log-transformed SOF, GS-331007, VEL and VOX AUC_{tau}. The 90% confidence intervals will be constructed for the ratio of geometric means of each PK parameters. The equivalence boundary is set as 50% to 200%. The equivalence boundary is based on exposure-response (efficacy and safety) relationships observed in the integrated adult data.

Dose ranging studies for SOF established that a dose of 200 mg results in suboptimal exposure compared to the 400 mg dose, and no clinically significant exposure-safety relationships were observed across a broad range of GS-331007 exposure. The Phase 1b dose ranging studies, GS-US-281-0102 and GS-US-338-1121, established the anti-HCV activity of VEL and VOX, respectively. At exposures observed in Phase 3 studies, maximum effect (E_{max}) models predict near maximal antiviral activity for all analytes: 90%, ≥99.5%, ≥90%, of E_{max} for SOF, VEL, and VOX, respectively.

In the Phase 3 population treated with SOF/VEL/VOX FDC (400/100/100 mg), virologic response rates were high across all treatment groups, HCV genotypes and exposure ranges for SOF, GS-331007, VEL and VOX, including for subjects with cirrhosis, with no consistent trends in exposure-efficacy relationships. Similarly, exposure-safety analyses in Phase 3 clinical studies showed a lack of relationship over a wide range of SOF/VEL/VOX FDC exposures. The observed safety and efficacy profile and the lack of exposure-response relationships across a wide range of SOF/VEL/VOX FDC exposures, the bounds of 50-200% support identification of a clinically relevant difference in SOF, GS-331007, VEL or VOX exposure in the pediatric population.

In all pediatric age groups, the targeted exposures for SOF, GS-331007, VEL and VOX are the adult equivalent for which safety and efficacy has been established. Assuming similar variability for SOF, GS-331007, VEL or VOX AUC_{tau} in the pediatric population compared to adults, the predicted 90% confidence interval (CIs) of the geometric mean ratio (GMR) will be contained within the bounds of 50% to 200%.

Individual patient management will be performed by maintaining exposures comparable to adults. In the event more than one subject in each cohort exhibits SOF, GS-331007, VEL or VOX exposures (AUC_{tau}) less than the 2.5th percentile of adult values, a dose assessment may be require for the cohort as appropriate.

The effect of age and SOF/VEL/VOX FDC dose on PK (SOF, GS-331007, VEL and VOX) will be assessed.

8.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements at various time points during the study, and by the documentation of AEs.

All safety data collected on or after the first dose of the study drug administration up to 30 days after the last dose of the study drug will be summarized by age cohort and treatment duration (8 weeks vs 12 weeks) according to the study drug taken.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration data page of the eCRF. Exposure data will be summarized by age cohort and treatment duration (8 weeks vs 12 weeks).

8.6.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any adverse event with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of the study drug or any adverse event leading to premature discontinuation of the study drug.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC, and PT) will be provided by age cohort and treatment duration (8 weeks vs 12 weeks):

- All AEs
- AEs of Grade 3 or above
- AEs of Grade 2 or above
- All treatment-related AEs
- Treatment-related AEs of Grade 3 or above
- Treatment-related AEs of Grade 2 or above
- All SAEs
- All treatment-related SAEs
- All AEs leading to premature discontinuation of the study drug

All AEs collected during the study will be presented in the data listings.

8.6.3. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by study visit along with the corresponding change from baseline.

Graded laboratory abnormalities will be defined using the laboratory toxicity grading scheme defined in Appendix 3.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase by at least one toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days, will be summarized by age cohort and treatment duration (8 weeks vs 12 weeks).

Values for missing safety laboratory data will not be imputed; however, a missing Day 1 result will be replaced with a screening result, if available. If no pretreatment laboratory value is available, the baseline value will be assumed to be normal (ie, no grade [Grade 0]) for the summary of graded laboratory abnormalities.

All laboratory abnormalities will be included in the listings of laboratory data.

8.6.4. Other Safety Evaluations

8.6.4.1. Tanner Pubertal Stage Assessment

Tanner Stages (Appendix 4) will be summarized by baseline Tanner Stage using frequency and percentage by gender for each age cohort and treatment duration (8 weeks vs 12 weeks).

8.6.4.2. Vital Signs (including Body Weight and Height)

Vital signs including body weight and height and change from baseline will be summarized at each visit.

8.6.4.3. Radiographic Bone Age Assessment

Radiographic bone age will be summarized by age cohort and treatment duration (8 weeks vs 12 weeks).

8.6.4.4. Bone Age Biomarkers Assessment

Bone turn-over biochemical marker will be summarized by age cohort and treatment duration (8 weeks vs 12 weeks).

8.6.4.5. Neuropsychiatric Assessments measured by PedsQL ™ Pediatric Quality of Life survey

The data from PedsQL ™ Pediatric Quality of Life survey will be summarized by visit and age cohort and treatment duration (8 weeks vs 12 weeks).

8.7. Efficacy Analysis

8.7.1. Analysis of the Key Efficacy Endpoint

The key efficacy endpoint is SVR12 on the FAS. The proportion of subjects with sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12) will be summarized by age cohort and treatment duration (8 weeks vs 12 weeks).

8.7.2. Secondary Analyses

The proportion of subjects with HCV RNA below the LLOQ over time (including SVR4 and SVR24) will be presented by age cohort and treatment duration (8 weeks vs 12 weeks) in tabular and graphical form. Descriptive summaries and listings will be provided for additional efficacy evaluations of the proportion of subjects who experience virologic failure, serum HCV RNA actual values and change from baseline, and other endpoint of interest may include ALT normalization.

8.8. Acceptability and Swallowability

Acceptability and swallowability of the study drug will be summarized using descriptive statistics. Swallowability will be assessed by the subject's ability or inability to swallow the solid dosage tablet formulations. Acceptability, including palatability, will be assessed quantitatively in the questionnaire administered to subjects and their parent/legal guardian on Day 1 and/or End of Treatment (Week 8 for DAA-naive subjects without cirrhosis or Week 12 for DAA-naive subjects with cirrhosis and DAA-experienced subjects with or without cirrhosis).

8.9. Sample Size

Assuming similar variability for SOF, GS-331007, VEL, or VOX AUC_{tau} in the pediatric population compared to adults, a sample size of 20 pediatric subjects per cohort will provide at least 80% power to target a 90% confidence interval of the geometric mean ratio (GMR) within the bounds of 50% to 200% when comparing with the adult population.

8.10. Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety data at intervals of approximately 6 months from the first subject enrolled. The DMC will recommend to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design,

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IEC. The investigator will not begin any study subject activities until approval from the IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed

and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IEC or local requirements. CCI [redacted]

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the sponsor, IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions or in accordance with local regulations. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled

- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Electronic Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as

described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead , the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review IMP supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IEC or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to IEC in accordance with local requirements and receive documented IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Pharmacokinetics, Safety and Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir Fixed Dose Combination in Adolescents and Children with Chronic HCV Infection

GS-US-367-1175, Amendment 1, 27 March 2019

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

PPD

28-3-2019
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed) Signature

Date Site Number

Appendix 2. Study Procedures Table

Appendix Table 1. Screening and On-Treatment Study Visits

	Screening	Day 1[a]	On-Treatment Study Week (±3 Days)					Early Termination[a]
			Week 1	Week 2[t,v]	Week 4[c]	Week 8[b]	End of Treatment[c]	
Clinical Assessments								
Informed Consent/Assent	X							
Determine Eligibility	X	X						
Medical History	X							
Parental Height, if known		X						
Complete Physical Examination	X	X					X	X
Symptom-Directed Physical Examination			X	X	X	X		
Tanner Pubertal Stage Assessment		X					X	X
Vital Signs[d]	X	X	X	X	X	X	X	X
Body Weight and Height	X	X	X	X	X	X	X	X
Radiographic Bone Age Assessment		X					X	X
AEs and Concomitant Medications	X[e]	X	X	X	X	X	X	X
FibroScan® (if available)	X[f]	X[f]						
Pregnancy Prevention Counseling[g]		X			X	X	X	X
SOF/VEL/VOX Swallowability Assessment	X[h]	X[h]						
SOF/VEL/VOX Acceptability Questionnaire[i]		X					X	X
Quality of Life Survey[j]		X					X	X

	Screening	Day 1[a]	On-Treatment Study Week (±3 Days)					Early Termination[a]
			Week 1	Week 2[t,v]	Week 4[c]	Week 8[b]	End of Treatment[c]	
Review of Study Medication Compliance				CCI	X	X	X	X
Study Drug Dispensing		X			X	X		
Return of Study Drug Bottles					X	X	X	X
Review Dosing Diary				X[c]	X[c]			
Laboratory Assessments								
Hematology, Chemistry	X	X	X	X	X	X	X	X
Coagulation	X	X					X	X
HCV RNA	X	X	X	X	X	X	X	X
HBV DNA[l]		X	X	X	X	X	X	X
CCI								
Serum or Urine Pregnancy Testing[n]	X	X		X[c]	X	X	X	X
Single sparse PK sample collected at anytime			X			X	X	X
Two sparse PK Samples collected pre-dose and between 15 minutes and up to 4 hours postdose				X[p]	X[p]			
CCI								
CCI								
Urinalysis	X	X		X[c]	X[c]			
Urine Drug Screen	X							
IL28B Genotyping	X[f]	X[f]						
Bone Age Biomarkers		X						X[w]

	Screening	Day 1[a]	On-Treatment Study Week (±3 Days)					Early Termination[a]
			Week 1	Week 2[t,v]	Week 4[c]	Week 8[b]	End of Treatment[c]	
HCV Genotyping	X							
HIV testing, HAV Antibody, HCV Antibody, HBsAg, HBsAb, HBcAb	X							
HbA1c Fibrotest®, APRI	X							
TSH	X						X	X
Alpha-1 anti-trypsin	X							
Approximate amount of blood drawn (mL) _ Cohort 1	22.1	12.3	9.3	11 3 CCI CCI	11.3	9.3	13.2	16.8
Approximate amount of blood drawn (mL) _ Cohort 2	22.1[u]	12.3	9.3	18[t]	11.3	9.3	13.2	16.8
Approximate amount of blood drawn (mL) _ Cohort 3	22.1[u]	12.3	8.3	8[v]	9.3	8.3	12.2	12.2

a Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to Day 1 and Early Termination (if applicable) to ensure an approximate 8-hour fast prior to the blood sample collection the next morning.
b The Week 8 Visit will only be completed for subject DAA-naïve with cirrhosis or DAA-experienced with or without cirrhosis, who are on 12 weeks of treatment.
c For subjects that are DAA-naive without cirrhosis, who are on 8 weeks of treatment, the End of Treatment visit will occur at Week 8.
For subjects that are DAA-naive with cirrhosis or DAA-experienced with or without cirrhosis, who are on 12 weeks of treatment, the End of Treatment Visit will occur at Week 12.
d Vital signs include blood pressure, pulse, respiratory rate, and temperature.
e From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures.
f FibroScan® and IL28B genotyping may be performed at Day 1 if not completed at Screening.
g Including partner pregnancy prevention for male participants (all subjects ≥ 12 years old and subjects < 12 years old at the discretion of the Investigator based on subject's pubertal status).
h Swallowability may occur at Day 1 if not completed during Screening.
i A questionnaire will be administered to subjects to assess acceptability, including palatability, on Day 1, EOT (Week 8 or Week 12), or Early Termination (as applicable). If the subject is unable to complete the questionnaires, the parent/legal guardian will assist to complete the questionnaire. The subjects' parent/legal guardian will also complete a questionnaire on EOT (Week 8 or Week 12) or Early Termination (as applicable).
j Quality of life survey will be completed by all subjects and their parent/legal guardian. Subject and parent/legal guardian is to review questionnaire and write/mark answers directly onto the questionnaire.

CCI

l HBV DNA testing for subjects HBcAb positive at Screening.

CCI

n All females of childbearing potential will have a serum pregnancy test at Screening. In addition, all females of childbearing potential will perform a urine pregnancy test at Day 1 and every 4 weeks during the dosing period and for a minimum of 30 days following the last dose of SOF/VEL/VOX FDC.

CCI

p Two sparse PK samples collected pre-dose and between 15 minutes and 4 hours postdose CCI

CCI

CCI

CCI

CCI

u In cohort 2 and cohort 3, for subject weighing ≤ 25 kg, the screening visit will be performed in two different days. Samples for chemistry, hematology, coagulation, TSH, HIV/HAV/HCV testing will be performed on one day (12 ml of blood will be collected) and all other samples including for HCV RNA, HCV genotype and IL28B will be collected on a different day within the screening window (10.1 ml of blood will be collected). If the subject's weight is > 25 kg, the screening visit blood draw can be completed in one day.

CCI

w In cohort 3 , Bone age biomarkers (CTX and P1NP) samples will not be collected at the Early Termination visit

Appendix 2. Study Procedures Tables

Appendix Table 2. Posttreatment Visits

	Posttreatment Study Week (±5 Days)		
	4 Weeks Posttreatment	**12 Weeks Posttreatment**	**24 Weeks Posttreatment[a]**
Clinical Assessments			
Symptom-directed Physical Exam	X	X	X
Tanner Pubertal Stage assessment		X	X
Vital Signs	X	X	X
Body weight and Height	X	X	X
AEs	X	X[b]	X[b]
Concomitant Medications	X		
Pregnancy Prevention Counseling[c]	X		
Quality of Life Survey		X	X
Laboratory Assessments			
Hematology, Chemistry	X		
HCV RNA	X	X	X
HBV DNA[d]	X	X	X
CCI [redacted]			
CCI [redacted]			
Urine Pregnancy Test	X		
Bone Age Biomarkers			X
Approximate amount of blood drawn (mL) _ All Cohorts	7.3	5	8.6

a Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to posttreatment Week 24 to ensure an approximate 8-hour fast prior to the blood sample collection the next morning.
b Only SAEs will be captured at posttreatment Week 12 and 24
c Including partner pregnancy prevention for male participants (all subjects ≥ 12 years old and subjects < 12 years old at the discretion of the Investigator based on subject's pubertal status)
d HBV DNA testing for subjects HBcAb positive at Screening
CCI [redacted]

Appendix 3. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Antiviral Toxicity Grading Scale Version: 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	 8.5 to 10.0 g/dL 85 to 100 g/L	 7.5 to < 8.5 g/dL 75 to < 85 g/L	 6.5 to < 7.5 g/dL 65 to < 75 g/L	 < 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months[#]**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
International Normalized Ratio of prothrombin time (INR)	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
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

An overlap between the Grade 1 scale and the Lab's normal range for absolute neutrophils may result for pediatric subjects. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L 3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L 2.5 to < 3.0 mEq/L 2.5 to <3.0 mmolL	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L 2.0 to < 2.5 mEq/L 2.0 to <2.5 mmolL	< 2.0 mEq/L < 2.0 mmol/L < 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L >ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L > 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L > 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L > 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month** **Infant, < 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Pediatric < 4 Years	NA	11.0 mEq/L to <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) **Adult**	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
LDL (Fasting) **Pediatric >2 to <18 years**	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL
** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male subjects >70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin **Pediatrics <16 years** **≥ 16 years**	- 3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < LLN g/dL 20 to < LLN g/L 2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L < 2.0 g/dL < 20 g/L	NA NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below Females	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection **Adult and Pediatric ≥ 10 Years**	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	>499 to 799 mg/m^2/24 h	>799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:

- Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.
- With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
- If the severity of a clinical AE could fall under either one of two grades (eg, the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit) **Pediatric ≤ 17 Years** (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic NA	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic 91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	> 179 mmHg systolic OR > 109 mmHg diastolic ≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss **Pediatric < 21 Years**	BMD t-score or z-score –2.5 to –1.0 BMD z-score –2.5 to –1.0	BMD t-score or z-score < –2.5 BMD z-score < –2.5	Pathological fracture (including loss of vertebral height) Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Appendix 4. Tanner Stages*

1. Pubic hair (male and female)	
Tanner I	no pubic hair at all (prepubertal Dominic state)
Tanner II	small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females)
Tanner III	hair becomes more coarse and curly, and begins to extend laterally
Tanner IV	adult-like hair quality, extending across pubis but sparing medial thighs
Tanner V	hair extends to medial surface of the thighs
2. Genitals (male) (One standard deviation around mean age)	
Tanner I	Testes, scrotum, and penis about same size and proportion as in early childhood
Tanner II	Enlargement of scrotum and testes; skin of scrotum reddens and changes in texture; little or no enlargement of penis (10.5-12.5)
Tanner III	Enlargement of penis, first mainly in length; further growth of testes and scrotum (11.5-14)
Tanner IV	Increased size of penis with growth in breadth and development of glans; further enlargement of testes and scrotum and increased darkening of scrotal skin (13.5-15)
Tanner V	Genitalia adult in size and shape
3. Breasts (female)	
Tanner I	no glandular tissue: areola follows the skin contours of the chest
Tanner II	breast bud forms, with small area of surrounding glandular tissue; areola begins to widen
Tanner III	breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast
Tanner IV	increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast
Tanner V	breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla.

* Chart referenced from Marshall WA, Tanner JM, variations in the pattern of pubertal changes in boys and girls {Marshall 1969, Marshall 1970}

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal, unless permanently sterile or with medically documented ovarian failure.

Women of any age with amenorrhea of $\geq$ 12 months may be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Study Drug Effects on Pregnancy and Hormonal Contraception

Data on the effects of SOF/VEL/VOX FDC on pregnant women is not available.

From nonclinical studies, there is no evidence that SOF, VEL, or VOX is genotoxic. Relevant nonclinical reproductive studies have demonstrated no adverse effect on fertility or embryo-fetal development for SOF, VEL, and VOX as individual agents.

Data from clinical pharmacokinetic interaction studies of SOF/VEL/VOX FDC have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception.

3) Contraception Requirements for Female Subjects

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Day 1 visit prior to enrollment. Pregnancy tests will be performed every 4 weeks during the dosing period and at the posttreatment Week 4 visit. They must also agree to one of the following from Screening until 30 days of the last dose of SOF/VEL/VOX FDC.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Tubal sterilization
  - Vasectomy in the male partner
  - Barrier methods (one female barrier and one male barrier must be used in combination)
    - Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
    - Male barriers: Male condom (with or without spermicide)
  - Hormonal methods
    - Oral contraceptives (progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel or etonorgestrel

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the last dose of SOF/VEL/VOX FDC.

4) Contraception Requirements for Male Subjects

During the study, male subjects with female partners of childbearing potential should use condoms until 30 days after the last dose of SOF/VEL/VOX FDC treatment when engaging in intercourse of reproductive potential. If their female partner is of childbearing potential (as defined above), their female partner must use 1 of the methods of birth control listed above from the date of Screening until 30 days after the last dose of SOF/VEL/VOX FDC.

Male subjects must agree to refrain from sperm donation until 30 days after the last dose of SOF/VEL/VOX FDC.

5) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

6) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.