Protocol No. CDI-31244-P2-001

An Open-Label Phase 2a Study Evaluating the Safety and Efficacy of Combination Treatment with 2 Weeks of the Non-Nucleoside Inhibitor CDI-31244 Plus 6 Weeks of Sofosbuvir/Velpatasvir in Subjects with Chronic Hepatitis C Genotype 1 Infection

Investigational Drug: CDI-31244

Study Number: HP-00078356

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PROTOCOL SYNOPSIS

Title: An Open-Label Phase 2a Study Evaluating the Safety and Efficacy of Combination Treatment with 2 Weeks of the Non-Nucleoside Inhibitor CDI-31244 Plus 6 Weeks of Sofosbuvir/Velpatasvir in Subjects with Chronic Hepatitis C Genotype 1 Infection.

Disease:

Chronic hepatitis C virus (HCV) infection.

Objectives:

The primary objective of this study is to evaluate the safety, tolerability, and preliminary efficacy of treatment with 2 weeks of CDI-31244 plus 6 weeks of sofosbuvir/velpatasvir (SOF/VEL) in subjects with chronic HCV genotype 1 infection. Secondary objectives include: a) evaluating the viral kinetics of circulating HCV RNA during and after treatment with CDI-31244 plus SOF/VEL, and b) evaluating the pharmacokinetics of CDI-31244 during treatment with CDI-31244 plus SOF/VEL.

Study Design:

This is an open-label phase 2a study to evaluate the safety, tolerability, and preliminary efficacy of treatment with 2 weeks of an oral non-nucleoside inhibitor CDI-31244 combined with 6 weeks of SOF/ VEL in adult subjects with chronic HCV genotype 1 virus infection.

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

- Age ≥ 18 years at screening.
- Documented chronic HCV infection based on any of the following:
  - Anti-HCV antibody positivity for at least 6 months prior to study enrollment, or
  - HCV genotype results for at least 6 months prior to study enrollment, or
  - HCV RNA present in plasma by a sensitive and specific assay for at least 6 months prior to study enrollment, or
  - Histologic evidence of chronic HCV infection.
- HCV genotype 1a or 1b infection by HCV genotyping performed at screening. (Note: No more than four subjects with HCV genotype 1b will be enrolled).
- Serum HCV RNA >1,000 IU/mL during screening.
- Must have a primary care provider(s) for medical management.
- Absence of advanced fibrosis or cirrhosis by liver biopsy, fibroscan (<8 kPa) or FibroTest/FibroSure (F2 or lower) within 1 year of screening. If the preceding fibrosis tests are not available, FibroTest/FibroSure will be done at screening.

- Females of childbearing potential must have a negative serum pregnancy test at screening and agree to use a medically reliable method of contraception until study completion. Effective contraception methods include: total abstinence (when lifestyle or sexual orientation of the subject precludes intercourse with a male partner); female sterilization; barrier methods of contraception (diaphragm or cervical/vault caps with spermicidal foam, gel, cream, or vaginal suppository); use of oral, injected, or implanted hormonal contraception or other forms that have comparable efficacy (failure rate <1%); or placement of an intrauterine device or intrauterine system.
- Male subjects must be willing to abstain from heterosexual intercourse or use a condom with spermicide throughout the study period.
- Be willing to have blood samples stored for future research.
- Available for at least 30 weeks for study participation.
- Written informed consent must be obtained before any study procedure is performed.

Exclusion Criteria:

- Nursing or pregnant.
- Active hepatitis B virus (HBV) infection, defined as positive hepatitis B surface antigen (HBsAg) at screening. If subject is negative for both HBsAg and hepatitis B surface antibody (HBsAb), but hepatitis B core antibody (HBcAb)-positive, plasma HBV DNA levels will be checked and subject excluded if HBV DNA is detected.
- Human immunodeficiency virus (HIV) infection.
- History of use of any HCV direct-acting antiviral therapy.
- Clinically significant illness other than HCV that may interfere with subject treatment, assessment, safety, or compliance with the protocol in the judgment of the investigator.
- Positive urine screen for amphetamines or cocaine.
- Known current heroin, morphine, or methadone use. Current narcotic use other than methadone is acceptable if medically indicated (documented in medical records) and prescribed by a physician.
- Substance abuse, including alcohol abuse, which in the opinion of the investigator is likely to interfere with medication adherence or study compliance.
- Gastrointestinal disorder that could interfere with the absorption of the study drug (e.g., structural defect, digestive failure or enzyme deficiencies with the exception of lactose intolerance) and/or history of bariatric surgery.
- Poor venous access interfering with required study blood collection.
- Significant history of drug allergy (such as anaphylaxis or hepatotoxicity) to the study medications.
- History of clinically significant chronic liver disease due to other etiology (e.g., hemochromatosis, autoimmune hepatitis, Wilson's disease, α1-antitrypsin deficiency,

alcoholic liver disease, known greater than moderate non-alcoholic steatohepatitis, and toxin exposures).

- Use of herbal/natural remedies for potential benefit to the liver within 30 days before study entry.
- Treatment with amiodarone within 180 days before study entry.
- Treatment with digoxin within 30 days before study entry.
- Treatment with rifabutin, rifampin, rifapentine, phenytoin, phenobarbital, St. John's wort, carbamazepine, oxcarbazepine, rosuvastatin, or atorvastatin within 10 days before study entry. However, switching to another statin is acceptable.
- Chronic systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days before study entry. Inhaled steroids are permitted per Investigator's discretion.
- Screening or baseline ECG with clinically significant findings.
- QTcF (QT interval corrected using Fridericia's formula) > 450 msec at screening.
- Clinically significant hematological and biochemical values at screening that may interfere with subject treatment, assessment, safety, or compliance with the protocol in the judgment of the investigator, including:
  - Absolute neutrophil count (ANC) <1,000 cells/mm^3.
  - Hemoglobin level < 10 g/dL.
  - Platelet count < 100,000 cells/mm^3.
  - Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2.
  - ALT or AST level ≥ 5 times upper limit of normal (ULN).
  - Direct bilirubin level ≥1.5 times ULN.
- History of hepatocellular carcinoma (HCC).
- History of malignant disease within previous 5 years (except for adequately treated basal cell carcinoma).
- History of clinically significant myopathy.

Investigational Drug:

CDI-31244

Study Drug Doses and Route of Administration:

- CDI-31244 (50 mg)
- Sofosbuvir 400 mg/velpatasvir 100 mg (Epclusa)

Study drug (CDI-31244 and sofosbuvir/velpatasvir [SOF/VEL]) will be provided as capsules (CDI-31244) or tablets (SOF/VEL) in bottles. Subjects will be instructed to take 8 capsules of CDI-31244 (400 mg total dose) and 1 tablet of SOF/VEL once daily with at least 8 oz. of plain

water in the morning upon awakening. During the period of SOF/VEL treatment alone, subjects will be instructed to take 1 tablet once daily.

Procedures:

- Screening evaluations will occur between 7 and 42 days before initial study drug administration.
- Day 1 is the day of baseline (pre-study drug) assessments and the first day of study drug administration. Clinic visits will occur at screening and baseline and through week 30 (i.e., 24 weeks after completion of treatment) for all subjects.
- Safety evaluations will consist of vital signs, physical examination, electrocardiogram (ECG), and additional clinical and laboratory data. Adverse events will be collected through 4 weeks after completion of treatment for all subjects.
- The primary and secondary efficacy outcomes will be measured throughout the study period by plasma HCV RNA.
- Pharmacokinetic (PK) parameters will be assessed through plasma CDI-31244, sofosbuvir, GS-331007 (sofosbuvir metabolite), and velpatasvir concentrations at Day 1 (pre-dose) and at 0 (pre-dose), 1, 2, 4, 6, 8, 12, and 24 hours after day 14 dosing.
- Viral kinetics (VK) will be assessed through plasma HCV RNA levels obtained at 2, 4, and 6 hours after Day 1 dosing.
- The total study duration is 30 weeks.

Primary and Secondary Efficacy Endpoints:

Primary efficacy endpoint:

- Proportion of subjects who achieve sustained virologic response 12 weeks after completion of treatment (SVR12).

Secondary efficacy endpoints:

- Proportion of subjects who achieve sustained virologic response 24 weeks after completion of treatment (SVR24).
- Time to achieve HCV RNA levels below the lower limit of quantification (LLOQ).
- Proportion of subjects with HCV RNA <LLOQ after Day 7 and Day 14 of CDI-31244 plus SOF/VEL treatment.
- Proportion of subjects with HCV RNA <LLOQ after Day 7 and Day 14, of CDI-31244 plus SOF/VEL treatment by genotype 1a or 1b.

Exploratory endpoints (using stored blood) will include:

- Immunologic, virologic, and host genetic/proteomic predictors of response to therapy.
- Effect of therapy on peripheral markers of T cell activation.

Sample Size, Power, and Number of Sites:

- A total of 12 subjects with treatment-naïve chronic HCV genotype 1 (either 1a or 1b) is consistent with the number of subjects in proof-of-concept pilot studies that evaluate novel therapies for HCV viremia (and cure) in patients with chronic HCV infection.
- Site: Institute of Human Virology (IHV), University of Maryland, Baltimore, MD.

Removal of Subjects from Study Drug or Assessment:

A subject must prematurely discontinue study drug under any of the following circumstances:

- The subject wishes study drug to be discontinued for any reason.
- The investigator wishes the subject to discontinue study drug, especially but not limited to the investigator concluding that further treatment puts the subject at unacceptable risk or study noncompliance.
- The subject develops a condition or begins a therapy that would have excluded entry into the study.
- The subject prematurely fails efficacy based on any of the following criteria, which must be confirmed by a repeat test within 7 days:
  - HCV RNA > LLOQ after 2 consecutive HCV RNA values <LLOQ.
  - Greater than 1 $\log_{10}$ increase in HCV RNA from nadir.

  Resistance assay test will be obtained for all subjects discontinuing study drug prematurely due to lack of efficacy.
- The subject has evidence of a severe drug allergy such as anaphylaxis.
- An adverse event with a Division of AIDS (DAIDS) Table for "Grading the Severity of Adult and Pediatric Adverse Events" grade 3 or greater toxicity that is related to study drug in the judgment of the investigator.

A subject has the right to discontinue study drug treatment at any time for any reason without prejudice to future medical care by the investigator or other physician at the institution. A subject who discontinues study drug should complete all scheduled study visits *provided that written consent to do so has not been withdrawn.* Subjects who prematurely discontinue study drug may be replaced.

A subject must be withdrawn from the study (and discontinue any study drug) if the subject requests such study discontinuation. The reason for withdrawal must be recorded in the subject's

case report form (CRF). If possible, the subject should complete the evaluations for the study week 6 visit *provided that written consent to do so has not been withdrawn*. Subjects who withdraw from the study may be replaced.

Retreatment:

Subjects who have virologic failure during the 6-week study drug treatment period, defined as either HCV RNA > LLOQ after 2 consecutive HCV RNA values < LLOQ or > 1 $\log_{10}$ increase in HCV RNA from nadir, will be discontinued from study drug treatment (Section 5.3.1). These subjects will receive additional treatment ("retreatment") with sofosbuvir/velpatasvir/ voxilaprevir (SOF/VEL/VOX) 400 mg/100 mg/100 mg once daily for 12 weeks with additional follow-up through 12 weeks after cessation of treatment (SVR12).

Subjects who complete the 6-week treatment period will be considered to have virologic (treatment) failure if they have detectable HCV RNA at the next study visit and thereafter throughout the study. These subjects will receive additional treatment ("retreatment") with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) 400 mg/100 mg/100 mg once daily for 12 weeks with additional follow-up through 12 weeks after cessation of treatment (SVR12).

Statistical Analysis:

Safety and efficacy will be assessed on an intent-to-treat basis for all subjects who have received study drug. Data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum and maximum) for continuous variables and frequency and percentages for categorical variables. Time to achieve HCV RNA levels LLOQ will also be summarized using descriptive statistics. Exploratory endpoints will be assessed using descriptive statistics. The incidence of all reported adverse events (AEs) and treatment-related AEs will be tabulated. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

Sponsor: Cocrystal Pharma, Inc.

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ABBREVIATION	DEFINITION
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BP	blood pressure
CBC	complete blood count
CK	creatine kinase
C_{max}	maximum plasma concentration of drug
C_{min}	minimum plasma concentration of drug
CRF	case report form
DAA	direct-acting antiviral
DAIDS	Division of AIDS
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
EC_{50}	concentration of an inhibitor where the response (or binding) of drug is reduced by half
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EOT-C	end of treatment with CDI-31244
EOT-SV	end of treatment with sofosbuvir and velpatasvir
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Lab Practice
GT	genotype
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen

ABBREVIATION	DEFINITION
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
IC_{50}	The half maximal inhibitory concentration (of drug)
ICH	International Conference on Harmonisation
IHV	Institute of Human Virology
IL28B	interleukin 28B
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
LC-MS	liquid chromatography–mass spectrometry
LLOQ	lower limit of quantification
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MCV	mean cell volume
NNI	non-nucleoside inhibitor
P	pulse rate
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamics
P-gp	P-glycoprotein
PK	pharmacokinetics
PT	prothrombin time
PTT	partial thromboplastin time
PW	post-treatment week
QTcF	QT interval corrected using Fridericia's formula
R	respiratory rate
RAV	resistance-associated variants

ABBREVIATION	DEFINITION
RBC	red blood cell
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SOF	sofosbuvir
SOT	start of treatment
SVR	sustained virologic response
SVR4	sustained virologic response, 4 weeks after treatment
SVR12	sustained virologic response, 12 weeks after treatment
SVR24	sustained virologic response, 24 weeks after treatment
T	Temperature
$t_{½}$	mean elimination half-life (of drug)
t_{max}	time to maximum concentration (of drug)
ULN	upper limit of normal
US	United States
VEL	velpatasvir
VK	viral kinetics
VOX	voxilaprevir
W	week
WHO	World Health Organization

1. INTRODUCTION

1.1. Background and Study Rationale

1.1.1. Chronic Hepatitis C

Chronic hepatitis C virus (HCV) infection afflicts approximately 1% of the global population, with an estimated prevalence of 71 million persons (Polaris Observatory HCV Collaborators 2017). It is one of the major causes of chronic liver disease, leading to cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) (Ly et al., 2012; Westbrook and Dusheiko, 2014). Chronic hepatitis C is an indolent disease characterized by persistent liver inflammation, leading to liver cirrhosis in about 10 to 20% of patients over a course of 20 to 30 years of infection (Westbrook and Dusheiko, 2014). The World Health Organization (WHO) estimates that 400,000 annual deaths are attributed to HCV infection, mainly due to complications of cirrhosis and HCC (World Health Organization 2017).

The advent of safe and highly effective direct-acting antiviral (DAA) therapy has revolutionized the treatment of chronic hepatitis C infection. Combination DAAs are substantially better in attaining cure than earlier interferon-based regimens. Sustained virologic response at 12 weeks (SVR12), defined, as absence of HCV RNA in plasma 12 weeks after cessation of HCV therapy, is synonymous with cure. Achieving SVR has been associated with reversal of liver fibrosis, and reduction in risk of hepatic decompensation, HCC, and liver-related mortality (Veldt et al., 2007). Under existing HCV treatment guidelines, recommendations are to treat for duration of 8-12 weeks of combination DAA therapy, which results in high rates of SVR across various viral and host characteristics (Kohli et al., 2014; AASLD/IDSA HCV Guidance Panel, 2015; European Association for the Study of the Liver 2017).

While most patients with chronic HCV infection are treated for 12 weeks, two regimens are recommended for a shorter 8-week treatment period. Ledipasvir/sofosbuvir (Harvoni) can be used for 8 weeks in HCV genotype 1 patients who are treatment naïve, without cirrhosis, non-blacks, not infected with HIV, and whose baseline HCV RNA level is <6 million IU/mL – a subset of the HCV population with a very good treatment response (Kowdley et al., 2014; AASLD/IDSA HCV Guidance Panel 2015). The more recent FDA-approved glecaprevir/ pibrentasvir (Mavyret), a fixed dose combination of NS3/4A protease inhibitor and NS5A inhibitor, can be used for 8 weeks to treat patients with DAA-naïve HCV genotypes 1-6 without cirrhosis based on data showing high SVR rates in this population (Zeuzem et al., 2018).

The high cost of HCV drugs is a barrier to treatment for many patients. Insurance providers often use a risk stratification model to prioritize who should receive treatment, generally favoring those with cirrhosis (fibrosis score of F4) over those without (Chua and Kottilil, 2017). This strategy tends to exclude treatment for younger, less advanced HCV-infected people who comprise the bulk of the untreated HCV epidemic. One way to mitigate this cost issue is the

development of a safe and effective regimen that shortens the current duration of treatment. Shorter duration of therapy could also enhance treatment adherence (Emmanuel et al., 2017).

Several clinical studies have evaluated treating patients with HCV infection for less than 8 weeks duration, with mixed results (Emmanuel et al., 2017). The SYNERGY study evaluated 50 treatment-naïve HCV genotype 1 patients treated for 4 weeks with either a 3-drug regimen (sofosbuvir, ledipasvir, NS3/4A protease inhibitor GS-9451) or 4-drug regimen (sofosbuvir, ledipasvir, GS-9451, and non-nucleoside inhibitor [NNI] GS-9669) (Kohli et al., 2015). Though well tolerated, both treatments resulted in excessive relapses and low cure rates – SVR rates of 40% (10/25) in the 3-drug group, and 20% (5/25) in the 4-drug group. In contrast, the LEPTON study evaluated patients who were either treatment-naïve or previously treated-HCV genotypes 1-3 with or without cirrhosis. Duration of therapy was 4 or 6 weeks for treatment-naïve patients without cirrhosis, 6 weeks for treatment-naïve patients with cirrhosis, and 6 or 8 weeks for previously treated patients with or without cirrhosis (Gane et al,. 2016). Approximately 4/15 (27%) treatment-naïve genotype 1 patients without cirrhosis treated for 4 weeks achieved SVR12, while 14/15 (93.3%) patients treated for 6 weeks achieved SVR12. These ultrashort treatment studies had several limitations, including small sample sizes and inclusion of patients mainly with HCV genotype 1 infection (Emmanuel et al., 2017).

1.1.2. Sofosbuvir/Velpatasvir

Sofosbuvir/velpatasvir (Epclusa) is the first fixed-dose combination drug to be approved by the FDA for the treatment of all HCV genotypes. Sofosbuvir inhibits HCV NS5B RNA-dependent RNA polymerase inhibitor, while velpatasvir inhibits HCV replication by binding to the NS5A protein (Greig 2016). Both NS5A and NS5B are essential for HCV replication. In phase 3 studies that evaluated treatment-naïve and treatment-experienced patients with or without compensated cirrhosis (ASTRAL-1 through-3), sofosbuvir/velpatasvir (SOF/VEL) treatment for 12 weeks resulted in SVR rates ranging from 95 through 99% (Feld et al., 2015; Foster et al., 2015). Among HCV patients with decompensated cirrhosis (ASTRAL-4), SVR12 rates were also acceptably high (83%) if SOF/VEL was taken for 12 weeks without ribavirin, and higher (94%) if taken with ribavirin (Curry et al., 2015). The most common adverse events (AEs), occurring in ≥ 10% of SOF/VEL-treated subjects, were headache and fatigue (Epclusa [U.S. package insert] 2017). An estimated 0.2% of subjects receiving 12 weeks of SOF/VEL treatment discontinued drug due to AEs (Curry et al., 2015; Feld et al., 2015; Foster et al., 2015; Epclusa [U.S. package insert] 2017).

Sofosbuvir/velpatasvir given for 12 weeks in ASTRAL 1-4 was also associated with high SVR rates despite the presence of pretreatment NS5A or NS5B resistance-associated variants (RAVs); in those patients with pretreatment RAVs, SVR12 was achieved in 100% (85/85) with NS5B RAVs and 97% (437/452) with NS5A RAVs (Curry et al., 2015; Feld et al., 2015; Foster et al., 2015). Sofosbuvir/velpatasvir has many favorable characteristics that may make it an ideal component of an ultrashort DAA regimen.

1.1.3. CDI-31244

CDI-31244 is an investigational agent that is a novel, highly potent, selective NNI of the HCV RNA-dependent RNA polymerase and with excellent antiviral activity across all genotypes (Cocrystal Pharma, Inc., data on file). CDI-31244 is designed to deliver high drug concentrations to the liver and is highly selective against HCV polymerase with no relevant in vitro effects against human DNA and RNA polymerases (Cocrystal Pharma, Inc., data on file). In the Phase 1b portion of the study that evaluated patients with HCV genotype 1 (Study no. CDI-31244-P1-001), CDI-31244 at a total daily dose of 400 mg (either 200 mg twice daily or 400 mg once daily) or 600 mg for 7 days resulted in mean HCV RNA viral load reductions of 3.0 $\log_{10}$ IU/mL by 48 hours. CDI-31244 as a once a day monotherapy resulted in greater mean HCV RNA viral load decline compared to dasabuvir (0.95 $\log_{10}$) the only approved NNI (Pockros 2013). As such, CDI-31244 is a strong candidate to combine with SOF/VEL to evaluate its potential as a highly effective and safe ultrashort DAA regimen.

The pharmacokinetics of CDI-32144 have been studied in single and multiple ascending doses in healthy and HCV-infected subjects (Study no. CDI-31244-P1-001). After administration of single doses ranging from 20 mg to 400 mg to healthy subjects under fasted conditions, the mean CDI-32144 plasma concentrations and values for maximum plasma concentration (C_{max}) and area under the curve to infinity ($AUC_{0-\infty}$) increased in a dose-related manner with a mean elimination half-life (t½) at the higher doses ranging from 2.91 to 12.6 hours. Administration of a 200 mg dose with a standard high fat/high calorie meal appeared to decrease the rate but not the extent of absorption. After administration of 200 mg or 400 mg once daily for 7 days to healthy subjects, there was a dose-related increase in C_{max} and AUC_{0-24} with mean t½ on day 7 of 14.0 hr (200 mg group) and 7.62 hr (400 mg group), consistent with that after a single dose.

Administration of 200 mg twice a day and 400 mg and 600 mg once daily to HCV-infected subjects resulted in dose-related increases in C_{max} and AUC for the dosing interval — AUC_{0-12} for twice daily and AUC_{0-24} for once daily. The mean t½ ranged from 15.8 to 19.8 hours, higher than that for healthy subjects. The AUC and C_{max} after dosing for 7 days were about 1.5- to 3-fold higher in HCV-infected subjects when compared with a healthy population for similar dose levels (200 mg and 400 mg) following acute (day 1) and extended exposure (day 7), and the mean t½ was longer, suggesting a possibly lower clearance in HCV-infected subjects.

The metabolism of CDI-31244 was investigated in humans using plasma samples collected from healthy volunteers who participated in the CDI-31244 Phase 1 study (Study no. CDI-31244-P1-001). The plasma samples on day 7 obtained from human subjects administered 400 mg CDI-31244 were analyzed for the presence of metabolites using liquid chromatography–mass spectrometry (LC-MS) analysis. Metabolites were structurally characterized based on their retention times, accurate mass, and the characteristics of their fragment ions. CDI-31244 was one of the most abundant circulating entities in the human plasma based on relative abundance measured by high-resolution MS peak area (23-27%). Nine metabolites of CDI-31244 were characterized in human plasma. The three most prominent metabolites were M402 or M9

(molecular mass 402; 20% abundance) formed by N-dealkylation of CDI-31244; M502 or M7 (molecular mass 502; 23-32% abundance), an O-dealkylation metabolite also seen in rat and dog plasma; and M678 or M2 (molecular mass 678; 18-25% abundance), a glucuronide conjugate of M7. There were 3 other metabolites > 1% relative abundance — M418 or M5 (molecular mass 418; 1-5% abundance), an oxidation and N-dealkylation metabolite also seen in rat plasma; M488 or M8 (molecular mass 488; 2% abundance) an O-dealkylation metabolite also seen in dog plasma; and M798 or M12 (molecular mass 798; 4% abundance), a glucuronide conjugate of CDI-31244 also seen in rat and dog plasma. All of these main human metabolites were represented in rat and/or dog plasma taken from the 14-day (Good Laboratory Practice) GLP toxicology studies.

Based on in vitro reaction phenotyping, CDI-31244 metabolism was primarily mediated by CYP3A4 (< 2% remaining over 60 minutes incubation) with a lesser contribution from CYP2C8 (60-85% remaining). CYPs 1A2, 2B6, 2C9, 2C19, and 2D6 showed minimal or no CDI-31244 turnover. Chemical inhibition demonstrated inhibition of CDI-31244 metabolism ranging between 17 to 53% by selective inhibitors for CYPs 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4, while the inhibitor for CYP1A2 had no effect. Collectively, the results of these two approaches indicate that the CYP metabolism of CDI 31244 is broadly based across the major human CYPs with the exception of CYP1A2, and suggests minimal likelihood that CDI-31244 would be involved in a CYP inhibition-mediated drug-drug interaction.

An *in vitro* study evaluated the metabolic stability of CDI-31244, sofosbuvir, and velpatasvir alone and in combination using cryopreserved human hepatocytes. No metabolic turnover was observed with velpatasvir, consistent with the reported minimal metabolic turnover of this compound in humans. Incubations of either CDI-31244 or sofosbuvir with human hepatocytes exhibited extensive metabolic turnover. Metabolic turnover data with CDI-31244 and sofosbuvir in triple combination with velpatasvir produced 20% and 30% reductions in their clearance values, respectively. Generally, low-level decreases in the metabolic turnover of CDI-31244 and sofosbuvir were found in this *in vitro* study, which in relation to the normal variability of drug plasma concentrations in humans, and the many other processes affecting drug disposition are not expected to translate into PK exposure changes *in vivo* in patients.

The urinary excretion of CDI-31244 over 120 hours was studied in 30 healthy subjects following single oral doses (20, 50, 100, 200 and 400 mg) under both fasting and fed conditions (Study no. CDI-31244-P1-001). For those subjects/cohorts in which urine concentrations were above the lower limit of quantitation, urinary excretion accounted for < 0.01% of the dose. This indicates that metabolism is the primary route of elimination of CDI-31244.

In studies in human liver microsomes, CDI-31244 had low direct inhibitory potency for CYP2B6 (IC_{50} = 33 µM), CYP2C8 (IC_{50} = 20 µM), CYP2C9 (IC_{50} = 14 µM) and CYP2C19 (IC_{50} = 2.1 µM) and minimal levels of direct inhibition (≤18% at 10 µM) for CYP1A, CYP2D6, and CYP3A. No evidence of time-dependent inhibition was observed. The mean total C_{max} on day 7

after administration of 400 mg once daily to HCV-infected subjects was 530 ng/mL, equivalent to 0.85 µM (Study no. CDI-31244-P1-001). Based on 99.2% binding-to-plasma protein, this represents an unbound concentration of 0.0068 µM. The associated AUC ratio for the most sensitive CYP (CYP2C19; IC_{50} = 2.1 µM → Ki = 1.05) is 1.003, below the threshold of 1.02 that indicates the need for a clinical DDI (drug-drug interaction) study. CDI-31244 is therefore unlikely to inhibit any of the CYP450 enzymes.

The potential inhibitory effects of CDI-31244 were studied on a range of human transporters including P-gp (P-glycoprotein), BCRP, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and MRP2. CDI-31244 showed inhibitory activity for OAT3, OATP1B1 and OATP1B3 transporters that did not indicate potential for DDI.

The anticipated unbound CDI-31244 C_{max} concentration, 0.0068 µM, for the 400 mg dose in this proposed study (calculated day 7 Phase 1b study PK data) is three orders of magnitude lower than the concentration (10 µM) that showed potential CYP2B6 induction. Consequently, no induction-mediated impact of CDI-31244 on the exposure to substrates of these CYP enzymes is predicted. However, since SOF and VEL are CYP2B6 substrates (Epclusa [U.S. package insert] 2017), the potential for reduced exposure to both drugs should be assessed by monitoring of plasma concentrations.

CDI-31244 is a substrate of P-gp, which may pose some DDI potential with drugs that are P-gp inhibitors.

More detailed information about CDI-31244 can be found in the Investigator's Brochure.

The primary objective of the current study is to evaluate the effect of 2 weeks of the highly potent NNI CDI-31244 combined with 6 weeks of SOF/VEL treatment on SVR rates in HCV genotype 1-infected subjects. In addition, the study will also evaluate kinetics of circulating HCV RNA during treatment, and the pharmacokinetics of CDI-31244 during treatment.

1.2. Risk/Benefit Assessment

The most common side effects in the phase 1a study of healthy volunteers receiving CDI-31244 were headaches (2/30 subjects, or 7%) in the single ascending dose cohort and dysgeusia (2/12 subjects, or 17%) in the multiple ascending dose cohort (Cocrystal Pharma, Inc., data on file). One healthy volunteer (receiving a single dose of CDI-31244 100 mg) experienced a grade 4 AE toxicity related to an elevated creatine kinase (CK) that occurred on study day 4 after dosing and was judged by the investigator to be related to study drug. CK-MB values were normal. This AE was not associated with signs and symptoms of myopathy, and resolved at follow-up testing on day 14. It is noteworthy that the subject had a similar asymptomatic grade 4 toxicity of elevated CK that was judged to be related to study drug in a prior open-label study with an investigational tyrosine kinase inhibitor. The most common side effects in the Phase 1b study of subjects with chronic HCV genotype 1 infection receiving CDI-31244 200 mg twice daily, 400 mg once daily,

or 600 mg once daily for 7 days were headache (4/16 subjects, 25%) and nasal congestion (2/16 subjects, 12%).

The AE data for SOF/VEL (Epclusa) in patients without cirrhosis or with compensated cirrhosis were derived from three Phase 3 clinical trials (ASTRAL-1, -2, and -3) that evaluated 1035 subjects infected with genotype 1-6 HCV, without cirrhosis or with compensated cirrhosis. Subjects received SOF/VEL for 12 weeks. The most common AEs that were judged to be related to study drug in patients receiving SOF/VEL were headache (22%), fatigue (15%), nausea (9%), asthenia (5%) and insomnia (5%) (Epclusa [U.S. package insert] 2017). Most of these AEs were mild in intensity. The proportion of subjects who permanently discontinued treatment due to AEs was 0.2% for subjects receiving SOL/VEL for 12 weeks (Epclusa [U.S. package insert] 2017). In ASTRAL-1, isolated, asymptomatic CK elevations ≥10 times ULN were reported in 1% of subjects treated with SOF/VEL and no subjects treated with placebo for 12 weeks; among subjects treated with SOF/VEL, similar CK elevations (≥ 10 times ULN) were reported in 2% of subjects in ASTRAL-2 and 1% of subjects in ASTRAL-3.

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected patients who were receiving or had completed treatment with HCV DAAs, and who were not receiving HBV therapy. HBV reactivations were characterized by an abrupt increase in HBV replication and were accompanied in some cases by acute hepatitis (i.e., increases in serum aminotransferase levels) and, in rare cases, liver failure and death (Bersoff-Matcha et al., 2017; Epclusa [U.S. package insert] 2017). As such, the current study will exclude patients with active HBV infection. In patients receiving amiodarone, coadministration of SOF-containing regimens can cause serious symptomatic bradycardia resulting in pacemaker intervention and fatal cardiac arrest (the latter with use of Harvoni [ledipasvir-sofosbuvir] (Epclusa [U.S. package insert] 2017). Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta-blocker drugs, or those with underlying cardiac comorbidities or advanced liver disease, may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Due to this concern, patients receiving amiodarone within 180 days before study entry or are expected to receive amiodarone during the study period will be excluded from the current study. Finally, there is also a potential risk for subjects to develop multiclass drug resistance if treatment in this study is unsuccessful.

There is a potential benefit for study participants of viral suppression and eradication (cure) of HCV. Achieving cure with SOF/VEL and other DAAs has resulted in reversal of liver fibrosis, as well as reductions in liver-related mortality, HCC, and liver decompensation (Westbrook and Dusheiko, 2014). Data gathered from this study may also lead to the eventual development of a new safe and effective treatment that substantially shortens the current course of treatment for patients with chronic HCV infection.

2. OBJECTIVES

- The primary objective of this study is to assess the safety, tolerability, and preliminary efficacy of short duration combination treatment with CDI-31244 plus SOF/VEL in subjects with chronic HCV genotype 1 infection.
- Safety (and tolerability) will be evaluated using adverse event, physical examination (including vital signs), electrocardiogram (ECG), and clinical laboratory data. Pharmacokinetics will be evaluated by plasma concentrations of CDI-31244, SOF, GS-331007 and VEL. Viral kinetics will be evaluated by serial plasma HCV levels.
- Efficacy will be evaluated by HCV RNA levels by the following primary and secondary endpoints:

Primary efficacy endpoint:

- Proportion of subjects who achieve sustained virologic response 12 weeks after completion of treatment (SVR12).

Secondary efficacy endpoints:

- Proportion of subjects who achieve sustained virologic response 24 weeks after completion of treatment (SVR24).
- Time to achieve HCV RNA levels below the lower limit of quantification (LLOQ).
- Proportion of subjects with HCV RNA <LLOQ after Day 7 and Day 14 ofCDI-31244 plus SOF/VEL treatment.
- Proportion of subjects with HCV RNA <LLOQ after Day 7 and Day 14 ofCDI-31244 plus SOF/VEL treatment by genotype 1a or 1b.

Exploratory endpoints (using stored blood) will include:

- Immunologic, virologic, and host genetic/proteomic predictors of response to therapy.
- Effect of therapy on peripheral markers of T cell activation.

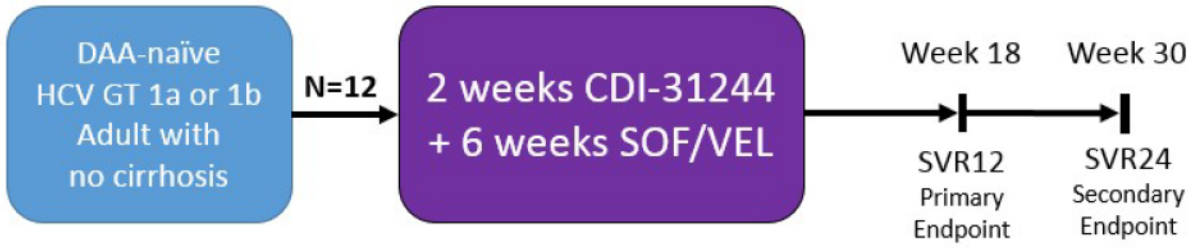
3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a single center, open-label phase 2a study to evaluate the safety, tolerability, and preliminary efficacy of treatment with 2 weeks of an oral NNI CDI-31244 combined with 6 weeks of SOF/VEL in adult subjects with chronic HCV genotype 1 virus infection. One site is planned to participate: Institute of Human Virology (IHV), University of Maryland, Baltimore, MD. Clinic visits will occur at screening and baseline, and through study week 30. Adverse events will be collected through study week 30.

Safety evaluations will consist of adverse event, physical examination (including vital signs), ECG, and clinical laboratory data. Efficacy and viral kinetics will be evaluated by HCV RNA levels. Pharmacokinetics will be evaluated by plasma CDI-31244, SOF, GS-331007 and VEL concentrations.

Figure 1: Illustration of Study Design



3.2. Outline of Visit Schedule

Also see Schedule of Events, Appendix A.

3.2.1. Screening and Baseline Evaluations

3.2.1.1. Screening Evaluations (Day –42 to -7)

The following screening assessments must be done to determine subject eligibility. Written consent will be obtained before conducting any study procedures.

- Screen for inclusion/exclusion criteria (see Section 5).
- Medical history.
- Physical examination, including weight, height, and vital signs (blood pressure, respiratory rate, heart rate, and temperature).
- Metabolic panel (serum concentrations of sodium, potassium, chloride, total bilirubin, alkaline phosphatase, alanine transaminase [ALT], aspartate transaminase [AST], blood urea nitrogen [BUN], creatinine, uric acid, calcium, glucose, total protein, albumin, cholesterol, lipase, creatine kinase [CK]).

- Complete blood count [hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume (MCV), segmented neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, cell morphology].
- Coagulation (Coagulation: prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR]).
- 12-lead electrocardiogram (ECG).
- FibroTest/FibroSure test, if no assessment of liver fibrosis by biopsy, fibroscan, or FibroTest/FibroSure has been conducted within 1 year of screening.
- Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb). Hepatitis B DNA PCR will be done if positive for HBcAb but negative for both HBsAg and HBsAb.
- Human immunodeficiency virus (HIV) antibody.
- Plasma HCV RNA level.
- HCV genotyping.
- Urine toxicology screen (for amphetamines and cocaine).
- Serum beta human chorionic gonadotropin (hCG) pregnancy test for females of childbearing potential (defined as a woman who is physiologically capable of becoming pregnant).
- Collect concomitant medication information.

3.2.1.2. Baseline Evaluations and First Dose of Study Drug (Day 1)

Screening tests (e.g., select laboratories) must be available before the subject is eligible for study participation. Once screening is completed and the subject meets all eligibility criteria, the subject will obtain baseline evaluations. Study drug administration may occur after completion of all baseline procedures.

Before Study Drug Administration:

- Review eligibility criteria and confirm eligibility of subject.
- Obtain complete medical history.
- Physical examination, including weight and vital signs (blood pressure [BP], respiratory rate [R], heart rate [HR], and temperature [T]).
- Collect concomitant medication information
- 12-lead ECG.

- Plasma HCV RNA level.
- Metabolic panel.
- Complete blood count.
- Coagulation.
- Urine beta hCG pregnancy test for females of childbearing potential.
- Blood for PAXgene RNA and DNA analysis.
- *IL28B* genotyping.
- Blood for HCV resistance assays.
- Blood sample for measurement of plasma concentrations of CDI-31244, SOF, GS-331007 and VEL.
- Blood for storage of plasma, serum, and peripheral blood mononuclear cells (PBMCs) for future research purposes.

Study Drug Administration (and Post-Study Drug Assessment):

- Administer first dose of CDI-31244 and SOF/VEL.
- Dispense study drug supply (remainder of 7-day supply).
- Reinforce study drug instruction: subjects are to take 8 CDI-31244 capsules and 1 tablet of SOF/VEL upon awakening with at least 8 oz. of plain water.
- Plasma HCV levels at 2, 4, and 6 hours after first dose of study drug.
- Dispense Study Drug Diary.
- Collect adverse event information
- Collect concomitant medication information.

3.2.2. Additional Study Evaluations

3.2.2.1. Days 2 and 3 Visits

- Obtain interval medical history.
- Obtain weight and vital signs (BP, R, HR, T).
- Plasma HCV RNA level.
- Collect adverse event information.
- Collect concomitant medication information.

- Evaluate Patient Diary and number of used and unused capsules/tablets.

3.2.2.2. Day 7 Visit

- Obtain interval medical history.
- Conduct targeted physical examination (if needed), including weight and vital signs (BP, R, HR, T).
- Plasma HCV RNA level.
- Urine beta hCG pregnancy test for females of childbearing potential.
- Metabolic panel.
- Complete blood count.
- Coagulation.
- Blood for PAXgene RNA analysis.
- Blood for storage of plasma, serum, and PBMCs.
- Collect adverse event information.
- Collect concomitant medication information.
- Evaluate Patient Diary and number of used and unused capsules/tablets.
- Dispense study drug supply (7-day supply).

3.2.2.3. Day 10 Visit

- Obtain interval medical history.
- Conduct weight and vital signs (BP, R, HR, T).
- Plasma HCV RNA level.
- Collect adverse event information.
- Collect concomitant medication information.
- Evaluate Patient Diary and number of used and unused capsules/tablets.

3.2.2.4. Day 14 Visit

This day is the end of treatment with CDI-31244 for all subjects.

Subjects will be asked to delay their study drug on day 14 until their study visit to accommodate PK sampling for plasma CDI-31244, SOF, GS-331007, and VEL levels.

- Obtain interval medical history.

- Conduct targeted physical examination (if needed), including weight and vital signs (BP, R, HR, T).
- Blood sample for measurement of plasma concentrations of CDI-31244, SOF, GS-331007, and VEL at 0 (pre-dose), 1, 2, 4, 6, 8, and 12 hours after dosing.
- Plasma HCV RNA level.
- Urine beta hCG pregnancy test for females of childbearing potential.
- Metabolic panel.
- Complete blood count.
- Coagulation.
- Blood for storage of plasma, serum, and PBMCs.
- Collect adverse event information.
- Collect concomitant medication information.
- Evaluate Patient Diary and number of used and unused capsules/tablets.
- Dispense study drug supply (28-day supply of SOF/VEL).

3.2.2.5. Day 15 Visit

- Blood sample for measurement of plasma CDI-31244, SOF, GS-331007, and VEL concentration (approximately 24 hr after day 14 dosing).

3.2.2.6. Week 3 Visit (± 2 days)

- Obtain interval medical history.
- Conduct targeted physical examination (if needed), including weight and vital signs (BP, R, HR, T).
- Plasma HCV RNA level.
- Blood sample for measurement of plasma concentrations of CDI-31244, SOF, GS-331007, and VEL.
- Metabolic panel.
- Complete blood count.
- Coagulation.
- Collect adverse event information.
- Collect concomitant medication information.

- Evaluate Patient Diary and number of used and unused capsules/tablets.

3.2.2.7. Week 6 Visit (± 3 days)

This visit describes assessments for their end of treatment visit.

- Obtain complete medical history.
- Conduct complete physical examination, including weight and vital signs (BP, R, HR, T).
- Plasma HCV RNA level.
- Blood sample for measurement of plasma concentrations of CDI-31244, SOF, GS-331007, and VEL.
- Urine beta hCG pregnancy test for females of childbearing potential.
- Metabolic panel.
- Complete blood count.
- Coagulation.
- Urinalysis.
- Blood for PAXgene RNA analysis.
- Blood for storage of plasma, serum, and PBMCs.
- 12-lead ECG.
- Evaluate Patient Diary and number of used and unused tablets.
- Collect adverse event information.
- Collect concomitant medication information

For all subjects who terminate study drug prematurely, continued assessments should occur *if consent to do so has not been withdrawn*. For subjects who terminate the study early, the subject should complete the evaluations for the study week 6 visit *provided that written consent to do so has not been withdrawn*.

3.2.2.8. Week 8, 10, and 14 Visits (± 3 days)

This visit describes post-treatment assessments for all subjects.

- Obtain interval medical history.
- Conduct targeted physical examination (if needed), including weight and vital signs (BP, R, HR, T).

- Plasma HCV RNA level.
- HCV resistance assay if HCV RNA >1,000 IU/mL.
- Metabolic panel (week 10 only).
- Complete blood count (week 10 only).
- Coagulation (week 10 only).
- Blood for storage of plasma, serum, and PBMCs.
- Collect adverse event information (week 8 and 10 only).
- Collect concomitant medication information.

3.2.2.9. Week 18 Visit (± 7 days)

This visit describes assessments for SVR12, the primary endpoint of the study.

- Obtain interval medical history.
- Conduct targeted physical examination (if needed), including weight and vital signs (BP, R, HR, T).
- Plasma HCV RNA level.
- HCV resistance assay if HCV RNA >1,000 IU/mL.
- Metabolic panel.
- Complete blood count.
- Coagulation.
- Blood for storage of plasma, serum, and PBMCs.
- Collect concomitant medication information.

3.2.2.10. Week 30 Visit (± 14 days)

This visit describes assessments for end of study for all subjects.

- Obtain complete medical history.
- Conduct complete physical examination, including weight and vital signs (BP, R, HR, T).
- Plasma HCV RNA level.
- HCV resistance assay if HCV RNA >1,000 IU/mL.
- Metabolic panel.

- Complete blood count.
- Coagulation.
- Blood for storage of plasma, serum, and PBMCs.
- Collect concomitant medication information.

3.2.2.11. Retreatment Visits (± 7 days)

This describes assessments during retreatment with standard of care regimen using SOF/VEL/VOX for 12 weeks. Study visits at initiation of retreatment, 4-weeks after initiation of retreatment, at the end of the 12-week retreatment period, at 4 weeks after completion of treatment, and at 12 weeks after completion of treatment.

- Obtain interim medical history.
- Conduct targeted physical examination (if needed), including weight and vital signs (BP, R, HR, T).
- Plasma HCV RNA level.
- Metabolic panel.
- Complete blood count.
- Collect adverse event information (except at 12 weeks after completion of treatment).
- Collect concomitant medication information.

SOF/VEL/VOX (4-week supply) will be dispensed at initiation of retreatment and at 4 weeks after initiation of retreatment (remaining 8-week supply). All bottles and unused pills will be returned by subjects to the study team by the end of the retreatment period visit. The most recent labs for each subject (plasma HCV RNA levels, metabolic panel, and complete blood count) will be used for the purpose of the subject's pre-SOF/VEL/VOX baseline.

4. DISCUSSION OF DESIGN

This is a single center, open-label phase 2a study to evaluate the safety, tolerability, and preliminary efficacy of treatment with 2 weeks of an oral NNI CDI-31244 combined with 6 weeks of SOF/VEL in adult subjects with chronic HCV genotype 1 virus infection. This design allows the most direct assessment of the safety and preliminary efficacy of CDI-31244 combined with SOF/VEL in this patient population.

Dose: The use of combined CDI-31244 with SOF/VEL is unknown. CDI-31244 is an investigational agent that is a novel, potent, and selective NNI of the HCV viral RNA polymerase. CDI-31244 has been evaluated in a phase 1a/1b randomized, placebo-controlled, double-blind study involving both healthy volunteers and patients with chronic HCV infection (Study no. CDI-31244-P1-001). The phase 1a portion of the study was conducted in healthy volunteers and involved two parts: a single ascending dose (SAD) and a multiple ascending dose (MAD) phase. In the SAD phase, 40 healthy volunteers (3:1 ratio CDI-31244: placebo) were enrolled. Subjects received single doses of CDI-31244 (cohorts of 20 mg, 50 mg, 100 mg, 200 mg, and 400 mg). In the MAD phase, 16 healthy volunteers were enrolled and randomized into 3 groups to receive study drug once daily for 7 days; 6 subjects received CDI-31244 200 mg; 6 received CDI-31244 400 mg; and 4 received placebo. Results of the phase 1a healthy volunteer SAD/MAD study showed that no serious AEs were reported and no discontinuations due to AEs occurred. One healthy volunteer (receiving a single dose of CDI-31244 100 mg) had a grade 4 toxicity AE related to an elevated CK that occurred on study day 4 and was judged by the investigator to be associated with study drug. This AE was not associated with signs and symptoms, and resolved on follow-up testing on day 14. CK-MB was normal. It is noteworthy that the subject had a similar asymptomatic grade 4 toxicity of elevated CK in a prior study involving an investigational tyrosine kinase inhibitor. The AE incidence rates in the SAD phase were 23% for the CDI-31244 groups combined and 50% for the placebo group; in the MAD phase, AE incidence rates were 25% for the CDI-31244 groups combined and 50% for the placebo group.

The phase 1b portion of the study enrolled 20 treatment-naïve subjects with HCV genotype 1 and an HCV RNA viral load ≥ 5 $\log_{10}$ IU/mL. This study had 3 dose-escalation phases involving the following CDI-31244 regimens: (1) 200 mg twice daily for 7 days (n=3), (2) 400 mg once daily for 7 days (n=7), and (3) 600 mg once daily for 7 days (n=6). Four subjects received placebo. One subject on 400 mg QD was withdrawn after a single dose and was not included in the PK/PD analysis. There were no serious AEs reported or discontinuations due to AEs. Adverse event incidence rates were 75% for the combined CDI-31244 groups and 100% for the placebo group. In addition, similar declines in HCV RNA viral load within 48 hours after initiation of treatment (3-log) were observed in the CDI-31244 400 mg total daily dose cohorts (200 mg twice daily, 400 mg once daily) and 600 mg cohort. No systemic accumulation of CDI-31244

was observed after 7-day treatment. This data supports the use of CDI-31244 400 mg as the maximum daily dose in the current study to achieve maximal reduction in viral load while minimizing CDI-31244 exposure.

Sofosbuvir/velpatasvir (Epclusa) is an FDA-approved fixed-dose combination of sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A replication complex inhibitor. This combination was approved by the FDA in 2016 and is indicated for the treatment of (a) adult patients with chronic HCV genotype 1 through 6, both with and without cirrhosis, and (b) adult patients with decompensated cirrhosis for use in combination with ribavirin. The recommended duration of treatment is 12 weeks. The present study will use the fixed dose combination for a period of 6 weeks.

Safety Endpoints: The safety assessments used in this trial are standard assessments for Phase 2a studies evaluating the safety of repeated dosing.

Efficacy Endpoints: Assessment of quantitative HCV RNA in plasma is the standard procedure for determining effectiveness of HCV therapy (including cure at SVR12). Both primary and secondary efficacy endpoints use quantitative HCV RNA levels as the main assessment measure. Additional assessments in the current study (e.g., assays to detect resistance-associated variants against NS5A and NS5B, and viral kinetic assays) are also standard measures in trials of HCV therapies that add additional value.

Length of Assessment: Efficacy assessments will be evaluated through 24 weeks following completion of treatment. This period spans a total of 30 weeks for all subjects. The 6-week period of combination CDI-31244-SOF/VEL therapy is necessary to determine whether HCV cure is possible with durations shorter than currently approved regimens. Absence of HCV viremia after 12 weeks of completion of therapy is the standard for determination of cure.

5. STUDY POPULATION

The investigators participating in this study have expertise in the diagnosis and management of patients with HCV. The participating center is the Institute of Human Virology, University of Maryland, Baltimore, MD. Subjects will be recruited from investigator and subinvestigator (associate investigator) clinical practices and referring physicians.

Investigators will diagnose subjects with HCV based on history, physical examination, and laboratory studies. Inclusion criteria for this study include patients (age ≥ 18 years) with chronic HCV genotype 1a or 1b. A maximum of 4 subjects with genotype 1b will be enrolled.

Participation in this study is voluntary. The nature of the study will be fully explained to each subject during the informed consent process. The subjects will have the opportunity to ask questions. An informed consent document will then be signed by the subject and the person performing the consent discussion, and retained by the investigator according to Good Clinical Practice (GCP). All documents will be retained by the investigator according to GCP. A copy of the signed informed consent document will be given to the subject.

Eligibility for enrollment will be based on the results of screening for the following inclusion and exclusion criteria.

5.1. Inclusion Criteria

Patients may be included in the study only if they meet **all** of the following criteria:

1. Age ≥ 18 years at screening.
2. Documented chronic HCV infection based on **any** of the following:
   - Anti-HCV antibody positivity for at least 6 months prior to study enrollment.
   - HCV genotype results for at least 6 months immediately prior to study enrollment.
   - HCV RNA present in plasma by a sensitive and specific assay for at least 6 months prior to study enrollment.
   - Histologic evidence of chronic HCV infection.
3. HCV genotype 1a or 1b infection by HCV genotyping performed at screening. (Note: No more than four subjects with HCV genotype 1b will be enrolled).
4. Serum HCV RNA >1,000 IU/mL during screening.
5. Must have a primary care provider(s) for medical management.
6. Absence of advanced fibrosis or cirrhosis by liver biopsy, fibroscan (<8 kPa) or FibroTest/FibroSure (F2 or lower) within 1 year of screening. If the preceding fibrosis tests are not available, FibroTest/FibroSure will be done at screening.
7. Females of childbearing potential must have a negative serum pregnancy test at screening and agree to use a medically reliable method of contraception until study completion.

Effective contraception methods include: total abstinence (when lifestyle or sexual orientation of the subject precludes intercourse with a male partner); female sterilization; barrier methods of contraception (diaphragm or cervical/vault caps with spermicidal foam, gel, cream, or vaginal suppository); use of oral, injected, or implanted hormonal contraception or other forms that have comparable efficacy (failure rate <1%); or placement of an intrauterine device or intrauterine system.

8. Male subjects must be willing to abstain from heterosexual intercourse or use a condom with spermicide throughout the study period.
9. Be willing to have blood samples stored for future research.
10. Available for at least 30 weeks for study participation.
11. Written informed consent must be obtained before any study procedure is performed.

5.2. Exclusion Criteria

Patients meeting any of the following criteria will not be eligible to participate in the study:

1. Nursing or pregnant.
2. Active hepatitis B virus (HBV) infection, defined as positive hepatitis B surface antigen (HBsAg) at screening. If subject is negative for both HBsAg and hepatitis B surface antibody (HBsAb), but hepatitis B core antibody (HBcAb)-positive, plasma HBV DNA levels will be checked and subject excluded if HBV DNA detected.
3. Human immunodeficiency virus (HIV) infection.
4. History of use of any HCV direct-acting antiviral therapy.
5. Clinically significant illness other than HCV that may interfere with subject treatment, assessment, safety, or compliance with the protocol in the judgment of the investigator.
6. Positive urine screen for amphetamines or cocaine.
7. Known current heroin, morphine, or methadone use. Current narcotic use other than methadone is acceptable if medically indicated (documented in medical records) and prescribed by a physician.
8. Substance abuse, including alcohol abuse, which in the opinion of the investigator is likely to interfere with medication adherence or study compliance.
9. Gastrointestinal disorder that could interfere with the absorption of the study drug (e.g., structural defect, digestive failure or enzyme deficiencies with the exception of lactose intolerance) and/or history of bariatric surgery.
10. Poor venous access interfering with required study blood collection.
11. Significant history of drug allergy (such as anaphylaxis or hepatotoxicity) to the study medications.
12. History of clinically significant chronic liver disease due to other etiology (e.g., hemochromatosis, autoimmune hepatitis, Wilson's disease, α1-antitrypsin deficiency,

alcoholic liver disease, known greater than moderate non-alcoholic steatohepatitis, and toxin exposures).

13. Use of herbal/natural remedies for potential benefit to the liver within 30 days before study entry.
14. Treatment with amiodarone within 180 days before study entry.
15. Treatment with digoxin within 30 days before study entry.
16. Treatment with rifabutin, rifampin, rifapentine, phenytoin, phenobarbital, St. John's wort, carbamazepine, oxcarbazepine, rosuvastatin, or atorvastatin within 10 days before study entry. However, switching to another statin is acceptable.
17. Chronic systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days before study entry. Inhaled steroids are permitted per Investigator's discretion.
18. Screening or baseline electrocardiogram (ECG) with clinically significant findings.
19. QTcF (QT interval corrected using Fridericia's formula) > 450 msec at screening.
20. Clinically significant hematological and biochemical values at screening that may interfere with subject treatment, assessment, safety, or compliance with the protocol in the judgment of the investigator, including:
    - Absolute neutrophil count (ANC) <1,000 cells/mm^3.
    - Hemoglobin level < 10 g/dL.
    - Platelet count < 100,000 cells/mm^3.
    - Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2.
    - ALT or AST level ≥ 5 times upper limit of normal (ULN).
    - Direct bilirubin level ≥1.5 times ULN.
21. History of hepatocellular carcinoma (HCC).
22. History of malignant disease within previous 5 years (except for adequately treated basal cell carcinoma).
23. History of clinically significant myopathy.

5.3. Removal of Subjects from Study Drug or Assessment

5.3.1. Study Drug Discontinuation

A subject must prematurely discontinue study drug under any of the following circumstances:

- The subject wishes study drug to be discontinued for any reason.
- The investigator wishes the subject to discontinue study drug, especially but not limited to the investigator concluding that further treatment puts the subject at unacceptable risk or study noncompliance.

- The subject develops a condition or begins therapy that would have excluded entry into study.
- The subject prematurely fails efficacy ("virologic failure") based on any of the two following criteria, which must be confirmed by a repeat test within 7 days:
  - HCV RNA > LLOQ after 2 prior consecutive HCV RNA values < LLOQ.
  - Greater than 1 $\log_{10}$ increase in HCV RNA from nadir.
- The subject has evidence of a severe drug allergy such as signs of anaphylaxis.
- An AE that is Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events grade 3 or greater toxicity that is related to study drug in the judgment of the investigator.

A subject has the right to discontinue study drug treatment at any time for any reason without prejudice to future medical care by the investigator or other physician at the institution. A subject who discontinues study drug should complete all scheduled study visits *provided that written consent to do so has not been withdrawn*. Subjects who prematurely discontinue study drug may be replaced.

5.3.2. Subject Withdrawal from the Study

A subject must be withdrawn from the study (and discontinue any study drug) if the subject requests such study discontinuation. The reason for withdrawal must be recorded in the subject's case report form (CRF). If possible, the subject should complete the evaluations for study week 12 visit *provided that written consent to do so has not been withdrawn*. Subjects who withdraw from the study may be replaced.

5.4 Retreatment

Subjects who have virologic (treatment) failure during the 6-week study drug treatment period, defined as either HCV RNA > LLOQ after 2 consecutive HCV RNA values < LLOQ or > 1 $\log_{10}$ increase in HCV RNA from nadir, will be discontinued from study drug treatment (Section 5.3.1). These subjects will receive additional treatment ("retreatment") with standard of care regimen using sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) 400 mg/100 mg/100 mg once daily for 12 weeks with additional follow-up through 12 weeks after cessation of treatment (SVR12).

Subjects who complete the 6-week treatment period will be considered to have virologic (treatment) failure if they have detectable HCV RNA at the next study visit and thereafter throughout the study. These subjects will receive additional treatment ("retreatment") with standard of care regimen using sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) 400 mg/ 100 mg/100 mg once daily for 12 weeks with additional follow-up through 12 weeks after cessation of treatment (SVR12).

Subjects receiving retreatment will have study visits at 4-weeks after initiation of retreatment, at the end of the 12-week retreatment period, at 4 weeks after completion of treatment (SVR4), and at 12 weeks after completion of treatment (SVR12). Procedures during retreatment are detailed in Section 3.2.2.11.

HCV resistance assays will be obtained in both subjects with virologic (treatment) failure during study drug treatment or in the post-treatment follow-up period.

5.5 Study Stopping Rules

The study will be stopped if 3 subjects (either during the treatment period or follow-up) are virologic (treatment) failures/relapse. In this situation, subjects receiving CDI-31244 will be discontinued from CDI-31244. Subjects receiving SOF/VEL will continue to receive SOF/VEL to complete a 12 week course of treatment.

6. TREATMENTS

6.1. Subject Assignment

This is an open-label study and all eligible patients will receive 2 weeks of CDI-31244 treatment concurrent with 6 weeks of SOF/VEL treatment.

6.2. Method of Assignment to Treatment

This is an open-label study.

6.3. Materials and Supplies

6.3.1. Formulation, Packaging, and Labeling

Study drug will be provided to the subject in bottles from the investigator through the participating hospital's outpatient pharmacy during various times through the study period. CDI-31244 is provided as 50 mg capsules (Cocrystal Pharma, Inc.). Epclusa (SOF 400 mg/VEL 100 mg) is commercially available as a fixed-dose single combination tablet (Gilead Sciences, Inc.).

Table 1: Study Drug Treatment and Packaging

Treatment	Study Drug	Frequency	Packaging
400 mg CDI-31244	Eight (50 mg) capsules	Once daily	Bottle
Epclusa (SOF/VEL)	One 400 mg/100 mg tablet	Once daily	Bottle

Study drug bottle will contain the following information:

- A precautionary statement that the investigational product is for limited use.
- Lot number.
- Storage conditions.
- Statement regarding date for reanalysis or retest.

6.3.2. Storage and Handling

The study drug will be provided to subjects in bottles. CDI-31244 should be stored at controlled room temperatures between 20º and 25 ºC (68-77 ºF). Epclusa (SOF/VEL) should be stored below 30 °C (86 ºF). No other special handling is required. Subjects will be instructed to return bottles and any unused study drug to the investigator at specified study visits.

6.3.3. Final Disposition of Clinical Supplies

At the end of the study, final study drug supply and accountability records will be reconciled as to drug shipped, drug consumed, and drug remaining. Any discrepancies noted will be documented.

Subject accountability for study drug will be ensured through subject interviews (during visits), diaries, and study drug reconciliation at selected visits before dispensing drug supply for the next visit interval. At selected clinic visits, subjects will be asked to return any unused study drug to the study site. Final drug accountability reconciliation will be performed at the subject visit occurring at the end of therapy or at early discontinuation. Unused study drug will be destroyed.

6.4. Dosage Administration

Following initial dosing on day 1, the investigator will provide the subject with the remainder of the 7-day study drug supply to continue on the following day. Subjects will receive an additional 7-day supply of study drug from the investigator at day 7 study visit. On day 14 visit, all subjects will receive an additional 28-day supply of SOF/VEL to complete their 6-week treatment regimen.

Subjects will be instructed to take study drug (8 capsules CDI-31244 plus 1 tablet SOF/VEL, or 1 tablet of SOF/VEL) with at least 8 oz. of plain water once daily in the morning throughout the treatment period. Subjects will be asked to delay their dose of study drug on day 14 until their study visit to allow for a pre-dose blood draw for plasma CDI-31244 concentrations.

The investigator is responsible for explaining the correct use of the study drug to the subject, verifying that instructions are followed properly, maintaining accurate records of study drug dispensing, and collection of all unused study drug, including empty drug packaging.

Subjects will be instructed to contact the investigator as soon as possible if a complaint or problem with the study drug or drug delivery system exists, so that the situation can be assessed.

6.5. Blinding

This is an open-label study. Both the subjects and selected study personnel with direct contact with the subject will know which study drug (CDI-31244, SOF/VEL) is administered.

6.6. Concomitant Therapy

Drugs that are inducers of P-gp and/or moderate-to-potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may significantly decrease plasma concentrations of CDI-31244, SOF or VEL, leading to potentially reduced therapeutic effect of CDI-31244 and Epclusa (Epclusa package insert, 2017). Velpatasvir is an inhibitor of drug transporters P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, and OATP2B1. As a result, coadministration of Epclusa (SOF/VEL) or CDI-31244 with drugs that are substrates of these transporters may increase the exposure of such drugs. Treatment with the following drugs is either prohibited or to be used with caution due to the potential for drug-drug interactions that may result in reduced drug efficacy or increase risk of AEs. Subjects receiving a prohibited medication during the study should be discontinued from study drug.

Table 2 is not all-inclusive and the use of other concomitant medications should be done with caution based on risk of potential drug-drug interactions. Questions about use of study drug with concomitant medications not listed in Table 2 can be directed to the sponsor.

Table 2: Medications that are Prohibited or to be Used with Caution

Drug Class	**Prohibited Agents**	**Clinical Comment**
Antiarrhythmics	amiodarone	Coadministration of amiodarone with SOF may result in serious symptomatic bradycardia. The mechanism is unknown.
Antiarrhythmics	digoxin	Coadministration of SOF/VEL may increase the concentration of digoxin.
Anticonvulsants	carbamazepine, phenytoin phenobarbital, oxcarbazepine	Coadministration is expected to decrease concentration of both SOF and VEL, leading to reduced therapeutic effect of SOF/VEL.
Antimycobacterials	rifabutin, rifampin, rifapentine	Coadministration is expected to decrease concentration of both SOF and VEL, leading to reduced therapeutic effect of SOF/VEL.
Herbal Supplements	St. John's wort (*Hypericum perforatum*)	Coadministration of SOF/VEL with St. John's wort, a P-gp inducer, is not recommended due to decreased concentration of SOF and VEL.
HMG-CoA Reductase Inhibitors	rosuvastatin, atorvastatin	Coadministration may significantly increase concentration of rosuvastatin and atorvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis.
Drug Class	**Use with Caution**	**Clinical Comment**
Antacids	Tums, Maalox, etc.	Antacid and SOF/VEL administration should be separated by 4 hr to avoid decreased concentration of VEL.
H2-receptor antagonists	nizatidine, famotidine, cimetidine, ranitidine	H2-receptor antagonists may be administered simultaneously with or 12 hours apart from SOF/VEL at dose that does not exceed dose comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors	dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	Coadministration of proton-pump inhibitors is not recommended. If medically necessary to coadminister, SOF/VEL should be administered with food and 4 hr before omeprazole 20 mg. Use of other proton-pump inhibitors has not been studied with SOF/VEL.

7. ADVERSE EVENT REPORTING

7.1. Definition of Adverse Event

For purposes of this trial, an AE will be defined as **any** new unfavorable or unintended sign, symptom, or disease or change of an existing condition, which occurs during or after treatment, whether or not considered treatment-related. If clinically significant laboratory values lead to or are associated with clinical symptom(s), the diagnosis should be reported as an AE. Lack of drug effect is not an AE in clinical trials because the purpose of the clinical trial is to establish drug effect.

Prior to enrollment, study site personnel will note the occurrence and nature of each subject's medical condition(s) in the appropriate section of the CRF. During the remainder of the study, site personnel will again note any change in the condition(s) and the occurrence and nature of any adverse events.

If a subject experiences an AE after the informed consent document is signed (entry) but the subject is never assigned to treatment (enrollment), the event will only be reported if the investigator believes that the event may have been caused by a protocol procedure.

All AEs occurring after the subject has entered the study (that is, after the informed consent document is signed) must be recorded in the CRF. If the study drug is discontinued for a subject, study site personnel must report and clearly document the circumstances and data leading to any such discontinuation, using designated CRFs. For AEs, the subject should be followed until the event resolves or stabilizes, with frequency of follow-up at the discretion of the investigator.

In cases where the investigator notices an unanticipated benefit to the subject, study site personnel should enter "unexpected benefit" with the actual event term (for example, the complete actual term would be "unexpected benefit—sleeping longer").

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported for tracking purposes. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

7.1.1. Reporting Procedures for All Adverse Events

Investigators are responsible for monitoring the safety of subjects who have entered this study and noting any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The investigator is responsible for appropriate medical care of subjects during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that caused the subject to discontinue the study. The subject should be

followed until the event is resolved or explained. Frequency of follow-up is left to the discretion of the investigator.

Adverse event information will be collected through 4 weeks after the completion of treatment for all subjects. Subjects who discontinue study drug at any time will have AEs collected through 4 weeks after the last study drug dose, provided consent to continue in the study has not been withdrawn.

The investigator is responsible for assessing and recording all adverse experiences. Each adverse experience will be recorded and classified for intensity, seriousness, and causality. All AEs either observed by the investigator or reported by the subject will be recorded regardless of causality. The investigator will follow the subject until an AE resolves or stabilizes.

It is the responsibility of the site investigator to report AEs to the IRB that constitute Reportable New Information within 5 working days of identification as per local IRB requirements.

7.1.2. Adverse Event Severity

The Division of AIDS (DAIDS) Table for "Grading the Severity of Adult and Pediatric Adverse Events" version 2.1 (March 2017) will be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. If the experience is not covered in the DAIDS criteria, the following guidelines should be used to grade severity:

- Mild (grade 1): Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
- Moderate (grade 2): Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicate.
- Severe (grade 3): Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
- Life-threatening (grade 4): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

The term "severe" is a measure of intensity and a severe AE is not necessarily serious.

7.1.3. Adverse Event Relationship to Study Drug

The relationship of an AE to the study drug should be based on the judgment of the investigator and assessed using the following the guidelines:

- Definitely: Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
- Probably: An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be

explained by the known characteristics of the subject's clinical state or by other interventions.

- Possibly: An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
- Unrelated: An event that can be determined with certainty to have no relationship to the study drug.

7.1.4. Serious Adverse Event Definition and Reporting Procedures

Any AE that meets the definition of serious noted below and occurs in a subject during the course of the study must be reported to the sponsor by telephone **within 24 hours** of the investigator becoming aware of the event. In addition, a serious adverse event (SAE) form must be completed by the investigator and faxed to the study sponsor **within 24 hours** of the investigator becoming aware of the event:

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In addition, the site investigator must report SAEs to their local IRB in accordance with the IRB's standard operating procedures and policies.

An SAE is defined as an AE that suggests a significant hazard or side effect, regardless of the relationship to study drug. An SAE includes, but may not be limited to, any event that:

- Results in death.
- Is life-threatening. This definition implies that the subject, in the view of the investigator, is at immediate risk of death from the event. It does not include an event that, had it occurred in a more serious form, might have caused death.
- Requires inpatient hospitalization or prolongs existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly or birth defect. This serious criterion applies if a subject exposed to an investigational product gives birth to a child with a congenital anomaly or birth defect.

Medical and scientific judgment will be exercised in deciding whether classification of an AE as serious is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the outcomes listed in the definition above. These should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependence or abuse.

Serious adverse events occurring after a subject is discontinued from the study will only be reported if the investigator believes that the event may have been caused by the study drug or a protocol procedure.

For the purpose of expedited reporting to regulatory agencies, the sponsor will be responsible for reporting any AE that is serious, unexpected, and believed to be related to study drug. An AE or suspected adverse reaction is considered "unexpected" if it is not consistent with the risk information described in the general investigational plan, investigator brochure, or elsewhere in the current investigational new drug application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure or investigational drug application referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure or investigational drug application listed only "cerebral vascular accidents."

7.1.5. Laboratory Tests

Clinical laboratory tests will be performed at the times specified in the Study Schedule (see Appendix A). All clinical laboratory assessments will be analyzed through the participating site's local laboratory or designee.

Laboratory values that fall outside a clinically accepted reference range or values that differ significantly from previous values must be further evaluated by the investigator. Investigators must document their review of each laboratory report by signing or initialing and dating each report.

Clinically significant laboratory abnormalities will be reported as AEs.

7.1.6. Safety Monitoring

The sponsor or designees will monitor safety data throughout the course of the study. The sponsor will review SAEs within time frames mandated by regulatory requirements and will review trends, laboratory analytes, and AEs at periodic intervals.

8. QUALITY CONTROL AND QUALITY ASSURANCE

The investigator agrees to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standard of GCP; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The investigator must allow study-related monitoring, audits, and inspection by the IRB, sponsor (or designee), government regulatory agencies, and, if applicable, University compliance and quality assurance groups of all trial-related documents and procedures.

The investigator shall prepare and maintain accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations.

9. DATA ANALYSIS METHODS

9.1. Determination of Sample Size

No formal sample size calculations were done. A total of 12 subjects with treatment-naïve chronic HCV genotype 1 (either 1a or 1b) is consistent with the number of subjects in proof-of-concept pilot studies that evaluate novel therapies for HCV viremia (and cure) in patients with chronic HCV infection.

9.2. Main Efficacy Variable

9.2.1. Quantitative Plasma HCV Levels

HCV genetic material (RNA) testing uses polymerase chain reaction (PCR) to identify an active hepatitis C infection. HCV quantitative testing (also called viral load) is the standard measure used before and during treatment to assess the benefit of treatment (as well as to measure viral kinetics).

9.3. Safety Variables

Safety evaluations will include collection of adverse event, physical examination, vital sign, ECG, and clinical laboratory data. Laboratory data will include evaluation of:

- Hematology: hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume (MCV), segmented neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, cell morphology, reticulocyte count.
- Metabolic panel: Serum concentrations of sodium, potassium, chloride, total bilirubin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, uric acid, calcium, glucose, total protein, albumin, cholesterol, lipase, creatine kinase (CK).
- Coagulation: prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR).
- Serum and urine beta hCG pregnancy test on females of childbearing potential.
- Urinalysis: specific gravity, pH, protein, glucose, blood, leukocyte esterase.

9.4. Future Use of Stored Specimens

Certain biologic samples for this study will be stored at the investigative site (University of Maryland, Institute of Human Virology) with the subject's consent and as approved by the local IRB. These samples will be de-identified and used to research immune response to hepatitis C, its complications, and other conditions for which individuals with hepatitis C are at increased risk to improve treatment. Cocrystal Pharma Inc. will be provided with a code-link that will allow linking the results from the biological specimens with phenotypic subject data while maintaining the blind of the identity of the subject. During the conduct of the study, a subject

can choose to withdraw consent to have these optional biological specimens stored for future research, in which case the specimens will be destroyed.

9.5. Statistical and Analytical Plans

9.5.1. General Considerations

Efficacy analyses will be done on an intent-to-treat (ITT) basis using the full analysis population. The full analysis population will include all subjects who have received study drug. The analysis of safety variables will also include all subjects who receive study drug.

All variables will be summarized by descriptive statistics. The statistics for continuous variables will include mean, median, standard deviation, and number of observations. Categorical variables will be tabulated using frequencies and percentages.

9.5.2. Handling of Missing Data

Missing data will not be imputed for safety analyses. For efficacy analyses, some missing values may be imputed using the last observation carried forward method.

9.5.3. Subject Disposition

Study subject disposition will be summarized. Subjects who discontinued study drug prematurely or withdrew from the study will be summarized and listed, with reason for early termination/withdrawal.

9.5.4. Subject Characteristics

Demographic and other baseline characteristics will be summarized by treatment group.

9.5.5. Treatment Compliance

Treatment compliance will be evaluated by visits. This will include the date the study drug was dispensed, the number of capsules/tablets dispensed, and the number of tablets and capsules returned.

9.5.6. Efficacy Analyses

9.5.6.1. Efficacy Analyses

Data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum and maximum) and for continuous variables and frequency and percentages for categorical variables. Time to achieve HCV RNA levels (below LLOQ) and viral kinetics will also be summarized using descriptive statistics. Exploratory endpoints will be assessed using descriptive statistics.

For the primary efficacy objective, we expect SVR12 to 70% or higher in this study. If the true suppression rate (SVR) is 70%, we will be able to estimate the probability of suppression to within approximately ±1.96[(.7)(1-.7)/12]1/2=0.26 based on a 95% confidence interval.

9.5.7. Safety Analyses

Treatment-emergent adverse events are defined as adverse events occurring after the first dose of study drug until 12 weeks after the last dose of study drug. The incidence of all reported AEs and treatment-related AEs will be tabulated by treatment group. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be listed and summarized by treatment group, MedDRA preferred term, severity, seriousness, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in one subject, the AE will be counted once as the worst occurrence. The incidence of AEs will be tabulated by system organ class and treatment group. AEs leading to premature discontinuation of study drug or withdrawal from the study will be summarized and listed in the same manner.

Summary statistics for actual values and for change from baseline will be summarized for laboratory results by treatment group and scheduled visit. Subjects with laboratory values outside of the normal reference range at any postbaseline assessment will be identified. For vital signs, descriptive statistics will be used to summarize the mean absolute values and change from baseline. Physical examination findings and changes from baseline will be summarized for each patient in data listings only.

9.5.8. Pharmacokinetic Analyses

Plasma concentration-time profiles of CDI-31244, SOF, GS-331007, and VEL will be determined over a 24-hour time period on day 14 at the following time intervals: 0 (pre-dose), 1, 2, 4, 6, 8, 12, and 24 hours after dosing. A sample will also be collected before the first dose on day 1.

The following pharmacokinetic parameters will be computed for each patient using non-compartmental analysis: maximum plasma concentration (Cmax), minimum plasma concentration (Cmin), time to maximum concentration (tmax), and area under the plasma concentration-time curve from 0 to 24 hours (AUC0-24).

Individual subject plasma concentrations and pharmacokinetic parameters will be listed and will be summarized by descriptive statistics. Individual subject and mean plasma concentration-time data will be presented graphically.

9.5.9. Pharmacokinetic/Pharmacodynamic Analysis

Relationships between the change from baseline in log10 RNA at day 14 and Cmin and AUC0-24 will be examined graphically. If suggested by the graphs, appropriate PK/PD models will be fit to the data.

9.5.10. Interim Analyses

No interim analyses are planned for this study.

10. ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the informed consent document. The investigator will ensure that written informed consent is obtained from each subject or legally authorized representative by obtaining the appropriate signatures and dates on the informed consent document before the performance of protocol evaluations or procedures.

10.1. Ethical Review

The investigator will provide the sponsor or its designee with documentation of the IRB approval of the protocol and the informed consent document before the study may begin at the investigative site. The name and address of the reviewing IRB are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB:

- Protocol and amendments.
- Informed consent document and updates.
- Investigational New Drug Application.
- Relevant curricula vitae, if required.
- Required safety and SAE reports.
- Any additional submissions required by the site's IRB.

The investigator must provide the following documentation to the sponsor, if applicable:

- The IRB periodic (e.g., quarterly, annual) reapproval of the protocol.
- The IRB approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB receipt of safety and SAE reports, as appropriate.

10.2. Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the 2013 version of the Declaration of Helsinki or the applicable guidelines on GCP, and all applicable federal, state, and local laws, rules, and regulations.

All data recorded in the CRF for subjects participating in this study will be transcribed from medical records. After reading the protocol, the investigator will sign the protocol signature page and return it to the sponsor or designee.

10.2.1. Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators (associate investigators), and name and address of the research facilities are included in the investigator file.

10.2.2. Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study subject) must be approved by the sponsor prior to seeking approval from the IRB, and before implementing.

The investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Important protocol deviations must be reported to the sponsor and the local IRB in accordance with IRB policies.

The sponsor may terminate the study at any time. The IRB must be advised in writing of study completion or early termination.

10.2.3. Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol or International Conference on Harmonisation Good Clinical Practice (ICH GCP). A protocol deviation may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or wellbeing. For example, important protocol deviations might include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations that constitute Reportable New Information to the IRB within 5 working days of identification of the protocol deviation as per local IRB requirements. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.2.4. Study Documentation, Privacy, and Records Retention

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the investigator for a minimum of 2 years (or longer if required by the local IRB).

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the

investigator will provide the applicable regulatory agencies and applicable IRB with direct access to original source documents.

Records containing subject medical information must be handled in accordance with the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and consistent with the terms of the subject authorization contained in the informed consent document for the study. Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the informed consent document. Furthermore, CRFs and other documents should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of subject identities.

10.3. Study Finances

This study is financed by Cocrystal Pharma, Inc.

10.4. Publications

Key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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APPENDIX A. SCHEDULE OF EVENTS

Study Visit Number	0	1		2	3	4	5	6	7	8	9	10	11	12	13	14
		Treatment										Post-Treatment				
Activity	Screening (D-42 to -7)	Baseline (D1)	D 1	D2	D3	D7	D10	D14 (W2)	D15	W3	W6	W8	W10	W14	W18	W30
Landmark Description			SOT					EOT-C			EOT-SV		SVR4		SVR12	SVR24
Administrative Procedures																
Recruitment/Informed Consent	X															
Inclusion/exclusion criteria	X	X														
Complete Medical History	X	X									X					X
Interval Medical History				X	X	X	X	X		X		X	X	X	X	
Administer 1st Dose of Study Drug			X													
Dispense Study Drug Supply			X			X		X								
Dispense Study Drug Diary			X													
Evaluate Patient Diary and number of used and unused study drug				X	X	X	X	X		X	X					
Clinical Procedures/Assessments																
Complete Physical Exam	X	X									X					X
Targeted Physical Exam, if needed						X		X		X		X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Adverse event			X	X	X	X	X	X		X	X	X	X			
Height	X															
Vital Signs (T, P, R, BP) and weight	X	X		X	X	X	X	X		X	X	X	X	X	X	X
12-lead ECG	X	X									X					

EOT-C, end of treatment with CDI-31244; EOT-SV, end of treatment with sofosbuvir and velpatasvir; SOT, start of treatment; SVR4, sustained virologic response 4 weeks after completion of treatment; SVR12, sustained virologic response 12 weeks after completion of treatment; SVR24, sustained virologic response 12 weeks after completion of treatment.

Study Visit Number	0	1		2	3	4	5	6	7	8	9	10	11	12	13	14
		Treatment										Post-Treatment				
Activity	Screening (D-42 to -7)	Baseline (D1)	D 1	D2	D3	D7	D10	D14 (W2)	D15	W3	W6	W8	W10	W14	W18	W30
Landmark Description			SOT					EOT-C			EOT-SV		SVR4		SVR12	SVR24
Clinical Laboratory Tests																
Quantitative HCV RNA [a]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
HCV genotype	X															
HCV FibroSure (if none done in previous year)	X															
HBsAg/HBcAb/HBsAb [b]	X															
HIV antibody	X															
IL28B genotyping		X														
Metabolic panel	X	X				X		X		X	X		X		X	X
Complete blood count	X	X				X		X		X	X		X		X	X
Coagulation panel	X	X				X		X		X	X		X		X	X
Urine toxicology screen	X															
Urinalysis		X									X					
Urine β-hCG (females of childbearing potential)		X				X		X		X	X					
Serum β-hCG (females of childbearing potential)	X															
Research Laboratory Tests																
Plasma PK [c]		X						X	X	X	X					
PAXgene RNA Assay		X									X				X	X
PAXgene DNA Assay		X														
PBMC Storage		X									X				X	X
Plasma Storage		X				X		X		X	X	X	X	X	X	X
Serum Storage		X				X		X		X	X	X	X	X	X	X
Resistance Assay [d]		X				X [d]		X [d]		X [d]	X [d]	X [d]	X [d]	X [d]	X [d]	X [d]

[a] Blood for plasma HCV levels to assess viral kinetics will be obtained at 2, 4, and 6 hour after day 1 dosing.

[b] Subject is excluded from study entry with active hepatitis B virus (HBV) infection, defined as positive hepatitis B surface antigen (HBsAg) at screening. If subject is negative for both HBsAg and hepatitis B surface antibody (HBsAb), but hepatitis B core antibody (HBcAb)-positive, plasma HBV DNA levels will be checked and subject excluded if HBV DNA detected.

[c] Blood for plasma CDI-31244, SOF, GS-331007, and VEL levels before the first dose (day 1) and at 0 (pre-dose), 1, 2, 4, 6, 8, 12, and 24 hour after day 14 dosing. Subjects will be asked to delay their study drug on day 14 until their study visit to accommodate PK sampling.

[d] Blood for resistance assays will also be obtained on any subject who discontinues study drug prematurely due to lack of efficacy, or have HCV RNA >1,000 IU/mL on post-treatment visit.

Subjects receiving retreatment will have study visits at 4 weeks after initiation of retreatment, at the end of the 12-week retreatment period, at 4 weeks after completion of treatment (SVR4), and at 12 weeks after completion of treatment (SVR12). Procedures during retreatment are detailed in Section 3.2.2.11.

APPENDIX B. PROTOCOL SIGNATURE PAGE

By signing this protocol, the investigator agrees to conduct the study in accordance with the protocol, generally accepted standards of good clinical practice, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study. In addition, the investigator agrees to provide the sponsor with accurate financial information to allow the sponsor to submit complete and accurate certification and disclosure statements as required by FDA regulations.

By signing this protocol, the sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written procedures to ensure that the trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of good clinical practice, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the study.

Investigator's Signature	Print Name	Date
Investigator's Signature	Print Name	Date

Site Address and Telephone

Sponsor's Signature		Date