CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir in Adolescents and Children with Chronic HCV Infection	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA	
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	118605 2016-002446-23 NCT03022981	
Indication:	Hepatitis C Virus Infection	
Protocol ID:	GS-US-342-1143	
Gilead Medical Monitor and Study Director:	Name: Telephone: Fax:	PPD PPD PPD
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
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Study Title:	A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir in Adolescents and Children with Chronic HCV Infection
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	118605 2016-002446-23 NCT03022981
Study Centers Planned:	Approximately 30 centers in United States and Europe
Objectives:	The primary objective of the PK Lead-in Phase is: • To evaluate the steady state pharmacokinetics (PK) and confirm the dose of sofosbuvir/velpatasvir fixed dose combination (SOF/VEL FDC) in pediatric subjects with chronic hepatitis C virus (HCV) infection The primary objective of the Treatment Phase of this study is: • To evaluate the safety and tolerability of SOF/VEL FDC for 12 weeks in pediatric subjects with chronic HCV The secondary objective of the PK Lead-in Phase is: • To evaluate the safety, tolerability, and antiviral activity of 7 days of dosing of SOF/VEL FDC in pediatric subjects with chronic HCV The secondary objectives of the Treatment Phase of this study are: • To determine the efficacy of SOF/VEL FDC for 12 weeks in pediatric subjects with chronic HCV infection, as assessed by the proportion of subjects with sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12) • To determine the proportion of subjects with SVR 4 and 24 weeks after cessation of treatment (SVR4 and SVR24) • To evaluate the proportion of subjects with virologic failure, including breakthrough/nonresponse 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 and VEL during treatment and after cessation of treatment
- To evaluate the effect of treatment with SOF/VEL FDC on quality of life as measured by PedsQL™ Pediatric Quality of Life survey
- To evaluate the effect of SOF/VEL FDC on growth and development of pediatric subjects during and after treatment
- To evaluate the acceptability, including palatability, of formulations used in the study

The exploratory objective of this study is:

Study Design:

Open-label, multi-cohort, two-part study evaluating the PK, safety, and antiviral activity of SOF/VEL 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 treatment-naive and treatment-experienced subjects will be eligible, with at least 20 and up to 40 subjects overall allowed to be treatment-experienced.

PK Lead-in Phase: The PK Lead-in Phase will evaluate and/or confirm age appropriate SOF/VEL FDC doses by analyzing PK, safety, and antiviral activity of SOF/VEL FDC through 7 days of dosing with intensive PK sample collection at steady state on Day 7. Three sequential age-based cohorts of at least 17 subjects each will be enrolled:

- Cohort 1: 12 to < 18 years old
- Cohort 2: 6 to < 12 years old
- Cohort 3: 3 to < 6 years old
  - At least 6 subjects weighing ≥ 17 kg
  - At least 6 subjects weighing < 17 kg

	PK Lead-in subjects in each cohort will immediately roll over into the Treatment Phase as they complete Day 7 of the PK Lead-in Phase. They will continue dosing with the same dose of SOF/VEL FDC with no interruption of study drug administration and will follow the Treatment Phase visit schedule for all subsequent visits. The PK and safety data through Day 7 of each cohort will be reviewed to confirm the appropriateness of the SOF/VEL FDC dose for the Treatment Phase in that age group as well as to determine the dose to be evaluated in the PK Lead-in Phase of the next age cohort. **Treatment Phase**: The Treatment Phase will be initiated sequentially by age group after confirmation of the age-appropriate SOF/VEL FDC dose as follows (including subjects that participated within the PK Lead-in Phase): • Group 1: Approximately 100 subjects aged 12 to < 18 years — Includes subjects enrolled in Cohort 1 • Group 2: Approximately 100 subjects aged 3 to < 12 years — Includes subjects enrolled in Cohorts 2 and 3
Number of Subjects Planned:	200
Target Population:	Adolescent and pediatric subjects
Duration of Treatment:	12 weeks
Diagnosis and Main Eligibility Criteria:	Chronic HCV-infected, treatment-naïve and treatment-experienced (at least 20 and up to 40 subjects), male and female subjects aged 3 to < 18 as determined at Day 1. See the Sections 4.2 and 4.3 for full eligibility 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 subjects in extenuating circumstances with Sponsor approval. **Screening assessments will include:** informed consent, determine eligibility, medical history, biological parental height (unless unknown eg, subject adopted, biological parent(s) deceased, may be performed at screening up to Day 1). Complete physical examination, vital signs, height and weight, adverse events (AEs), concomitant medications, transient elastography test (if available, may be performed at Screening up to Day 1), SOF/VEL FDC swallowability assessment (may be performed at screening up to Day 1), safety laboratory tests (including hematology, chemistry, and coagulation),

hemoglobin A1c (HbA1c), thyroid stimulating hormone [TSH], alpha-1 anti-trypsin (AAT), serology (hepatitis A virus [HAV], HCV, and hepatitis B virus [HBV]), serology and/or antigen testing for HIV, HBV DNA for HBcAb positive subjects, HCV RNA, HCV genotyping, serum β-human chorionic gonadotropin (β-hCG - females of childbearing potential only), urinalysis, urine drug screen, Fibrotest®, and AST to Platelet Ratio Index (APRI).

On-Treatment assessments will include: complete or symptom-directed physical examination (as applicable), vital signs, body height and weight, 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, subject dosing diary, safety laboratory tests (including hematology, chemistry, and coagulation), TSH (at Screening, Week 12 and Early Termination), HCV RNA, HBV DNA for HBcAb positive subjects at Screening, HCV viral sequencing sampling, urine pregnancy testing (females of childbearing potential only), urinalysis, IL28B (at Day 1 only), a quality of life survey (at Day 1, Week 12 and Early Termination), Tanner Pubertal Stage assessment (at Day 1, Week 12 and Early Termination), and radiographic bone age assessment (at Day 1 and Early Termination). Acceptability will be completed by the subject (including palatability assessment) and parent/legal guardian (at Day 1, Week 12 and Early Termination).

CCI [redacted]

<u>On-treatment PK assessments include the following:</u>

- For subjects enrolled in the PK Lead-in Phase (Cohorts 1, 2 and 3)
  - — Completion of a Subject Dosing Diary from Day 1 through 7
  - — Intensive PK sampling on Day 7

<u>Cohorts 1 and 2:</u>

For Cohorts 1 and 2, plasma samples will be collected for PK analyses following dosing of study drug on Day 7 at the following time points: 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose (with predose also serving as t=24).

Cohort 3:

For Cohort 3, plasma samples for PK analyses will be collected at the following time points: 0 (predose), 0.5, 1, 2, 3, 4, 8, and 12 hours postdose (with predose also serving as t=24).

For all Cohorts, following completion of the Day 7 visit, subjects will then return for scheduled study visits outlined in the Treatment Phase and will continue dosing with SOF/VEL FDC with no interruption of study drug administration.

- For all enrolled subjects:
  - Single sparse PK sample collected anytime at Week 1 and Week 12
  - Two sparse PK samples collected at Week 4 and Week 8, CCI
    - Predose
    - Between 15 minutes to 4 hours postdose

CCI

Posttreatment assessments will include: vital signs, body weight and height, symptom-directed physical examination, AEs (only SAEs will be captured at posttreatment Week 12 and posttreatment Week 24), concomitant medications, pregnancy prevention counseling for subjects of child bearing potential (only posttreatment Week 4), safety laboratory tests (including hematology and chemistry tests), (only posttreatment Week 4), HBV DNA for HBcAb positive subjects, HCV RNA, HCV viral sequencing, and urine pregnancy test for females of child bearing potential (only posttreatment Week 4), a quality of life survey (posttreatment Weeks 12 and 24), Tanner Pubertal Stage Assessment (posttreatment Weeks 12 and 24), and radiographic bone age assessment (posttreatment Week 24).

Test Product, Dose, and Mode of Administration:	Test product: SOF/VEL FDC products for oral administration are available as: • 400 mg SOF and 100 mg VEL tablet (adult strength tablet) • 200 mg SOF and 50 mg VEL tablet (lower strength tablet) • 50 mg SOF and 12.5 mg VEL oral granules in a packet (non-tablet product) Dosages and formulations by age group: • 12 to < 18 years of age: — SOF/VEL FDC 400/100 mg tablet; administered once daily — Subjects unable to swallow the SOF/VEL FDC 400/100 mg tablet formulation as determined by the Swallowability Assessment at Screening will be re-assigned to (2 x 200/50 mg tablets). If subjects are unable to swallow the reduced strength SOF/VEL FDC 200/50 mg tablet formulation they will be re-assigned to SOF/VEL FDC oral granule formulation (8 x 50/12.5 mg packets). — Subjects unable to swallow the reduced strength SOF/VEL FDC 200/50 mg tablet formulation as determined by the Swallowability Assessment at Screening will be re-assigned to SOF/VEL FDC oral granule formulation (4 x 50/12.5 mg packets). • 6 to < 12 years of age: — SOF/VEL FDC 200/50 mg tablet; administered once daily — Subjects unable to swallow the reduced strength SOF/VEL FDC 200/50 mg tablet formulation as determined by the Swallowability Assessment at Screening will be re-assigned to SOF/VEL FDC oral granule formulation (4 x 50/12.5 mg packets). • 3 to < 6 years of age: — SOF/VEL FDC 200/50 mg oral granules (4 x 50/12.5 mg packets) administered once daily, for subjects who weigh ≥17 kg. — SOF/VEL FDC 150/37.5 mg oral granules (3 x 50/12.5 mg packets) administered once daily, for subjects who weigh < 17 kg.

Reference Therapy, Dose, and Mode of Administration:	None

Criteria for Evaluation:

Safety:	AEs, 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 subjects in the PK Lead-in, the steady-state PK of VEL, SOF, and its major metabolite (GS-331007) will be assessed at Day 7. Plasma PK parameters such as C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, AUC_{tau}, CL/F, Vz/F and $t_{1/2}$ will be estimated, as appropriate. Intensive PK and safety results from the PK Lead-in Phase of each cohort will be reviewed to confirm the appropriateness of the evaluated SOF/VEL FDC dose for the Treatment Phase in that age group. For all subjects in the Treatment Phase, sparse PK blood samples will be collected at all visits while on treatment. The PK of SOF, its primary metabolite GS-331007, and VEL will be assessed.
Statistical Methods:	For the PK Lead-in, the primary plasma PK parameters are AUC_{tau}, for SOF, GS-331007, and VEL. All PK parameters will be summarized by cohort. The effect of age and SOF/VEL FDC dose on PK will be explored. For the Treatment Phase, the primary safety endpoint is review of any AEs with a focus on AEs that lead to discontinuation of study drug. The key efficacy endpoint is SVR12 in all enrolled and treated subjects. The point estimate of the SVR12 rate and the 2-sided 95% exact confidence interval based on the Clopper-Pearson method will be provided. The secondary efficacy endpoints include SVR4 and SVR24. Clinically relevant subgroup analyses on SVR12 may be conducted as appropriate (ie, assuming that adequate numbers of patients in these subsets are available for analysis).

All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation, median, Q1, 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 percent 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.

With approximately 100 subjects enrolled into 12 to < 18 years of age group and approximately 100 subjects enrolled into 3 to < 12 years of age group, a 2-sided 95% exact confidence interval of the SVR12 rate in each age group will extend at most 20%

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
β-hCG	beta-human chorionic gonadotropin
AAT	alpha-1 anti-trypsin
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
ANOVA	analysis of variance
APRI	AST to platelet ratio index
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
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
CHF	congestive heart failure
CK	creatine kinase
C_{last}	last observed quantifiable drug concentration
CL/F	apparent oral clearance after administration of the drug
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)
CRF	case report form(s)
CRO	contract (or clinical) research organization
CSR	clinical study report
CVA	cerebral vascular accident
DAA	direct acting antiviral
dL	deciliter
DNA	deoxyribonucleic acid
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form(s)
eSAE	electronic Serious Adverse Event
ESPGHAN	European Society for Paediatric Gastroenterology
EU	European Union
FAS	full analysis set

FDA	(United States) Food and Drug Administration
FDC	Fixed-Dose Combination
FEV_1	forced expiratory volume in one second
FSH	follicle stimulating hormone
GCP	Good Clinical Practice (Guidelines)
GCSF	granulocyte colony stimulating factor
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GLSM	geometric least-squares mean
GMR	geometric mean ratio
GSI	Gilead Sciences, Inc.
GT	genotype (viral)
HAV	hepatitis A Virus
Hb	hemoglobin
HbA_{1c}	hemoglobin A_{1c}
HBsAg	hepatitis B surface antigen
HBsAb	hepatitis B surface antibody
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
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
IMB	intermenstrual Bleeding
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IU/mL	international Units Per Milliliter
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
kg	kilogram
L	liter

LAM	lactational amenorrhea method
LLN	lower limit of the normal range
LLOQ	lower limit of quantification
LLT	lower-Level Term
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
MH	Mantel-Haenszel
mL	milliliter
Min	minute
mmHg	millimeters mercury
NASPGHAN	North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition
NI	nucleotide Inhibitor
NS5A	nonstructural protein 5A
NS5B	nonstructural protein 5B
PBMC	peripheral blood mononuclear cell(s)
PEG	peginterferon alfa-2a
PG	pharmacogenomic
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic
PT	prothrombin time
PT	referred Term
PVE	Pharmacovigilance and Epidemiology
RAV	resistance-associated variants
RBC	ped blood cell count
RBV	ribavirin
RNA	ribonucleic acid
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	standard deviation
SNP	single nucleotide polymorphism
SOC	standard-of-care
SOC	system organ class
SOF	sofosbuvir
SOP	standard operating procedure
SUSAR	suspected Unexpected Serious Adverse Reaction
SVR	sustained Virologic Response
TEN	toxic epidermal necrolysis
T_{last}	the time (observed time point) of C_{last}

T_{max}	the time (observed time point) of C_{max}
TND	target not detected
TSH	thyroid stimulating hormone
t½	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
VOX	voxilaprevir
WBC	white blood cell count

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. The global prevalence of chronic hepatitis C is estimated to average 3% {Esteban 2008}. 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}. In addition, in an internal analysis using administrative claims data and data from an epidemiology database, Gilead Sciences, Inc. (Gilead) estimated that there are approximately 7000 cases of HCV infection in the US among those 16 years of age or younger. Globally, there are estimated to be 6.6 million viremic infections in those 15 years of age or younger {El-Sayed 2015}.

The natural history of chronic HCV-infection in children 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}.

The goal of HCV treatment in both pediatric and adult populations is eradication of the virus, thereby preventing hepatic inflammation, hepatic fibrosis, cirrhosis, and liver failure resulting in either death or need for liver transplantation. This goal, however, is limited by the nature of the disease and the fact that not all patients are suitable candidates for currently approved treatments. In addition, pediatric treatment is controversial as the current treatment options are limited and severe side effects and tolerability can significantly limit or preclude their use. Despite well-established guidelines for the treatment of HCV in adults, there is no universal consensus on when or if to treat chronic HCV-infection in children. In 2010, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) issued guidance for clinical trial development for chronic HCV-infection in children and in 2012, the North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) issued a practice guideline {Mack 2012, Wirth 2010}. In the guideline, the ESPGHAN and NASPGHAN suggested that the primary goal of treatment in children is to eradicate the infection to prevent late complications. Hence, the goal is not the treatment of an ongoing liver disease, but rather the prevention of a future one.

Pegylated-interferon (Peg-IFN) and weight-based ribavirin (RBV) is currently considered the standard of care for the treatment of HCV-infection in children. Current recommendations are that patients with GT-2 or GT-3 be treated with Peg-IFN+RBV for 24 weeks and those with GT-1 or GT-4 should receive 48 weeks of therapy. Successful treatment of GT-1, however, has proved very difficult to achieve in spite of additional therapy or increased duration of treatment. A number of pediatric studies have reported that despite 48 weeks of treatment, sustained virologic response (SVR24) was observed in only 36% to 53% of subjects with GT-1, while response rates were > 80% in subjects with GT-2 or GT-3 {Wirth 2012}. Safety and efficacy data in pediatric patients with GT-5 or GT-6 are limited.

Most children treated with Peg-IFN+RBV experience at least 1 adverse event due to treatment {Wirth 2012}. Although most of these events are mild to moderate in severity, many of them result in dose reductions of 1 or both of the drugs. The most common adverse events have consisted of influenza-like illness (91%), headache (62%), and injection site reactions (45%), often leading to poor compliance and/or discontinuation from treatment.

Additionally, the concern for growth and development in this age group and the role that both Peg-IFN and RBV potentially play in reducing growth rates has initiated significant debate among pediatric hepatologists as to whether these treatments should even be considered in the pediatric population {Serranti 2011}. Many pediatricians currently advocate delay of treatment past adolescence or even into adulthood when options with DAAs are possible {Serranti 2011}. Unfortunately, in the 25% of pediatric patients who do meet the criteria for treatment (elevated transaminases and viral loads), the option of Peg-IFN+RBV therapy remains inadequate in regard to both efficacy and safety due to the many risks associated with this treatment.

Recently, the first direct-acting antivirals have been approved for treatment of HCV in children. Sofosbuvir and ledipasvir/sofosbuvir are indicated for use in adolescents {Harvoni 2017, HARVONI® 2017, SOVALDI® 2017} and were highly effective and well-tolerated regimens in clinical trials {Balistreri 2017, Wirth 2017}.

1.2. Sofosbuvir/Velpatasvir Fixed-Dose Combination

Sofosbuvir/velpatasvir FDC is a coformulation of SOF 400 mg and VEL 100 mg into a single tablet for the treatment of chronic HCV infection. This fixed-dose combination combines two unique mechanisms of action into a single tablet:

- Sofosbuvir, a nucleotide analog HCV NS5B polymerase inhibitor.
- Velpatasvir, an HCV NS5A inhibitor that has potent in vitro anti-HCV activity across all genotypes.

Sofosbuvir/velpatasvir FDC is currently approved in the US, EU and other regions for the treatment of HCV.

1.2.1. General Information

Please refer to the SOF/VEL FDC IB for additional information on SOF/VEL FDC. Information in the IB includes:

- In Vitro Anti-Hepatitis C Virus Activity
- Nonclinical Pharmacokinetics and In Vitro Metabolism
- Nonclinical Pharmacology and Toxicology

1.2.2. Additional Clinical Trials of SOF/VEL FDC

In addition to studies detailed in the IB, information from the following clinical studies with SOF/VEL FDC is provided: Study GS-US-342-1553, GS-US-342-1446, and preliminary Cohort 1 and 2 PK Lead-in Phase results from current study GS-US-342-1143.

1.2.2.1. Study GS-US-342-1553

This open-label, multicenter study assessed the antiviral efficacy, safety, and tolerability of SOF/VEL FDC + RBV for 24 weeks in subjects with chronic HCV infection who have participated in prior Gilead sponsored HCV treatment studies. This study was conducted in the US, New Zealand, and Australia.

Study Design and Subject Population

A total of 69 subjects were enrolled and treated. The majority of subjects were male (76.8%), 26.1% had cirrhosis and most subjects (78.3%) had baseline HCV RNA ≥ 800,000 IU/mL. Of the 69 subjects who received SOF/VEL FDC+RBV, a total of 32 subjects (46.4%) had HCV genotype 1a, 5 subjects (7.2%) had HCV genotype 1b, 14 subjects (20.3%) had HCV genotype 2, and 18 subjects (26.1%) had HCV genotype 3.

All of the subjects had been treated with a DAA regimen in a Gilead-sponsored study: 40.6% (28 subjects) had been treated with SOF/VEL FDC+VOX, 39.1% (28 subjects) had been treated with SOF/VEL FDC, and 20.3% (14 subjects) had been treated with SOF/VEL FDC+RBV. Overall, 66 subjects (95.7%) completed study treatment. Three subjects prematurely discontinued study treatment: 1 subject due to an AE of irritability, 1 subject due to lack of efficacy, and 1 subject due to a protocol violation.

Conclusions

The conclusions from this study were as follows:

- Treatment with SOF/VEL FDC+RBV for 24 weeks in subjects who had failed prior treatment with SOF+VEL ± VOX ± RBV resulted in a high SVR12 rate (91.3%)
  - Among subjects with genotype 1 HCV infection, the SVR rate was 97.3%
  - Among subjects with genotype 2 HCV infection, the SVR rate was 92.9%
  - Among subjects with genotype 3 HCV infection, the SVR12 rate was 77.8%

- The presence of baseline resistance-associated variants (RAVs) had an impact on the SVR12 rate in subjects with genotype 3 HCV infection, with an SVR12 rate of 76.9% for subjects with RAVs compared with an SVR12 rate of 100.0% for subjects without RAVs. Virologic relapse in subjects with genotype 3 was associated with enrichment or emergence of NS5A RAVs.

- Treatment with SOF/VEL FDC+RBV for 24 weeks was safe and well tolerated. There was a low incidence of Grade 3 or 4 AEs, SAEs, and discontinuations due to AEs. Most Grade 3 and 4 laboratory abnormalities were consistent with the known effects of RBV.

1.2.2.2. Study GS-US-342-1446

This open-label, multicenter study assessed the antiviral efficacy, safety, and tolerability of SOF/VEL for 12 weeks in subjects who received placebo in study GS-US-342-1138 (ASTRAL1). This study was conducted in the US, Canada, Europe, and Asia.

Study Design and Population

A total of 111 subjects were enrolled and treated. The majority of subjects were male (58.6%), 17.1% had cirrhosis and most subjects (73.0%) had baseline HCV RNA ≥ 800,000 IU/mL. Of the 111 subjects who received SOF/VEL FDC, a total of 63 subjects (56.8%) had HCV genotype 1; 20 subjects (18.0%) had HCV genotype 2; 19 subjects (17.1%) had HCV genotype 4; 9 subjects (8.1%) had HCV genotype 6. The majority of subjects (99.1%) completed study treatment; 1 subject (0.9%) prematurely discontinued study treatment due to an AE.

Conclusions

The conclusions from this study were as follows:

- Treatment with SOF/VEL FDC for 12 weeks in treatment-naive and treatment-experienced subjects resulted in a high SVR12 rate (97.3%). High SVR12 rates were achieved across all HCV genotypes and subgroups, and the overall SVR12 rate was similar to that observed in subjects who received SOF/VEL FDC for 12 weeks in the parent study (Study GS-US-342-1138 [99.0%; 618 of 624 subjects]).

- All subjects with pretreatment NS5A or NS5B NI RAVs achieved SVR12. Virologic relapse in a single subject with genotype 1a infection was associated with emergence of the NS5A RAV Y93H. No NS5B NI RAVs emerged at relapse.

- SOF/VEL FDC was generally well tolerated with low rates of Grade 3 and 4 AEs, SAEs, discontinuations due to AEs and Grade 3 and 4 laboratory abnormalities.

1.2.2.3. Study GS-US-342-1143

Preliminary pharmacokinetic and safety data from the ongoing GS-US-342-1143 study are available for 74 adolescent subjects (N=17 from PK Lead-in Cohort 1 and N=57 from the Treatment Phase), and for 20 subjects 6 to < 12 years of age (N=20 from PK Lead-in Cohort 2).

Adolescent subjects 12 to < 18 years of age:

Preliminary pharmacokinetic data are available for 16 of the seventeen adolescent subjects 12 to <18 years of age enrolled in the intensive PK Lead-in Cohort 1 (Table 1-1). Mean exposures (AUC_{tau}) of VEL and GS-331007 were comparable to observed exposures in the adult subjects in the Phase 2/3 SOF/VEL clinical program. Mean SOF exposures were higher in adolescents as compared with adults; however, the SOF exposures in adolescents were within the range of SOF exposures shown to be safe in the adult Phase 2/3 SOF/VEL clinical program (Table 1-1).

Based on preliminary safety data in 74 adolescent subjects, treatment with SOF/VEL FDC 400/100 mg for 12 weeks was generally safe and well tolerated. Fifty one subjects (69%) had an AE, and most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. One subject, with a medical history of depression, anxiety and post-traumatic stress disorder, had a Grade 3 SAE of exacerbated post-traumatic stress disorder, a Grade 3 SAE of suicidal ideation, and a Grade 4 SAE of suicidal attempt; all SAEs were assessed as not related to study drug by the investigator. No subject discontinued study drug because of an AE. The most common AEs (≥ 10%) were headache (18, 24%), nausea (13, 18%) and fatigue (9, 12%). Most of the lab abnormalities were Grade 1 or Grade 2. Six subjects had Grade 3 lab abnormalities (hemoglobin [1 subject], hyperglycemia [1 subject], low neutrophils levels [2 subjects], and urinalysis positive for red blood cells [2 subjects, both females of child bearing potential with menses at the time of urinalysis]), and no subject had Grade 4 laboratory abnormalities.

Table 1-1. Steady-state PK and Statistical Comparisons of SOF, GS-331007 and VEL PK in Adolescent Subjects (12 to < 18 years old; PK Lead-in) and Adult Subjects (Phase 2/3 Population PK Analysis)

PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI)
	Adolescents N=16*	Adult Phase 2/3 N=1428**	
SOF			
AUC_{tau} (ng•h/mL)	3070 (40.1)	1260 (37.2)	237 (205, 275)
C_{max} (ng/mL)	1600 (48.2)	566 (31.4)	266 (232, 303)
GS-331007			
AUC_{tau} (ng•h/mL)	13900 (25.8)	14000 (28.0)	100 (89.5, 112)
C_{max} (ng/mL)	1180 (37.1)	868 (27.6)	133 (119, 150)
VEL			
AUC_{tau} (ng•h/mL)	4480 (47.0)	2970 (50.2)	150 (122, 184)
C_{max} (ng/mL)	630 (48.3)	259 (53.9)	245 (195, 307)

Note: preliminary data presented to 3 significant figures.
* N=17 enrolled; N=16 evaluable for PK analysis due to 1 subject vomiting within ~ 3 hours of dosing
** N= 982 (SOF) or 1425 (VEL) from Ph 2/3

Subjects 6 to < 12 years of age:

Preliminary pharmacokinetic data are available for 20 subjects 6 to <12 years of age, who enrolled in the intensive PK Lead-in Cohort 2 (Table 1-2). Seventeen subjects received SOF/VEL 200/50 mg, while 3 subjects erroneously received an adult dose of 400/100 mg (one subject from Day 1 through Day 14 and two subjects from Day 1 through day 8) followed by the correct dose 200/50 mg for the remainder of the study. Mean exposures (AUC_{tau}) of VEL and SOF were comparable to observed exposures in the adult subjects in the Phase 2/3 SOF/VEL clinical program. Mean GS-331007 exposures were lower as compared with adults; however, GS-331007 exposures in 6 to <12 year olds were within the range of GS-331007 exposures associated with efficacy in the adult Phase 2/3 SOF/VEL clinical program (Table 1-2).

Based on preliminary safety data available in 20 subjects enrolled in Cohort 2, treatment with SOF/VEL FDC for 12 weeks was generally safe and well tolerated. Twelve subjects (60%) had an AE, and most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. One subject, a 6 year old female, had a Grade 3 SAE of auditory hallucinations from Day 37 to Day 49. The event was considered by the investigator as drug related and resulted in premature study drug discontinuation. The most common AEs (≥ 2 subjects) were abdominal pain (5, 25%), cough (3, 15%), vomiting (2, 10%), nasopharingitis (2, 10%), and pruritus (2, 10%). All lab abnormalities were Grade 1.

Table 1-2. Steady-state PK and Statistical Comparisons of SOF, GS-331007 and VEL PK in Pediatric Subjects (6 to <12 years old; PK Lead-in) and Adult Subjects (Phase 2/3 Population PK Analysis)

PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI)
	Pediatrics N=17*	Adult Phase 2/3 N=1428**	
SOF			
AUC_{tau} (ng•h/mL)	1760 (39.1)	1260 (37.2)	137 (119, 158)
C_{max} (ng/mL)	1330 (52.1)	566 (31.4)	219 (192, 249)
GS-331007			
AUC_{tau} (ng•h/mL)	9910 (31.0)	14000 (28.0)	71.0 (63.7, 79.1)
C_{max} (ng/mL)	992 (28.0)	868 (27.6)	115 (103, 128)
VEL			
AUC_{tau} (ng•h/mL)	3700 (44.7)	2970 (50.2)	121 (99.4, 148)
C_{max} (ng/mL)	560 (48.5)	259 (53.9)	215 (172, 268)

Note: preliminary data presented to 3 significant figures.
* N=20 enrolled; N=17 evaluable for PK analysis as 3 subjects received SOF/VEL FDC 400/100 mg during the PK Lead-in
** N= 982 (SOF) or 1425 (VEL) from Ph 2/3

In summary, based on preliminary data available, SOF/VEL FDC 400/100 mg administered to adolescents, and SOF/VEL FDC 200/50 mg administered to subjects 6 to <12 years of age, was safe and well tolerated, and resulted in SOF, GS-331007, and VEL exposures within the range of exposures associated with safety and efficacy in the adult Phase 2/3 SOF/VEL program. As such, the adult dose of SOF/VEL FDC 400/100 mg is considered appropriate for use in the adolescent population (12 to <18 years of age), and the reduced dose of SOF/VEL FDC 200/50 mg is considered appropriate for children 6 to <12 years of age.

1.2.3. Rationale for This Study

This clinical study is designed to evaluate the efficacy and safety of treatment with SOF/VEL FDC for adolescents and children with chronic HCV infection. The population of the study will be subjects with chronic HCV infection, with 20 to 40 having failed prior treatment.

Currently Peg-IFN and weight-based RBV is considered the SOC for the treatment of HCV-infection in children. Therefore, there is a need for new treatments for HCV in the pediatric population that combine potent and sustained efficacy with improved tolerability and safety. The primary aim for new treatments of pediatric patients with HCV is to eliminate the need to use Peg-IFN and RBV. In this way, pediatric patients would be able to avoid the necessity of weekly injections, which can be traumatic and burdensome, and significantly reduce the serious adverse events seen with Peg-IFN administration and the adverse events seen with its administration within HCV infected subjects.

A single regimen of SOF/VEL FDC for 12 weeks resulted in SVR rates >95% in subjects with all HCV genotypes and was well tolerated in the phase 3 clinical program. The availability of a single, pangenotypic regimen is anticipated to be especially beneficial in areas where genotype diversity is high and genotyping may not be readily available or routinely done. Access to treatment for patients with HCV infection would be expanded as a result.

1.3. Rationale for Dose Selection of SOF/VEL FDC

Sofosbuvir is an approved pan-genotypic nucleotide analog HCV NS5B polymerase inhibitor, which, when combined with VEL, a second generation NS5A inhibitor, in a fixed-dose combination was well-tolerated and resulted in high SVR rates in a broad range of HCV genotypes after 12 weeks of treatment in Phase 3 studies.

Sofosbuvir 400 mg, once daily, when dosed in combination with RBV with or without Peg-IFN has demonstrated broad genotypic efficacy and favorable safety profile in over 1700 HCV-infected subjects across multiple patient populations in Phase 2 and 3 trials. This dose is the approved marketed dose of sofosbuvir for the treatment of HCV-infection and, as such, was selected for co-formulation with VEL into a fixed-dose combination tablet.

Velpatasvir 100 mg was administered in combination with SOF 400 mg for 12 weeks to 237 HCV-infected subjects in Phase 2 studies. VEL 100 mg was selected for co-formulation with SOF based on the Phase 2 safety, PK and antiviral activity (studies GS-US-342-0102, GS-US-342-0109, and GS-US-337-0122 [Cohort 4]).

Sofosbuvir 400 mg and VEL 100 mg are the doses evaluated in the Phase 3 ASTRAL program and in the commercially available FDC tablet.

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.

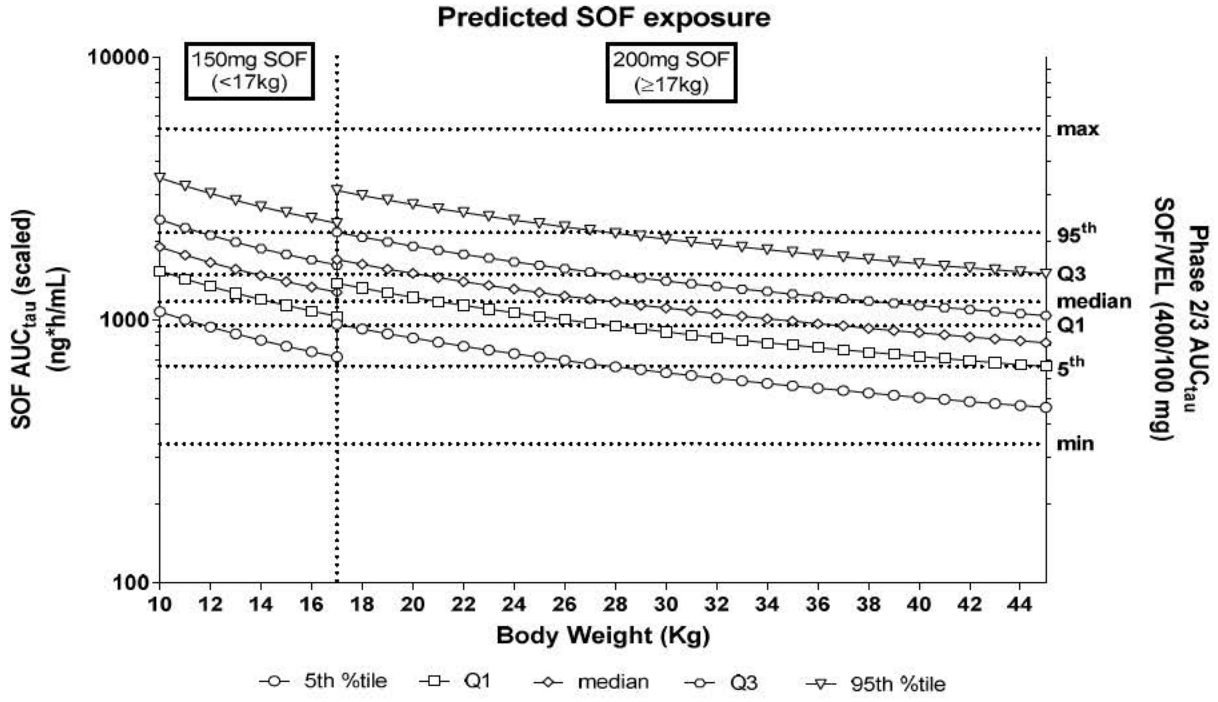
Velpatasvir is also a substrate for P-gp and BCRP. VEL has low systemic clearance in nonclinical species and low metabolic turnover by CYP2B6, CYP2C8 and CYP3A4. It is eliminated through biliary excretion as unchanged parent drug and metabolites (76.6% of the administered dose is recovered as VEL in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

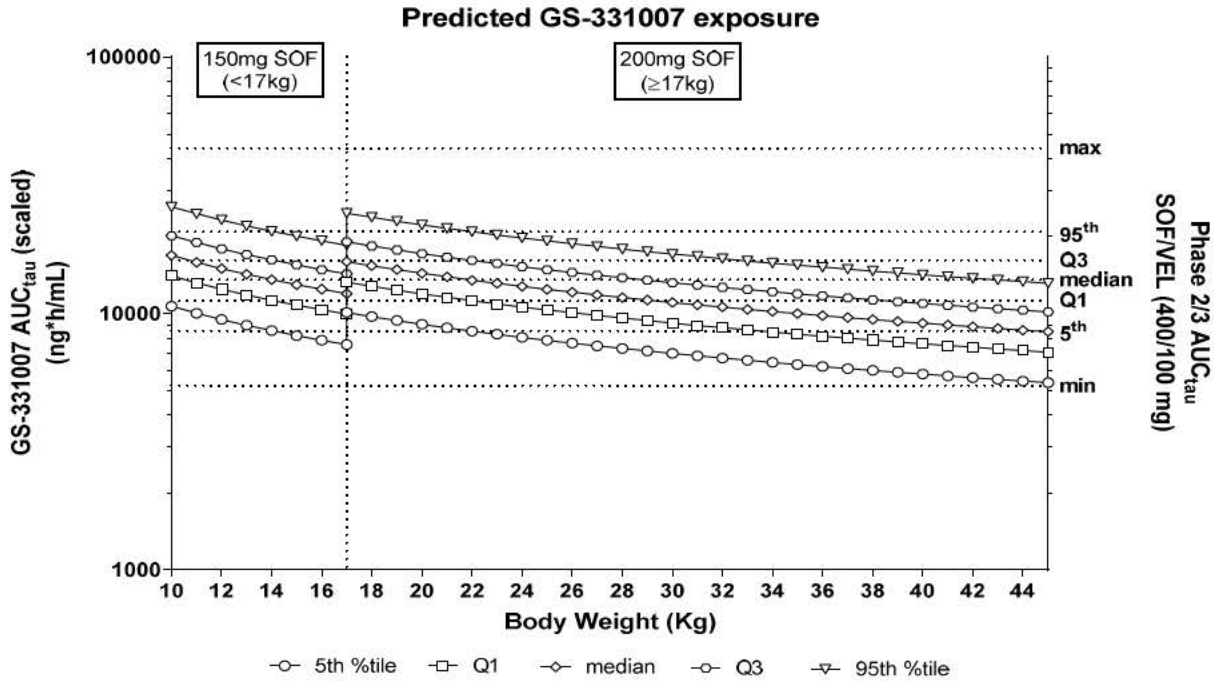
Selection of doses of SOF/VEL FDC for adolescents and younger age groups will target systemic exposures similar to those observed in adults at the proposed marketed dose, and will take into account body weight/body surface area, the potential ontogenic changes in transporters and metabolic enzymes that govern the disposition of SOF and VEL, and the results obtained in older age groups. 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 and CYP3A4 to adults from a young age (~3-6 years of age) {Johnson 2006}; however, little is known about the developmental regulation of Pgp, CES, and CatA.

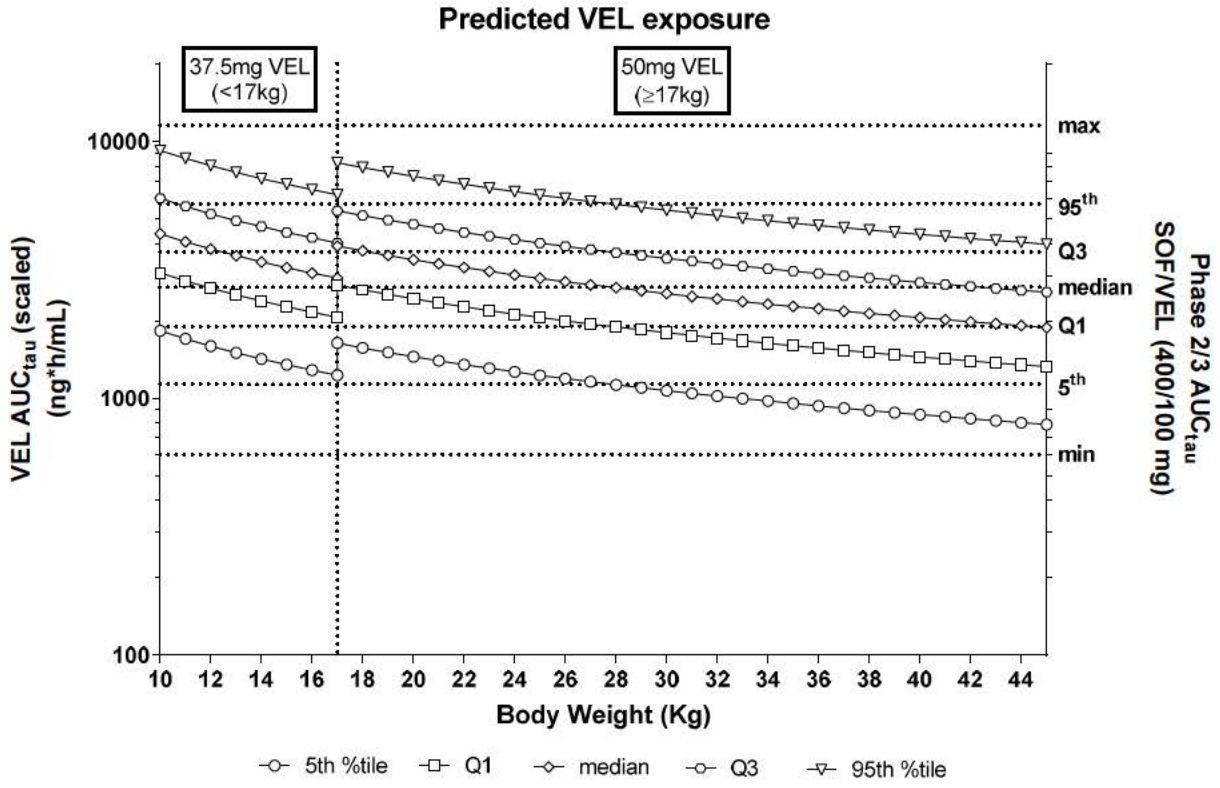
In this current study, the adult clinical dose of SOF/VEL FDC 400/100 mg is being evaluated in adolescents (12 to <18 years old), while a lower dose SOF/VEL FDC 200/50 mg is being evaluated in children (6 to <12 years old). As described in Section 1.2.2.3, the appropriateness of these doses is supported by data from the Cohort 1 and Cohort 2 PK Lead-in subjects, respectively, which demonstrated SOF, GS-331007 and VEL exposure to be within the range of adult exposures associated with safety and efficacy in the Phase 2/3 SOF/VEL adult population (Table 1-1 and Table 1-2).

In Cohort 3 (3 to <6 years old), a dose of SOF/VEL FDC 200/50 mg is proposed for evaluation in children weighing ≥17 kg, whereas a dose of SOF/VEL FDC 150/37.5 mg is proposed for evaluation in children weighing < 17 kg. These proposed doses are supported by scaling of adult exposures based on correlations between body weight and clearance capacity (liver volume/size for VEL and SOF, and renal capacity for GS-331007) for the expected body weight range in children (3 to < 6 years of age) as demonstrated in Figure 1-1. Based on this scaling approach, these doses of SOF/VEL FDC are expected to achieve mean systemic exposures of SOF, GS-331007, and VEL within the range of those observed in the Phase 2/3 adult population. Safety and PK data in children who enroll in the PK Lead-in Cohort 3 will be evaluated to confirm the appropriateness of the dose for this age group.

Figure 1-1. **Predicted SOF, GS-331007 and VEL AUC_{tau} following administration of SOF/VEL FDC 200/50 mg or 150/37.5 mg to Children 3 to <6 years of age who are ≥ 17 kg or < 17 kg, respectively**







1.4. 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.

Given that the current SOC for the treatment of children infected with HCV is Peg-IFN and RBV and the regimens are long in duration, relatively toxic, and not well tolerated, there continues to be a need for new treatments for HCV that combine potent and sustained efficacy with improved tolerability and safety.

The combination of SOF plus VEL is anticipated to offer greater antiviral efficacy which could result in a shorter treatment duration and/or lead to a regimen without RBV or interferon. These in turn could result in reduction in adverse events. SOF/VEL FDC could also potentially be of benefit in patients who have failed prior treatment with SOF+/-RBV+/- Peg-IFN.

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

1.5. 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 the PK Lead-in phase is:

- To evaluate the steady state pharmacokinetics (PK) and confirm the dose of sofosbuvir/velpatasvir (SOF/VEL FDC) in pediatric subjects with chronic hepatitis C virus (HCV) infection

The primary objective of the Treatment Phase of this study is:

- To evaluate the safety and tolerability of SOF/VEL FDC for 12 weeks in pediatric subjects with chronic HCV

The secondary objective of the PK Lead-in Phase is:

- To evaluate the safety, tolerability, and antiviral activity of 7 days of dosing of SOF/VEL FDC in pediatric subjects with chronic HCV

The secondary objectives of the Treatment Phase of this study are:

- To determine the efficacy of SOF/VEL FDC for 12 weeks in pediatric subjects with chronic HCV infection, as assessed by the proportion of subjects with sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12)
- To determine the proportion of subjects with SVR 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure, including breakthrough/nonresponse 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 and VEL during treatment and after cessation of treatment
- To evaluate the effect of treatment with SOF/VEL FDC on quality of life as measured by PedsQL™ Pediatric Quality of Life survey
- To evaluate the effect of SOF/VEL FDC on growth and development of pediatric subjects during and after treatment
- To evaluate the acceptability, including palatability, of formulations used in the study

The exploratory objective of this study is:

3. STUDY DESIGN

3.1. Endpoints

The appropriateness of the SOF/VEL FDC dose will be assessed by evaluating the steady-state PK of the VEL, SOF, and GS-331007 at Day 7 (C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, AUC_{tau} and $t_{1/2}$). The primary endpoint of the PK Lead-in Phase is to determine steady-state PK, is AUC_{tau} of VEL, SOF, and its major metabolite (GS-331007).

The primary endpoint of the Treatment Phase is assessment of any AEs with a focus on AEs that lead to discontinuation of study drug.

The secondary endpoints of the PK Lead-in Phase are:

- Antiviral activity measurements, including assessment of HCV RNA from baseline through Day 7.
- Any AE leading to permanent discontinuation of study drug.

The secondary endpoints of the Treatment Phase are:

- The proportion of subjects with sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12). 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 breakthrough/nonresponse and relapse
- The proportion of subjects with HCV RNA < LLOQ on treatment
- Emergence of viral resistance to SOF and /or VEL during treatment and treatment is discontinued
- HCV RNA change from Day 1
- Quality of life endpoints and neuropsychiatric assessments as measured by PedsQL™ Pediatric Quality of Life survey
- Growth and development measurements including height and weight percentiles, Tanner Stage, parental height, and bone age
- Acceptability assessed by swallowability and palatability

3.2. Study Design

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

3.3. Study Treatments

3.3.1. PK Lead-in Phase

The PK Lead-in Phase will evaluate and/or confirm the age appropriate SOF/VEL FDC dose by analyzing PK, safety, and antiviral activity of SOF/VEL FDC through 7 days of dosing for each cohort. Three cohorts of at least 17 subjects each will be sequentially enrolled:

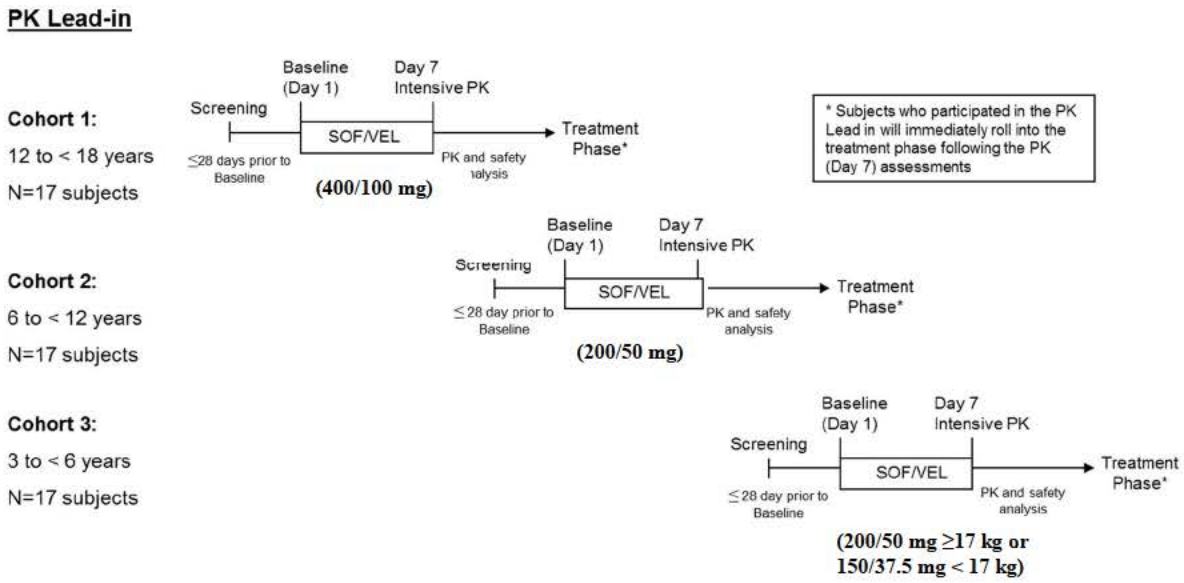
- Cohort 1: 12 to < 18 years old
- Cohort 2: 6 to < 12 years old
- Cohort 3: 3 to < 6 years old
  - At least 6 subjects weighing ≥ 17 kg
  - At least 6 subjects weighing < 17 kg

The study will start with Cohort 1. Subjects will receive a SOF/VEL FDC 400/100 mg adult tablet or 2 x 200/50 mg tablets (if determined necessary based on SOF/VEL swallowability assessment) once a day for 7 days with intensive PK conducted on Day 7. If unable to swallow the tablet formulations, the subjects will receive SOF/VEL FDC 400/100 mg oral granules (8 x 50/12.5 mg packets).

Cohort 2: Subjects will receive SOF/VEL FDC 200/50 mg tablets once daily. If unable to swallow the tablet formulations, the subjects will receive SOF/VEL FDC 200/50 mg oral granules (4 x 50/12.5 mg packets).

Cohort 3: Subjects will receive SOF/VEL FDC 200/50 mg oral granules (4 × 50/12.5 mg packets) once daily for subjects weighing ≥17 kg. SOF/VEL FDC 150/37.5 mg oral granules (3 × 50/12.5 mg packets) will be administered once daily for subjects weighing <17 kg.

Figure 3-1. PK Lead-in Phase Study Schema



3.3.2. Treatment Phase

The Treatment Phase will be initiated sequentially by age group (12 to < 18), (6 to <12) and (3 to <6) as defined in Cohorts 1, 2, and 3 of the PK Lead-in Phase. Subjects who participated in the PK Lead-in will immediately rollover into the Treatment Phase with no interruption of study drug administration until the appropriateness of the dose has been confirmed by PK and safety results from the PK Lead-in. The first visit in the Treatment Phase for the subjects who participated within the PK Lead-in Phase will be the Week 4 visit. Additional subjects will be enrolled in the Treatment Phase of each age group upon confirmation of the appropriateness of the dose from the PK Lead-in Phase. If a subject is unable to swallow the tablet formulations, they will be assigned to SOF/VEL FDC oral granules formulation.

CCI [redacted]

The study will enroll both treatment naïve and treatment experienced pediatric subjects with at least 20 and up to 40 subjects allowed to be treatment experienced. Approximately 200 total subjects, including subjects from the PK Lead-in Phase, will be enrolled in the Treatment Phase as follows:

- Group 1: Approximately 100 adolescent subjects (12 to < 18 years of age)
- Group 2: Approximately 100 pediatric subjects (3 to < 12 years of age)

All subjects who do not attain SVR or have viral relapse will be encouraged to discuss treatment with SOC therapy with their healthcare provider.

3.4. Duration of Treatment

3.4.1. PK Lead-in Phase

Subjects (at least 17 subjects per cohort) enrolled in the PK Lead-in Phase will receive treatment for 7 days and then participate in an intensive PK evaluation on Day 7.

Following completion of the Day 7 intensive PK visit, subjects will continue dosing with SOF/VEL FDC with no interruption of study drug administration and will continue in the Treatment Phase of the study to receive 12 weeks of treatment.

3.4.2. Treatment Phase

Subjects enrolled in the Treatment Phase will receive treatment for 12 weeks and will then return for follow-up visits at 4, 12, and 24 weeks after discontinuation of therapy.

The total time to complete all study visits is approximately 40 weeks including:

- 28 day (4 week) screening period
- 12 week treatment period
- 24 week posttreatment period

3.5. 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 from nadir
- HCV RNA ≥LLOQ through 8 weeks of treatment

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.

3.6. 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 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.
- Subject noncompliance

- Pregnancy of female subject or female partner of male subject.
- Efficacy failure as defined in Section 3.5.
- Significant protocol violation that impacts subject safety
- Subject 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Subjects who meet any of the following criteria must stop treatment with SOF/VEL 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 >15x ULN, 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
- Any Grade 4 adverse event assessed as related to administration of SOF/VEL FDC

3.7. 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.

3.8. Reconsent

When a subject reaches the age of consent in their country/region, they will be invited to consent as an adult to allow them to continue participating in the clinical trial.

3.9. CCI [redacted]

[redacted]

3.10. Pediatric Registry Study

All subjects (those who attain SVR24 or those who do not attain SVR24) who do not initiate other experimental or approved anti-HCV therapy will be eligible to participate in the Pediatric Registry Study. The objectives of the registry study are to evaluate growth, quality of life, and long-term viral suppression (if applicable). The pediatric registry study is described in a separate protocol (GS-US-334-1113). This follow-up study will continue for 5 years.

3.11. Biomarker Testing

3.11.1. CCI

[redacted]

3.11.2. Samples for Optional Future Research

CCI [redacted]

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 200 subjects will be enrolled in this study.

In order to manage the total study enrollment, Gilead Sciences, Inc. at its sole discretion, may suspend screening and/or discontinue the enrollment at any site at any time (upon written notice to the site). Discontinuation of the enrollment phase may result in the immediate ineligibility of all subjects screened but not yet enrolled, regardless of the progress or outcome of the screening assessments performed.

4.2. Inclusion Criteria

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

1) Parent or legal guardian able to provide written informed consent prior to any screening evaluations and willing to comply with study requirements. Subjects will provide assent if possible, in accordance with IRB/IEC/local requirements and the investigator's discretion.
2) 3 years 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) Treatment-naïve is defined as having never been exposed to an approved or experimental HCV-specific direct acting antiviral agents or prior treatment of HCV with interferon or ribavirin.
    b) Treatment-experienced is defined as prior treatment failure or intolerance to a regimen containing interferon with or without RBV and with or without a protease inhibitor that was completed at least 8 weeks prior to Day 1.
    c) Interferon intolerant: Subject who discontinued therapy (≤ 12 weeks total) due to ≥ 1 adverse event
6) A negative serum pregnancy test is required at screening and a negative urine test is required at Day 1 for female subjects of child bearing potential.
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 IMP 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) Prior use of an HCV NS5A inhibitor
2) Current or prior history of clinical hepatic decompensation (eg, ascites, jaundice, encephalopathy, variceal hemorrhage)
3) Any of the following laboratory parameters at screening:
   a) INR > 1.2 × ULN
   b) Platelets < 50,000/mm^3
   c) albumin < 3.5 g/dL
   d) ALT > 10 x the upper limit of normal (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
4) Chronic liver disease of a non-HCV etiology (eg, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency)
5) Evidence of hepatocellular carcinoma (HCC) or other malignancy (with the exception of certain resolved skin cancers)
6) Co-infection with HIV, acute HAV, or HBV (Hepatitis B Surface Ag positive at screening)
7) Current or prior history of any of the following:
   a) Significant cardiovascular, pulmonary, or neurological disease
   b) Evidence of a gastrointestinal malabsorption syndrome that may interfere with absorption of orally administered medications
   c) History of solid organ or bone marrow transplantation
   d) 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.

8) 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

9) Sexually-active males or females of childbearing potential who are not willing to use an effective method of contraception during the study

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

11) Investigational agents taken within the past 28 days (except with the express approval of the Sponsor)

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

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Description and Handling of SOF/VEL FDC

5.1.1. Formulation

The SOF/VEL FDC 400/100 mg tablets are pink, diamond-shaped, film-coated tablets, debossed with "GSI" on one side and "7916" on the other side. In addition to the active ingredients, the SOF/VEL FDC tablets contain copovidone, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

Placebo tablets to assess swallowability of SOF/VEL FDC 400/100 mg tablet are of similar size and shape. The placebo tablets are pink, diamond-shaped, film-coated tablets debossed with "GSI" on one side and "7916" on the other side. The tablets contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol, and iron oxide red.

The SOF/VEL FDC 200/50 mg tablets are pink, oval-shaped, film-coated tablets, debossed with "GSI" on one side and "S/V" on the other side. In addition to the active ingredients, the SOF/VEL FDC tablets contain copovidone, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

Placebo tablets to assess swallowability of SOF/VEL FDC 200/50 mg tablet are of similar size and shape. The placebo tablets are capsule-shaped, plain-faced, film-coated orange tablets and contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, iron oxide red, and ferrosoferric oxide.

The SOF/VEL FDC 50/12.5 mg oral granules are white, round, and film-coated. In addition to the active ingredients, the SOF/VEL FDC oral granules contain the following inactive ingredients: copovidone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, amino methacrylate copolymer, talc, stearic acid, and L-tartaric acid.

5.1.2. Packaging and Labeling

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

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

SOF/VEL FDC 200/50 mg tablets are packaged in white, high density polyethylene (HDPE) bottles, with or without polyester packing material. Each bottle contains 28 tablets and is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

Placebo tablets to assess swallowability of SOF/VEL FDC 200/50 mg tablet are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and polyester packing material, and desiccant. Each bottle is enclosed with a white, continuous thread, child resistant screw cap with an induction-sealed, aluminum faced liner.

SOF/VEL FDC oral granules are packaged in aluminum foil packets. Each packet contains twenty five (25) oral granules, which is equivalent to 50 mg of SOF and 12.5 mg of VEL. Twenty eight (28) packets are packed in a carton.

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

5.1.3. Storage and Handling

SOF/VEL FDC 400/100 mg and 200/50 mg tablets as well as oral granules packets 50/12.5 mg 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 placebo tablets to assess swallowability of SOF/VEL FDC tablets 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 FDC tablets.

Sufficient quantities of SOF/VEL FDC to complete the entire study will be shipped to the investigator or qualified designee from the Gilead Supply Management Team (or its designee).

5.2. Dosage and Administration of SOF/VEL FDC

Subjects 12 to < 18 years old enrolled in the PK Lead-in Cohort 1 or in the Treatment Phase

SOF/VEL FDC 400/100 mg tablets will be administered once daily with or without food. Subjects determined unable to swallow the placebo to match the 400/100 mg SOF/VEL FDC tablet will be re-assigned to 2 x 200/50 mg SOF/VEL FDC tablets daily. Subjects unable to swallow the reduced strength SOF/VEL FDC 200/50 mg tablets will be reassigned to SOF/VEL FDC oral granule formulation (8 x 50/12.5 mg packets).

Subjects 6 to < 12 years old enrolled in the PK Lead-in Cohort 2 or in the Treatment Phase

SOF/VEL FDC 200/50 mg tablets will be administered once daily with or without food. Subjects determined unable to swallow the placebo tablet 200/50 mg SOF/VEL FDC will be reassigned to SOF/VEL FDC oral granule formulation (4 x 50/12.5 mg packets).

Subjects 3 to < 6 years old enrolled in the PK Lead-in Cohort 3 or in the Treatment Phase

SOF/VEL FDC 50/12.5 mg oral granules in a packet will be administered once daily with or without food. Subjects who weigh ≥ 17kgs will be assigned to 200/50 mg SOF/VEL FDC oral granules (4 x 50/12.5 mg packets) and subjects who weigh < 17 kgs will be assigned to 150/37.5 mg SOF/VEL FDC oral granules (3 x 50/12.5 mg packets). The instructions dosing of oral granules are defined in Section 5.2.1.

Subjects should be instructed that if vomiting occurs within 3 hours of dosing an additional tablet or granules packets should be taken according to the dosing instructions above. If vomiting occurs more than 3 hours after dosing, no replacement dose is required that day.

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

If it is after 18 hours then it is considered 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.

5.2.1. SOF/VEL FDC Oral Granules Subject Dosing Instructions

The SOF/VEL 50/12.5 mg oral granules are packaged in aluminum foil packets for oral administration. The administration of the full dose from all of the packets must be completed within 30 minutes. After each dose, ensure the packets are empty and the subject should be instructed that all empty packets should to be returned at the next study visit.

Due to the bitter taste of the active ingredient(s), the oral granules have been taste-masked. Oral granules may be taken directly by mouth and swallowed or mixed into food as directed below.

If oral granules are swallowed without food:

1) Carefully cut with scissors or tear open 1 packet. Avoid crushing or spilling the contents. If any granules are crushed, do not administer and open new packet.
2) Parent/legal guardian should be instructed to empty the content of packet into the child's mouth and chase with water or milk. The oral granules should not be chewed. The oral granules should not be poured directly into a liquid as they may sink and stick to the bottom of the container.
3) Repeat these steps immediately for any additional packets assigned.
4) If the child cannot take the whole packet at one time the granules may be divided into two or three portions until each packet is completely empty.
5) The full dose should be administered within **30 minutes**.

If oral granules are administered with food:

The granules should not be chewed and the selected food should be a soft, non-acidic food that is at or below room temperature. Examples of foods that can be used include: pudding (except fruit-flavored varieties), chocolate syrup, whipped cream, and ice cream (except fruit-flavored varieties). Foods to avoid include: yogurt and fruit-based foods such as applesauce, thick/sticky foods such as peanut butter and foods that have chunks that require chewing.

Once a food is selected, administer the granules as follows:

1) Carefully cut with scissors or tear open 1 packet. Avoid crushing or spilling the contents. If any granules are crushed, do not administer and open new packet.
2) Carefully sprinkle the packet contents onto a spoon and take care to avoid spilling the granules. Without spilling the granules, carefully add the selected food to the spoon and mix/cover the granules as needed. If necessary, the granules from the packet may be divided into two or three portions and administered to the child.
3) Parent/legal guardian should be instructed to immediately have the child swallow the granules and food without chewing. If not immediately, the granules need to be swallowed within **15 minutes** after placing on the food. If the granules have not been taken within **15 minutes** after placing on the food, discard and prepare a new dose.
4) After dosing, ensure that no oral granules remain on the spoon or in the child's mouth.
5) Repeat these steps immediately for any additional packets assigned.
6) The full dose should be administered within **30 minutes**.

5.3. Prior and Concomitant Medications

Concomitant medications taken within 30 days prior to screening, up to and including 30 days after the last dose of study drug need to be recorded in the source documents and eCRFs (including all blood products).

Investigational agents or devices for any indication are prohibited from **28 days prior to the Day 1** visit through the end of treatment.

Concomitant use of certain medications or herbal/natural supplements (such moderate to potent inducers of drug transporters or metabolizing enzymes, eg, P-gp, CYP2B6, CYP2C8, or CYP3A) with the study drug may result in pharmacokinetic interactions resulting in increases or decreases in exposure of the study drug or these medications.

The use of amiodarone is prohibited from **60 days prior to Day 1** through the end of treatment. Additionally, investigators should refer to the product/package inserts of other medications for age-related recommendations or contraindications related to their use.

Table 5-1 below contains examples of medications that are prohibited from **21 days prior to Day 1** through the end of treatment and those medications which may be used with caution.

Table 5-1. Disallowed 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]	Phenytoin, Carbamazepine, Phenobarbital,	
Antimycobacterials[b]	Rifampicin, Rifabutin, Rifapentine	
Cardiac Medications	Amiodarone[d]	Digoxin[e], vitamin K antagonists[f]
Herbal/Natural Supplements[b]	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[f]		Rosuvastatin[g] , Atorvastatin
Other	Bosentan[b], Modafinil[b], Sulfasalazine[c], Methotrexate[c]	

a Co-administration of omeprazole or other proton pump inhibitors is not recommended. If it is considered medically necessary to co-administer, SOF/VEL FDC should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton pump inhibitors has not been studied. H2-receptor antagonists must not exceed a dose of 40 mg famotidine or equivalent and can be taken simultaneously with SOF/VEL FDC and/or staggered by 12 hours. Antacids that directly neutralize stomach acid (ie Tums, Maalox) may not be taken within 4 hours (before or after) of SOF/VEL FDC administration.
b May result in a decrease in the concentration of study drugs.
c May result in an increase in the concentration of study drugs and/or concomitant medications
d May result in symptomatic bradycardia. Mechanism is not currently known. The use of amiodarone is prohibited from 60 days prior to Day 1 through the end of treatment.
e Monitor for signs and symptoms of digoxin toxicity.
f If vitamin K antagonists are used, close monitoring of International Normalized Ratio (INR) is recommended as liver function may improve during treatment with study drug.
g Use with SOF/VEL FDC may result in an increase in the concentration of HMG-CoA Reductase Inhibitors, rosuvastatin and atorvastatin. Titrate rosuvastatin dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg/day. Use atorvastatin with caution and at the lowest necessary dose. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.

Medications for disease conditions **excluded** from the protocol (eg, HIV infection) are not listed under this Concomitant Medication section and are disallowed in the study. Should subjects have a need to initiate treatment with any excluded concomitant medication, the Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded 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 excluded medication.

Subjects may not take any approved HCV medications during their participation in the study period.

5.4. Accountability for SOF/VEL FDC

The investigator is responsible for ensuring adequate accountability of all used and unused 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 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

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 group.

6.2. Pretreatment Assessments

6.2.1. 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. The following procedures/assessments are to be performed and documented at screening:

- Obtain written informed consent
- Obtain medical history, including:
  - Hepatitis C treatment history:
    - Interferon intolerant: Subject who discontinued therapy (≤ 12 weeks total) due to ≥ 1 adverse event
    - Interferon non-responder: Subject who did not achieve undetectable HCV RNA levels while on treatment
    - Relapse/breakthrough: Subject who achieved undetectable HCV RNA during treatment or within 4 weeks of the end of treatment but did not achieve a sustained virologic response (SVR)
- Complete physical examination
- Vital signs
- Body weight and height

- Biological parental height, unless unknown (eg, subject adopted, biological parent (s) deceased), will be collected at screening up to Day 1 visit.
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.
- Review of concomitant medications
- Ask subject and/or parent/legal guardian if the subject is able to swallow and tolerate taking pills. Perform SOF/VEL FDC swallowability assessment.
- Perform transient elastrography (if available); may be done at any time during Screening up to and including on 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
  - HIV testing, HCV antibody, HBV surface antigen (HBsAg), HBV surface antibody (HBsAb), HBV core antibody (HBcAb), HAV antibody
  - HBV DNA testing for subjects HBcAb positive at Screening
  - HbA_{1c}
  - Fibrotest®
  - APRI
  - TSH
  - Alpha-1 anti-trypsin (AAT)
- Obtain urine sample 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 serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (CRF/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 CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Day 1 Assessments

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

- Reconfirm eligibility
- Perform complete physical examination
- Tanner Pubertal Stage Assessment
- Vital signs
- Body weight and height
- Biological parental height, unless unknown (eg, subject adopted, biological parent (s) deceased), will be collected at screening up to Day 1 visit.
- A single X-ray of the left wrist, hand, and fingers for Bone Age Assessment
- Assessment of AEs and concomitant medications
- Perform transient elastrography (if available); if not performed 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)
- Ask subject and/or parent/legal guardian if the subject is able to swallow and tolerate taking pills. Perform SOF/VEL FDC swallowability assessment if not performed at screening.
- SOF/VEL Acceptability Questionnaires
- Quality of life survey: Subject is to review questionnaire and write/mark answers directly onto the questionnaire. Parent/legal guardian completes the parent/guardian questionnaire.

- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - IL28B Genotype
  - Viral sequencing (archive)
  - CCI [redacted]
- Obtain urine samples for the following procedures:
  - Urinalysis
  - Urine pregnancy test for females of childbearing potential only

6.2.2.1. Drug Administration

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

- Perform SOF/VEL FDC swallowability assessment (if not previously completed at screening).
- Dispense study drug(s) as directed by the IWRS
- Instruct the subject on the packaging, storage, administration of study drug, and provide dosing diary and instructions.
- Observe the subject taking the first dose of study drug (with or without food) and record the time of first dose.
- Subject or parent/legal guardian (as applicable) will complete the relevant acceptability questionnaires.
- CCI [redacted]

6.3. PK Lead-in Phase: Treatment Assessments

6.3.1. Day 3 (Telephone Call)

The site staff will perform the following assessments over the telephone with the subject and/or subject's parent/legal guardian on Day 3:

- Assessment of AEs and concomitant medications
- Review Subject Dosing Diary with subject and/or subject's parent/legal guardian

6.3.2. Day 7 – Intensive PK (+3 days)

The Day 7 intensive PK visit should occur on the protocol-specified visit date based on the baseline visit. For the purposes of scheduling, the Day 7 intensive PK visit may be performed within +3 days of the protocol-specified visit date (subjects will continue daily dosing through the intensive PK Visit).

Subjects should come in a fasted state for the Day 7 intensive PK visit (i.e., no food or drink except water at least 8 hours prior to the Day 7 intensive PK visit). Subject and/or parent/legal guardians should be instructed that the Day 7 dose of SOF/VEL FDC must **not** be taken prior to the visit and until the evaluations listed below are completed.

If the subject has already dosed prior to the Day 7 clinic visit or is **not** in a fasted state, the Day 7 intensive PK assessments must not be completed. The subject and/or parent/legal guardians should be instructed to return in a fasted state within 3 days (Days 8, 9, or 10) for the intensive PK visit.

If dosing non-compliance is identified per Subject Dosing Diary or study drug count on or prior to the Day 7 visit, the Day 7 intensive PK assessments must not be completed. The subject and/or parent/legal guardians should be counseled regarding proper dosing and be scheduled to return for the Day 7 intensive PK visit no sooner than 3 days following compliant dosing and no later than Day 11 (i.e., return on Day 10 or Day 11). If dosing non-compliance is due to an AE, consultation with the Gilead Medical Monitor is required regarding the potential of rescheduling the Day 7 intensive PK visit.

In both scenarios described above, the subject should be reminded or the parent/legal guardian should be reminded that the subject should not to take the SOF/VEL FDC prior to arriving at the clinic on the day of the re-scheduled intensive PK visit. All Day 7 intensive PK assessments listed below should be completed when the subject returns.

The following evaluations are to be completed at the Day 7 intensive PK visit:

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

- Assessment of AEs and concomitant medications
- Perform study drug accountability
- Review Subject Dosing Diary
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
- Obtain urine samples for the following procedures:
  - Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, the intensive PK sampling will not be completed. The positive result will be confirmed with a serum pregnancy test.
  - Urinalysis
- Perform intensive PK sampling:
  - Blood samples will be collected at 0 (predose, ≤ 30 minutes prior to dosing). After collection of the predose sample, subjects will be provided a standardized meal. Within 5 minutes after consuming the standardized meal, subjects will be dosed with SOF/VEL FDC per dosing requirements.
  - Postdose blood samples will be collected as follows:
    - For Cohorts 1 and 2: 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose (with predose also serving as t= 24).
    - For Cohort 3 only: 0.5, 1, 2, 3, 4, 8, and 12 hours postdose (with predose also serving as t = 24).
  - Subjects will be restricted from food intake until after collection of the 4-hour postdose blood sample, except for subjects in Cohort 3. Please also refer to the PK manual for details about standardized meals and PK sample processing instructions.

After completing the Day 7 intensive PK visit subjects will then continue to the Week 4 visit in Treatment Phase (described in Section 6.5.2) with no interruption in dosing.

6.4. Treatment Phase: Treatment Assessments

6.4.1. Weeks 1 (± 3 days)

Subjects who participated in the PK Lead-in will start study visits in the Treatment Phase at Week 4.

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
- Review Subject Dosing Diary
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
  - Single sparse PK sample collected anytime

6.4.2. Weeks 4 and 8 (± 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

- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
  - Two sparse PK samples collected at Week 4 and Week 8, predose and between 15 minutes and 4 hours postdose [redacted]
  - HBV DNA testing for subjects HBcAb positive at Screening
- Obtain urine sample for:
  - Urine pregnancy test for females of childbearing potential only
- Review medication compliance with subject and/or parent/legal guardian (subject should return all study drug at these visits)
- Review Subject Dosing Diary
- Dispense study drug as directed by the IWRS

6.4.3. Week 12 (± 3 days) or Early Termination

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

- Perform complete physical examination
- Tanner Pubertal Staging 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)

- Subjects 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/legal guardian completes the parent/guardian questionnaire.
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
  - TSH
  - Single sparse PK sample collected anytime
  - HBV DNA testing for subjects HBcAb positive at Screening
- Obtain urine sample for:
  - Urine pregnancy test for females of childbearing potential only
- Review medication compliance with subject and/or parent/legal guardian.
- Review Subject Dosing Diary
- Subjects should return all bottles/packets of study drug at the Week 12 Visit

6.5. Posttreatment Assessments

6.5.1. 4-Week Posttreatment Visit (± 5 days)

The following procedures/assessments are to be completed at this site 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
  - Viral sequencing (archive)
  - HBV DNA testing for subjects HBcAb positive at Screening
- Obtain urine sample for:
  - Urine pregnancy test for females of childbearing potential only

6.5.2. 12-Week Posttreatment Visit (± 5 days)

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

- Perform symptom-directed physical examination
- Tanner Pubertal Stage assessment
- Vital signs
- Body weight and height
- Assessment of SAEs
- Quality of life survey: Subject is to review questionnaire and write/mark answers directly onto the questionnaire. Parent/legal guardian completes the parent/guardian questionnaire.
- Obtain blood samples for:
  - HCV RNA
  - Viral sequencing (archive)
  - HBV DNA testing for subjects HBcAb positive at Screening

6.5.3. 24-Week Posttreatment Visit (+5 days)

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

- Perform symptom-directed physical examination
- Tanner Pubertal Stage Assessment
- Vital signs
- Body weight and height measurements
- Assessment of SAEs
- Quality of life survey: Subject is to review questionnaire and write/mark answers directly onto the questionnaire. Parent/legal guardian completes the parent/guardian questionnaire.
- A single X-ray of the left wrist, hand, and fingers for Bone Age Assessment
- Obtain blood samples for:
  - HCV RNA
  - Viral sequencing (archive)
  - HBV DNA testing for subjects HBcAb positive at Screening

6.6. CCI [redacted]

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[redacted]

6.7. 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.

6.8. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (eg, 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 3.6, 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.

6.9. Breakthrough Futility Assessment

A futility assessment will be performed after the first 10 subjects complete Week 8 on study or have viral breakthrough at or prior to Week 8. If 3 or more of the first 10 subjects enrolled have viral breakthrough at or prior to Week 8 or are non-responders (HCV RNA $\geq$ LLOQ through 8 weeks of treatment), then further enrollment of subjects will be suspended. Virologic breakthrough is defined as confirmed HCV RNA $\geq$ LLOQ while on treatment after two consecutive visits with HCV RNA < LLOQ.

If a holding rule has been met and following an internal safety review, it is deemed appropriate to restart enrollment, a request to restart enrollment with pertinent data will be submitted to the appropriate regulatory agencies. Enrollment will only resume after review by the appropriate regulatory agencies. Any subject on treatment when a holding rule has been met will be allowed to continue to treatment.

Subjects with known or suspected study drug non-adherence will not be considered to meet the definition of virologic breakthrough, relapse, or non-responder for the purpose of this futility assessment.

6.10. Procedures and Specifications

6.10.1. 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 bilirubin (reflex to 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 HCV, HBV (HBsAg, HBsAb, HBcAb) and HAV. 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 SNP, rs12979860, with sequence specific forward and reverse primers and allele specific fluorescently labeled TaqMan® 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 $A1_c$ ($HbA1_c$), TSH (reflex Free T4), alpha-1 anti-trypsin (AAT), Fibrotest, and APRI.

6.10.2. 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 for all subjects during screening.

6.10.3. 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 (including ECG, as applicable); 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.

6.10.4. 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.

6.10.5. 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, posttreatment Week 12, and posttreatment Week 24 will be calculated. Parental heights will be recorded at Screening or Day 1, unless unknown (eg, subject adopted, biological parent(s) deceased, etc).

6.10.6. Bone Age Assessment

A single X-ray of the left wrist, hand, and fingers will be performed at Day 1 Visit and posttreatment Week 24. Local radiologist will determine bone age from x-ray.

6.10.7. Acceptability Assessment

- Swallowability:

A SOF/VEL FDC swallowability assessment for the tablet formulation will be performed at screening up to Day 1.

12 to < 18 years of age:

Subjects who have indicated that they can take pills will be observed taking a placebo to match the 400/100 mg SOF/VEL FDC tablet. This will confirm the swallowability of the 400/100mg tablet formulation size.

- If a subject is unable to swallow the 400/100 mg SOF/VEL FDC placebo tablet, the subject will repeat the assessment with a placebo to assess swallowability of the 200/50 mg SOF/VEL FDC tablet.
- If unable to swallow the 200/50 mg low dose SOF/VEL FDC tablet, the subject will be assigned to SOF/VEL FDC oral granules formulation.

6 to < 12 years of age:

Subjects who have indicated that they can take pills will be observed taking a placebo to match the 200/50 mg low dose SOF/VEL tablet. This will confirm the swallowability of the 200/50 mg tablet size.

- If a subject is unable to swallow the 200/50 mg SOF/VEL low dose placebo tablet, the subject will be assigned to SOF/VEL FDC oral granules formulation.

3 to < 6 years of age:

Subjects will be administered SOF/VEL oral granules. There will not be any placebo provided to assess swallowability for this formulation.

Acceptability and palatability:

For all age groups, a questionnaire will be administered to subjects to assess acceptability and palatability of the formulation they received on Day 1, Week 12 and Early Termination (as applicable). If the subject is unable to complete the questionnaires, the parent/legal guardian will assist to complete the questionnaire on their behalf. The subject's parent/legal guardian will also complete a questionnaire on Week 12 or Early Termination (as applicable) for their assessment of acceptability of the formulation the subject received.

6.10.8. 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.

6.10.9. Body Mass Index (BMI)

BMI is calculated by the following equation.

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

6.10.10. 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)]

6.10.11. Viral Sequencing (Archive)

Plasma samples will be collected at Day 1 and each subsequent visit for viral sequence analysis. Unused samples may be archived.

6.10.12. HBV DNA

HBV DNA will only be tested in subjects who test positive for the hepatitis B core antibody (HBcAb) test at Screening. HBV DNA testing will occur at Screening, Weeks 4, 8, and 12 or early termination and all posttreatment visits.

6.10.13. Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period and for a minimum of 30 days following the last dose of SOF/VEL. 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.

6.10.14. 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/legal guardian at Day 1, End of Treatment, 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).

Each survey will be administered to the subject for the current age group 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, 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 (e.g., 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 sub-investigator 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 sub-investigator 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 obtaining informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/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 CRF/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 occur 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.

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: E-mail:	PPD 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 CRF/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 IRB or 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 have access to unblinded data and will make recommendations regarding the study according to the DMC charter.

7.5. Toxicity Management

See Section 3.6 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 post study drug follow-up period, to Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the CRF/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 Sections 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study 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 or 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 CRF/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 CRF/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 the PK Lead-in phase is:

- To evaluate the steady state pharmacokinetics (PK) and confirm the dose of sofosbuvir/velpatasvir (SOF/VEL FDC) in pediatric subjects with chronic hepatitis C virus (HCV) infection

The primary objective of the Treatment Phase of this study is:

- To evaluate the safety and tolerability of SOF/VEL FDC for 12 weeks in pediatric subjects with chronic HCV

The secondary objective of the PK Lead-in Phase is:

- To evaluate the safety, tolerability, and antiviral activity of 7 days of dosing of SOF/VEL FDC in pediatric subjects with chronic HCV

The secondary objectives of the Treatment Phase of this study are:

- To determine the efficacy of SOF/VEL FDC for 12 weeks in pediatric subjects with chronic HCV infection, as assessed by the proportion of subjects with sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12)
- To determine the proportion of subjects with SVR 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure, including breakthrough/nonresponse 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 and VEL during treatment and after cessation of treatment
- To evaluate the effect of treatment with SOF/VEL FDC on quality of life as measured by PedsQL™ Pediatric Quality of Life survey
- To evaluate the effect of SOF/VEL on growth and development of pediatric subjects during and after treatment
- To evaluate the acceptability, including palatability, of formulations used in the study

The exploratory objective of this study is:

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8.1.2. Primary Endpoint

The appropriateness of the SOF/VEL FDC dose will be assessed by evaluating the steady-state PK of the VEL, SOF, and GS-331007 at Day 7. Estimated PK parameters will include C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, AUC_{tau}, CL/F, Vz/F and $t_{1/2}$, as appropriate). The primary PK endpoint of the PK Lead-in Phase is AUC_{tau} of VEL, SOF, and its major metabolite (GS-331007).

The primary endpoint of the Treatment Phase is assessment of any AEs with a focus on AEs that lead to discontinuation of study drug.

8.1.3. Secondary Endpoint

The secondary endpoints of the PK Lead-in Phase are:

- Antiviral activity measurements, including assessment of HCV RNA from baseline through Day 7.
- Any AE leading to permanent discontinuation of study drug.

The secondary endpoints of the Treatment Phase are:

- The proportion of subjects with sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12). 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 breakthrough/nonresponse and relapse
- The proportion of subjects with HCV RNA < LLOQ on treatment
- Emergence of viral resistance to SOF and /or VEL during treatment and treatment is discontinued
- HCV RNA change from Day 1
- Quality of life endpoints and neuropsychiatric assessments as measured by PedsQL™ Pediatric Quality of Life survey
- Growth and development measurements including height and weight percentiles, Tanner Stage, parental height, and bone age
- Acceptability assessed by swallowability and palatability

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 FDC. Last dose of the study drug refers to the last dose of SOF/VEL FDC and will be used in the definition of treatment-emergent AEs and laboratory abnormalities as well as the efficacy endpoints of SVR at various posttreatment timepoints.

8.2.1. Analysis Sets

8.2.1.1. Efficacy Analysis Set

The analysis set for antiviral activity analyses is defined as the Full Analysis Set (FAS) which includes who were enrolled into the study and took at least one dose of the study drug.

8.2.1.2. Safety Analysis Set

The primary analysis set for safety analyses will include subjects who took at least one 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 date of the last dose of the study drug plus 30 days.

8.2.1.3. Pharmacokinetics Analysis Sets

Intensive PK Lead-in Analysis Set

The intensive PK analysis set will include all PK Lead-in subjects who took at least one dose of the study drug and for whom at least one non-missing PK concentration data, during the intensive sampling period was reported by PK lab. The PK analysis set will be used for detailed pharmacokinetic analysis of VEL, SOF, or its primary metabolite(s).

PK Analysis Set

The PK analysis set will include all enrolled subjects who took at least one dose of study drug and for whom at least one observed concentration data VEL, SOF, or its primary metabolite(s) are available. The PK analysis set will be used for analysis of general PK and single sample plasma concentrations and used for Population PK analysis.

8.2.2. Data Handling Conventions

Missing data can have an impact upon the interpretation of the trial data. Other than the endpoints discussed below, in general, 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 (i.e., ≥ LLOQ detected). If a data point is missing and is not bracketed, the missing data point will also be termed a failure (i.e., ≥ 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 that did not complete the study will be included in summary statistics. For example:

- If a subject received 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 summary statistics for that time point. If the subject is missing a predose value, then the subject will be excluded from the calculation of 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 (i.e., 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 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. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the lower limit of quantitation (LLOQ) at post baseline time points, where LLOQ is corrected for the dilution factor (i.e., reported LLOQ/dilution factor) for determination of summary and order statistics.

For the presentation of summary and order statistics, if at least 1 subject has a concentration value of BLQ for the time point, then the minimum value will be displayed as "BLQ." If more than 25% of the subjects have a concentration data value of BLQ for a given time point, then the minimum and Q1 values will be displayed as "BLQ." If more than 50% of the subjects have a concentration data value of BLQ for a given time point, then the minimum, Q1, and median values will be displayed as "BLQ." If more than 75% of the subjects have a concentration data value of BLQ for a given time point, then the minimum, Q1, median, and Q3 values will be displayed as "BLQ." If all subjects have concentration data values of BLQ for a given time point, then all order statistics (minimum, Q1, median, Q3, and maximum) and summary statistics will be displayed as "BLQ."

8.3. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods.

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

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

8.4. Efficacy Analysis

8.4.1. Analysis of the Key Efficacy Endpoint

The key efficacy endpoint is SVR12 on the FAS. The analysis of SVR12 will be performed after all enrolled subjects have been followed through posttreatment Week 12 or discontinued from the study. The point estimate of the SVR12 rate and the 2-sided 95% exact CIs based on Clopper-Pearson method will be calculated.

8.4.2. Secondary Analyses

The proportion of subjects with HCV RNA below the LLOQ over time (including SVR4 and SVR24) will be presented 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, quality of life endpoints and other endpoint of interest may include ALT normalization.

Exploratory analyses may be performed to assess the relationship between demographic, baseline characteristics (including baseline viral load, genotype, age, sex, race, ethnicity, baseline ALT level), and antiviral activity (HCV RNA reduction, proportion of subjects with HCV RNA < LLOQ at various time points during and following discontinuation of active therapy).

Details on efficacy analyses will be described in the statistical analysis plan.

8.5. 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**.**

8.5.1. Extent of Exposure

A subject's extent of exposure to the study drug will be generated from the study drug administration page of eCRF. Exposure data will be summarized.

8.5.2. 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:

- 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

8.5.3. 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.

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 (i.e., no grade [Grade 0]) for the summary of graded laboratory abnormalities.

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

8.5.4. Other Safety Evaluations

8.5.4.1. Tanner Pubertal Stage Assessment

Tanner Stages (Appendix 4) will be summarized by baseline Tanner Stage using frequency and percentage by gender.

8.5.4.2. Vital Signs (including Body Weight and Height)

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

8.5.4.3. Bone Age Assessment

Bone age will be summarized.

8.5.5. Acceptability

Acceptability of the study treatments will be evaluated by assessing swallowability of the solid dosage tablet formulations (if subject is able to swallow the tablet), evaluation of palatability of all formulations, and a questionnaire administered to subjects and their parent/legal guardian on Day 1, Week 12, and Early Termination (as applicable).

8.6. Pharmacokinetic Analysis

PK analysis will be performed for PK Lead-in using the intensive PK Lead-in analysis set. The concentration data of VEL, SOF and metabolites (GS-566500 and GS-331007) over sampling time will be listed and summarized by nominal time and cohort. Pharmacokinetic parameters (e.g., AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, and $t_{½}$) will be listed and summarized by cohort using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum). Plasma concentrations of the analytes over time will be plotted in semi logarithmic and linear formats as mean ± standard deviation.

To evaluate if the exposures of SOF, GS-331007 and VEL achieved in pediatric subjects of this study are similar to the exposures observed in adult subjects, SOF, GS-331007 and VEL 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 and VEL AUC_{tau}. The secondary endpoints of this analysis will be the C_{max} of SOF, VEL and GS-331007 and C_{tau} of VEL. The 90% confidence intervals will be constructed for the ratio of geometric means of each PK parameters. The equivalence boundary is set as 70% to 200%.

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 1 dose ranging study GS-US-281-0102 established the anti-HCV activity of VEL and the E_{max} models indicated that subjects will experience near maximal antiviral response (99.5% of E_{max}) at a VEL dose of 100 mg. In the Phase 2/3 population treated with SOF/VEL FDC 400/100 mg, virologic response rates were high across all HCV genotypes and quartiles of exposure for VEL, SOF and GS-331007, including for subjects with cirrhosis, with no consistent trends in exposure-efficacy or exposure-safety relationships. Given the observed safety and efficacy profile and the lack of exposure-response across all quartiles of SOF/VEL exposure, the bounds of 70-200% support identification of a clinically relevant difference in SOF, GS-331007 or VEL exposure in the pediatric population.

In all pediatric age groups, the targeted exposures for SOF, GS-331007 and VEL are the adult equivalent for which safety and efficacy has been established. Assuming similar variability for SOF, GS-331007 or VEL AUC_{tau} in the pediatric population compared to adults, the predicted 90% CIs of the geometric mean ratio (GMR) will be contained within the bounds of 70% to 200%.

In the event more than one subject in each cohort exhibits VEL, SOF, or GS-331007 AUC_{tau} exposures less than the 2.5^{th} percentile of adult values, a dose adjustment may be required for the cohort as appropriate.

8.7. 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 every 6 months from the first subject enrolled in order to protect subject welfare and preserve study integrity. The DMC is to provide recommendation to the sponsor 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, conduct, and the need for additional meetings or an alternative meeting schedule.

The DMC's specific activities will be defined by a mutually agreed upon 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.

8.8. Sample Size

With approximately 100 subjects enrolled into the 12 to < 18 years of age group and approximately 100 subjects enrolled into the 3 to < 12 years of age group, a 2-sided 95% exact confidence interval of the SVR12 rate in each age group will extend at most 20%.

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 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. Institutional Review Board (IRB)/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 IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/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 IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/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 IRB or 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 IRB or IEC or local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

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, IRB/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, CRF/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, eCRF and query forms, IRB/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. 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. The 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 (e.g. 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 IRB/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 the IRB/IEC in accordance with local requirements and receive documented IRB/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, e.g. 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 CRF/eCRF.

The monitor is responsible for routine review of the CRF/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 CRF/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), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

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Appendix 4. Tanner Stages*
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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 Safety and Efficacy of Sofosbuvir/Velpatasvir in Adolescents and Children with Chronic HCV Infection

GS-US-342-1143, Protocol Amendment 4, 15 June 2018

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

PPD

June 15, 2018
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. PK Lead-in: Screening and On-Treatment Study Visits

	Screening (-28 days)	On-treatment		
		Day 1[i]	Day 3 Telephone call	Day 7 (+ 3 days)
Clinical Assessments				
Informed Consent / Assent	X			
Determine Eligibility	X	X		
Medical History	X			
Parental Height	X[a]	X[a]		
Complete Physical Examination	X	X		
Symptom-directed Physical Examination				X
Tanner Pubertal Stage Assessment[b]		X		
Vital Signs[c]	X	X		X
Body Weight and Height[d]	X	X		X
Bone Age Assessment		X		
AEs and Concomitant Medications	X	X	X	X
Transient Elastography, if available	X[e]	X[e]		
Pregnancy Prevention Counseling[f]		X		
SOF/VEL Swallowability Assessment	X[g]	X[g]		
SOF/VEL Acceptability Questionnaires		X		
Quality of Life Survey		X[h]		
Review of Study Medication Compliance				X
Study Drug Dispensing[i]		X		
Subject Dosing Diary[j]		X	X	X
Laboratory Assessments				
Hematology, Chemistry, Coagulation	X	X		X
HbA1c, Fibrotest®, APRI	X			
TSH	X			
Alpha-1 anti-trypsin	X			

	Screening (-28 days)	On-treatment		
		Day 1[i]	Day 3 Telephone call	Day 7 (+ 3 days)
HIV testing, HCV antibody, HBsAg, HBsAb, HBcAb, and HAV antibody	X			
HBV DNA[k]	X			
HCV RNA	X	X		X
HCV Genotyping	X			
Viral Sequencing[l]		X		X
Serum or Urine Pregnancy Testing[m]	X	X		X
IL28B Genotyping		X		
Urinalysis	X	X		X
Urine Drug Screen	X			
CCI				
Intensive PK				X[o]

a Biological parental height, if not collected at Day 1.
b 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.
c Vital signs include blood pressure, pulse, respiratory rate and temperature.
d Height should be without shoes and should be collected by the same personnel, if possible.
e May be performed at Screening up to Day 1.
f 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).
g Swallowability can occur at Day 1 if not completed during screening.
h 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.
i Day 1 assessments must be performed prior to dosing. The IWRS system will provide direction on the specifics of each subject's study drug dispensing.
j CCI .
k HBV DNA testing done only when subjects are HBcAb positive at Screening.
l Plasma samples will be collected and stored for potential HCV sequencing and other virology studies.
m Females of childbearing potential only. Serum pregnancy test performed at screening and for confirmation of positive urine pregnancy test.
n For subjects who provide consent, a blood sample should be drawn at the Day 1 visit. If not obtained at this visit, the sample may be drawn at any time during the study.
o **Cohorts 1 and 2**, plasma samples will be collected for PK analyses following dosing of study drug on Day 7 at the following time points: 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose. **Cohort 3**, plasma samples for PK analyses will be collected at the following time points: 0 (predose), 0.5, 1, 2, 3, 4, 8, and 12 hours postdose. Subjects should come in a fasted state for the Week 4 or Week 8 intensive PK visit (i.e., no food or drink except water at least 8 hours prior to the Week 4 or Week 8 intensive PK visit). Subjects and/or parents/legal guardians should also be instructed that the Week 4 or Week 8 dose of SOF/VEL FDC must **not** be taken prior to the visit and until the evaluations listed below are completed.

Appendix Table 2. Treatment Phase: Screening and On-Treatment Study Visits

	Screening[i,k] (-28 days)	Day 1[k]	Week 1[k]	Week 4	Week 8	Week 12	Early Termination
Clinical Assessments							
Informed Consent / Assent	X						
Determine Eligibility	X	X					
Medical History	X						
Parental Height	X[a]	X[a]					
Complete Physical Examination	X	X				X	X
Symptom-Directed Physical Examination			X	X	X		
Tanner Pubertal Stage Assessment[b]		X				X	X
Vital Signs[c]	X	X	X	X	X	X	X
Body Weight and Height[d]	X	X	X	X	X	X	X
Bone Age Assessment		X					
AEs and Concomitant Medications	X	X	X	X	X	X	X
Transient Elastography, (if available)	X[e]	X[e]					
Pregnancy Prevention Counseling[f]		X				X	X
SOF/VEL Swallowability Assessment	X[g]	X[g]					
SOF/VEL Acceptability Questionnaire[h]		X				X	X
Quality of Life Survey[i]		X				X	X
Review of Study Medication Compliance				X	X	X	X
Study Drug Dispensing[j]		X		X	X		
Subject Dosing Diary[l]		X	X	X	X	X	
Laboratory Assessments							
Hematology, Chemistry, Coagulation	X	X	X	X	X	X	X
HbA1c, Fibrotest®, APRI	X						
TSH	X					X	X
Alpha-1 anti-trypsin	X						
HIV testing, HCV Antibody, HBsAg, HBsAb, HBcAb, HAV Antibody	X						
HBV DNA[m]	X			X	X	X	X
HCV RNA	X	X	X	X	X	X	X
HCV Genotyping	X						

	Screening[j,k] (-28 days)	Day 1[k]	Week 1[k]	Week 4	Week 8	Week 12	Early Termination
Viral Sequencing[n]		X	X	X	X	X	X
Serum or Urine Pregnancy Testing[o]	X	X		X	X	X	X
IL28B Genotyping		X					
Urinalysis	X	X					
Urine Drug Test	X						
CCI							
Single PK			X			X	X
Two sparse PK Samples collected predose and between 15 minutes and up to 4 hours postdose[q]				X	X		
CCI							

a Biological parental height, if not collected at Day 1.
b 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.
c Vital signs include blood pressure, pulse, respiratory rate, and temperature.
d Height should be without shoes and should be collected by the same personnel, if possible.
e May be performed at Screening up to Day 1.
f 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).
g Swallowability can occur at Day 1 if not completed during screening.
h A questionnaire will be administered to subjects to assess acceptability and palatability of the formulation they received on Day 1, Week 12, and Early Termination (as applicable). If the subject is unable to complete the questionnaires, the parent/legal guardian will complete the questionnaire on their behalf. The subjects' parent/legal guardian will also complete a questionnaire on Week 12 or Early Termination (as applicable) for their assessment of acceptability of the formulation the subject received.
i 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.
j Day 1 assessments must be performed prior to dosing. The IWRS system will provide direction on the specifics of each subject's study drug dispensing.
k Subjects rolling over from PK Lead-in will not be required to repeat screening, Day 1 or Week 1 visits in the Treatment Phase.
l CCI
m HBV DNA testing done only when subjects are HBcAb positive at Screening.
n Plasma samples will be collected and stored for potential HCV sequencing and other virology studies.
o Females of childbearing potential only. Serum pregnancy test performed at screening and for confirmation of positive urine pregnancy test.
p For subjects who provide consent, a blood sample should be drawn at the Day 1 visit. If not obtained at this visit, the sample may be drawn at any time during the study.
q CCI
r CCI

Appendix Table 3. Treatment Phase: Posttreatment Visits Following Primary Study

	4 Weeks Posttreatment	12 Weeks Posttreatment	24 Weeks Posttreatment
Clinical Assessments			
Vital Signs	X	X	X
Body Weight and Height[a]	X	X	X
Symptom-directed Physical Exam	X	X	X
AEs	X	X[b]	X[b]
Concomitant Medications	X		
Quality of Life Survey[c]		X	X
Tanner Pubertal Stage Assessment[d]		X	X
Bone Age Assessment			X
Pregnancy Prevention Counseling[e]	X		
Laboratory Assessments			
Hematology, Chemistry	X		
HCV RNA	X	X	X
Viral Sequencing[f]	X	X	X
Urine Pregnancy Test[g]	X		
HBV DNA[h]	X	X	X

a Height should be without shoes and should be collected by the same personnel, if possible.
b At Posttreatment Week 12 and 24, only SAEs will be captured.
c Quality of life survey will be completed by all subjects and their parent/legal guardian at 12-Week and 24-Week Posttreatment visits. Subject and parent/legal guardian is to review questionnaire and write/mark answers directly onto the questionnaire.
d 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.
e 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).
f Plasma samples will be collected and stored for potential HCV sequencing and other virology studies.
g Females of childbearing potential only.
h HBV DNA testing done only when subjects are HBcAb positive at screening.

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
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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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** 3.0 to <LLN mmol/L **Infant <1 Year** 3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	3.0 to <LLN mEq/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** 5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L **Infant <1 Year** >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** 55 to 64 mg/dL 3.03 to 3.58 mmol/L **Infant, < 1 Month** 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
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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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** **Pediatric 1 Year–14 Years** **Pediatric < 1 Year**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L 3.0 to <LLN mg/dL 0.96 to <LLN mmol/L 3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L 2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L 2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.0 mg/dL < 0.31 mmol/L < 1.5 mg/dL < 0.47 mmol/L < 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days** **Infant, ≤ 14 Days** (non-hemolytic) **Infant, ≤ 14 Days** (hemolytic)	> 1.0 to 1.5 × ULN NA NA	> 1.5 to 2.5 × ULN 20.0 to 25.0 mg/dL 342 to 428 µmol/L NA	> 2.5 to 5.0 × ULN > 25.0 to 30.0 mg/dL > 428 to 513 µmol/L 20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 5.0 × ULN > 30.0 mg/dL > 513 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** **Infant < 1 Year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN N/A	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L 1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L 0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L < 0.5 mg/dL < 27 µmol/L
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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bicarbonate **Adult and Pediatric ≥ 4 Years** **Pediatric < 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN NA	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L 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 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 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 (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

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	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
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 menarche until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women of any age with amenorrhea of > 12 months may be considered post-menopausal if their follicle stimulating hormone (FS) level is in the post-menopausal 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 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 from clinical pharmacokinetic interaction studies of SOF have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Non-clinical toxicity studies of SOF have demonstrated no adverse effect on fertility or embryo-fetal development

Data from clinical pharmacokinetic interaction studies of VEL have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Non-clinical toxicity studies of GS-5816 have demonstrated no adverse effect on fertility or embryo-fetal development.

However, the risks of treatment with SOF/VEL FDC during pregnancy in humans have not been evaluated. Please refer to the latest version of the investigator's brochure for additional information.

3) Contraception Requirements for Female Subjects of Childbearing Potential

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. A pregnancy test will be performed 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 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
  - Essure micro-insert system
  - 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 (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel or etonorgestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

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 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 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 FDC.

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

5) Unacceptable Methods of Contraception

Birth control methods that are unacceptable include periodic abstinence (e.g., 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 the last dose of SOF/VEL FDC. Subjects who become pregnant or who suspect that they are pregnant must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant must report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.