Paritaprevir/Ritonavir/Ombitasvir plus Dasabuvir for Treatment-Naive and Treatment-Experienced Non-Cirrhotic Patients with Hepatitis C Virus Genotype 1b Receiving Hemodialysis (PIVOTAL)

Version	1.0
Protocol Date	24 April, 2016
Investigational Product	Ombitasvir, paritaprevir/ritonavir, dasabuvir
Development phase	3b
Study Design	Prospective, multicenter, open-label, interventional trial
Sponsor	Abbvie
Medical Monitor	Department Ministry of Health and Welfare, Executive Yuan, Taiwan Taiwan Joint Institutional Review Board
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SPONSOR SIGNATURE PAGE

Protocol No.:

Title: Ombitasvir/Paritaprevir/Ritonavir plus Dasabuvir for Treatment-Naive and Treatment-Experienced Non-Cirrhotic Patients with Hepatitis C Virus Genotype 1b Receiving Hemodialysis

Sponsor Abbvie

Name: _____

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Signature: _____

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Date: _____

INVESTIGATOR SIGNATURE PAGE

Protocol No.:

Title: Ombitasvir/Paritaprevir/Ritonavir plus Dasabuvir for Treatment-Naive and Treatment-Experienced Non-Cirrhotic Patients with Hepatitis C Virus Genotype 1b Receiving Hemodialysis

I, the undersigned, have reviewed this protocol, and I agree to conduct this study with the information contained in this protocol, and in accordance with the principles of Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice.

Name: _____ Signature: _____

Date: _____

Affiliation & Address: _____

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PROTOCOL SYNOPSIS

Version	1.0
Protocol Date	24 April, 2016
Protocol No.	
Title	Ombitasvir/Paritaprevir/Ritonavir plus Dasabuvir for Treatment-Naive and Treatment-Experienced Non-Cirrhotic Patients with Hepatitis C Virus Genotype 1b Receiving Hemodialysis
Diagnosis	Chronic hepatitis C, genotype 1b
Participating Center	National Taiwan University Hospital, Taipei, Taiwan National Taiwan University Hospital, Yun-Lin Branch, Yun-Lin, Taiwan Taipei City Hospital, Ren-Ai Branch, Taipei, Taiwan Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan China Medical University Hospital, Taichung, Taiwan Taichung Veterans General Hospital, Taichung, Taiwan Tung's Taichung MetroHarbor Hospital, Taichung, Taiwan Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi, Taiwan National Cheng Kung University Hospital, Tainan, Taiwan
Phase of Trial	3b
Investigational Product	Ombitasvir/paritaprevir/ritonavir 12.5 mg/75 mg/50 mg tablet Dasabuvir 250 mg tablet Acronym: PrOD
Dose	Ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD (2 tablet once daily) Dasabuvir 250 mg BID (1 tablet twice daily)
Duration	12 weeks
Treatment allocation	Open-label
Estimated Sample Size	Treatment-naïve: 35 Treatment-experienced: 15
Main Inclusion Criteria	1. Ages of 20 to 70 yeas 2. Male or female 3. Body mass index (BMI) 18.5-35.0 kg/m^2 4. Chronic HCV infection, defined as patients who meet as least one of the two following criteria:

	• Anti-HCV antibody (Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, Illinois, USA) or HCV RNA > 1,000 IU/mL for at least 6 months before screening • Positive HCV RNA > 1,0000 IU/mL (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL) at the time of screening with a liver biopsy consistent with chronic HCV infection 5. HCV genotype 1b (HCV GT-1b) infection (Abbott RealTi*me* HCV genotype II, Abbott Molecular Inc. Illinois, USA) 6. Treatment-naïve or treatment-experienced (including patients who relapsed, who had virological breakthrough, or who were null-responsive to IFN-based therapies) 7. HCV RNA > 10,000 IU/mL at screening 8. Absence of cirrhosis with documented results of one of the following criteria: • Liver biopsy within 24 months prior to or during screening demonstration the absence of cirrhosis, e.g. METAVIR score ≤ 3 or Ishak score ≤ 4. • A screening transient elastography (Fibroscan) result of < 12.5 kPa • A screening Fibrosis Index Based on 4 markers (FIB-4) of ≤ 1.45 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) of ≤ 2 • Subjects with non-qualifying FIB-4/APRI or Fibroscan result may only be enrolled if they have a qualifying liver biopsy within 24 months prior to or during screening 9. Estimated glomerular filtration (eGFR) rate < 15 mL/min/1.73m^2 as assessed by modified of diet in renal disease (MDRD) equation, and receiving regular hemodialysis
Main Exclusion Criteria	1. HCV infection other than HCV GT-1b 2. HBV or HIV coinfection 3. Presence of cirrhosis (Child-Pugh class A, B or C) 4. Any primary cause of liver disease other than chronic HCV infection, including but not limited to the following • Hemochromatosis • Alfa-1 antitrypsin deficiency • Wilson's disease

	• Autoimmune hepatitis • Alcoholic liver disease • Drug-induced hepatitis 5. Screening laboratory analyses showing any of the following results • Hemoglobin (Hb) level < 10 g/dL • Absolute neutrophil count (ANC) < 1,500 cells/μL • Platelet count < 60,000 cells/mm^3 • International normalized ratio (INR) > 2.0 • Albumin (Alb) < 2.8 g/dL • Bilirubin (Bil) > 3.0 mg/dL • Alanine aminotransferase (ALT) > 5X upper limit of normal (ULN) • Aspartate aminotransferase (AST) > 5X upper limit of normal (ULN) • Serum alfa-fetoprotein (AFP) > 100 ng/mL 6. Presence of hepatocellular carcinoma (HCC) on imaging studies such as computed tomography (CT) scan or magnetic resonance imaging (MRI) 7. History of malignancy (except cutaneous melanoma) within 5 years at the screening 8. Organ transplantation other than cornea and hair (prior renal transplantation with graft failure not included) 9. Prior exposure to investigational agents for HCV (direct acting antiviral agents, host-targeting agents, or therapeutic vaccines) 10. Pregnancy 11. Unwilling to have contraception during the study period 12. Unwilling to provide informed consent
Primary endpoint	1. Sustained virological response (SVR_{12}): HCV RNA level <LLOQ 12 weeks after the completion of therapy (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL) 2. Treatment-emergent adverse event (AE)-related withdrawal rate
Secondary endpoint	1. Sustained virological response (SVR_{24}): HCV RNA level < LLOQ 24 weeks after the completion of therapy (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim,

	Germany, low limit of quantification (LLOQ): 25 IU/mL) 2. Rapid virological response (RVR): HCV RNA level < LLOQ at week 4 of treatment(Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL) 3. End-of-treatment virological response (EOTVR): HCV RNA level < LLOQ at the end of treatment (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL) 4. Fibrosis Index Based on 4 markers (FIB-4): changes of FIB-4 before treatment and at the end-of-follow-up 5. FibroScan: changes of liver stiffness before treatment and at the end-of-follow-up
Resistance	1. Resistance information will be analyzed for any subjects who has sequencing performed on baseline samples: • The resistance-associated variants (RAVs) at signature amino acid position at baseline identified by population nucleotide sequencing and comparison to the appropriate prototype reference standard sequence 2. Resistance information will be analyzed for subjects who fail to achieve SVR_{12} and who have on-treatment HCV RNA ≥ 1,000 IU/mL • The RAVs at signature amino acid position at baseline identified by population nucleotide sequencing comparison to the appropriate prototypic reference sequence • The RAVs in available post-baseline samples identified by population and/or clonal nucleotide sequencing and comparison to the baseline sequencing • The RAVs in available post-baseline samples identified by population and/or clonal nucleotide sequencing and comparison to the appropriate prototypic reference sequence 3. The most prevalent amino acid RAVs identified by population sequencing and those emerging or becoming enriched in isolates from at least 2 subjects in the study will be summarized. Furthermore, the persistence of the detected amino acid RAVs will also be reported.

Proposed Statistical Analysis	Variables/Time Points of Interest: sustained virological response (SVR_{12}): HCV RNA level < LLOQ 12 weeks after the completion of therapy (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL) Statistical Methods 1. Treatment-naïve: • Alfa-error: 0.05, beta-error: 0.20, two-tailed statistics • Controlled arm (null-hypothesis): peginterferon alfa-2a plus low-dose ribavirin for 48 weeks (SVR_{24}: 64%) (Liu CH, et al. Pegylated interferon-α2a with or without low-dose ribavirin for treatment-naive patients with hepatitis C virus genotype 1 receiving hemodialysis: a randomized trial. Ann Intern Med 2013;159:729-38.) • PrOD arm: estimated to be 94% • Sample estimation in PrOD arm: 35 2. Treatment-experienced: not designed to evaluate formal statistical hypotheses, and no sample size calculation performed because of the lack of SVR_{12} rate data by peginterferon alfa-2a plus low-dose ribavirin retreatment.

Flow Chart

Study Visit	0	1	2	3	4	5	6	7	8	9	10	11	12
Procedure	Screening	Treatment							EOT	Follow-up		EOF	Extended follow-up
Study Week	-4 to -1	Day 1	1	2	4	6	8	10	12	16	20	24	36
Informed Consent	X												
Inclusion/Exclusion	X												
Demographic	X												
Height	X												
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X												
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	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			
Abdominal US	X								X			X	
ECG	X	X							X			X	X
Pregnancy test[1]	X	X			X		X		X	X			
Hemogram[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation profile[3]	X	X							X			X	X
Biochemistry	X[4]	X[4]	X	X	X	X	X	X	X[4]	X	X	X[4]	X[4]
Serology	X[5]	X							X			X	X

Virology	**X**[6]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Urinalysis	**X**	**X**			**X**		**X**		**X**			**X**	**X**
Human genetics[7]	**X**												
FibroScan or Liver[8] **biopsy**	**X**								**X**			**X**	
Resistant variants[9]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Archive serum sample	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

EOT: end of treatment, EOF: end of follow-up

[1] For pre-menopausal women with child birth potential, testing for urine beta human chorionic gonadotropin (β-HCG). If the urine sample is unable to collect, consider serum β-HCG test

[2] Including hemoglobin level, white blood cell count, absolute neutrophil count, platelet count.

[3] Including prothrombin time, activated partial thromboplastin time.

[4] Including albumin, total bilirubin (T-Bil), direct bilirubin (D-Bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutaryl transpeptidase (γ -GT), creatinine (Cre), blood urea nitrogen (BUN), sodium (Na), potassium (K), chloride (Cl), calcium (Ca), inorganic phosphorus (P), magnesium (Mg), uric acid (UA), fasting glucose (GluAC), glycated hemoglobin (HbA1c), triglyceride (TG), cholesterol (CHO), low density lipoprotein (LDL), high density lipoprotein (HDL), iron (Fe), total iron binding capacity (TIBC), ferritin. Others include AST, ALT with/without T-Bil, D-Bil, ALP/r-GT.

[5] Including anti-HCV, HBsAg, anti-HBs, anti-HBc, anti-HIV. Others include anti-HCV.

[6] Including HCV RNA, HCV genotype/subgenotype. Others include HCV RNA.

[7] Including interleukin 28B (IL28B) genotypes.

[8] For patients with failed or unreliable Fibroscan evaluation, liver biopsy to stage the hepatic fibrosis is suggested and is optional. In patients who receive liver biopsy to stage the hepatic fibrosis, the EOF liver biopsy is also optional.

[9] All samples tested were stored until the completion of the study. Tests for all subjects for resistant associated variants (RVAs) of interests at NS3, NS5A, and NS5B regions at the screening time point. Others were tested for subjects who fail to achieve SVR12 or who have on-treatment HCV RNA ≥ 1,000 IU/mL.

ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
AFP	Alfa Fetoprotein
AIDS	Acquired Immune Deficiency Syndrome
ALB	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
ANTI-HBc	Hepatitis B Virus Core Antigen Antibody
ANTI-HBs	Hepatitis B Virus Surface Antigen Antibody
ANTI-HCV	Hepatitis C Virus Antibody
ANTI-HIV	Human Immunodeficiency Virus Antibody
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BID	Twice Daily Dose
BIL	Bilirubin
BMI	Body Mass Index
BP	Blood Pressure
BT	Body Temperature
Ca	Calcium
CBC	Complete Blood Count
CHC	Chronic Hepatitis C
CHO	Cholesterol
CI	Confidence Interval
CL	Chloride
CRF	Case Report Form
CT	Computed Tomography
CYP	Cytochrome P
DAA	Direct Acting Antiviral
D-Bil	Direct Bilirubin
DDI	Drug Drug Interaction
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate

EIA	Enzyme Immune Assay
EOF	End of Follow-up
EOT	End of Treatment
EOTVR	End-of-treatment Virologic Response
ESA	Erythrocyte Stimulating Agent
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
FE	Iron
GCP	Good Clinical Practice
GLUAC	Fasting Glucose
GT	Genotype
Hb	Hemoglobin
HbA1c	Glycated Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCT	Hematocrit
HCV	Hepatitis C Virus
HD	Hemodialysis
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
IFN	Interferon
IL28B	Interleukin 28B
INR	International Normalized Ratio
IRB	Institutional Review Board
IU	International Unit
K	Potassium
L	Liter
LDL	Low Density Lipoprotein
LLOQ	Lower Limit of Quantification
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MDRD	Modified of Diet in Renal Disease Equation
mg	Milligram
Mg	Magnesium
mL	Milliliter
MRI	Magnetic Resonance Imaging
NA	Sodium

PI	Principle Investigator
PK	Pharmacokinetics
PO	Per Os
PR	Pulse Rate
PrOD	Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir
PT	Prothrombin Time
QD	Once Daily Dose
RAV	Resistance Associated Variant
RBV	Ribavirin
RBC	Red Blood Cell Count
RNA	Ribonucleic Acid
RR	Relative Risk
RR	Respiratory Rate
RVR	Rapid Virologic Response
SAE	Serious Adverse Event
SD	Standard Deviation
SUSAR	Suspected Unexpected Severe Adverse Reaction
SVR	Sustained Virologic Response
T-Bil	Total Bilirubin
TG	Triglyceride
TIBC	Total Iron Binding Capacity
TVR	Telaprevir
UA	Uric Acid
ULN	Upper Limit of Normal
US	Ultrasonography
WBC	White Blood Cell count
B-HCG	Beta Human Chorionic Gonadotropin
γ-GT	Gamma-Glutaryl Transpeptidase
µg	Microgram

Table of Contents

1. INTRODURCTION

1.1 Overview

Hepatitis C virus (HCV) infection remains a major co-morbidity in hemodialysis patients.[1-3] The incidence and prevalence rates of HCV infection in hemodialysis patients are much higher than those in the general population, and are attributed to high rates of nosocomial HCV transmission.[4-6] With regard to HCV genotype distribution, HCV genotype 1 (GT-1) infection is the most prevalent type of infection worldwide and the genotype distribution in HCV-infected individuals receiving hemodialysis (HD) is similar to that observed in HCV-infected individuals with normal renal function.[7-9] Compared to non-HCV infected hemodialysis patients, HCV-infected patients have increased risks of liver-related morbidity and mortality.[10] Although HCV-infected hemodialysis patients who receive renal transplantation have survival advantages over those who remain on maintenance dialysis, these patients still have poor patient and graft survival, as well as have poor responses to interferon (IFN)-based therapy.[11-13] In contrast, hemodialysis patients who eradicate HCV infection have improved biochemical, virologic and histologic responses, whether on maintenance dialysis or after renal transplantation.[14,15]

1.2 Clinical experience of IFN-based Therapy

Approximately one third of hemodialysis patients with chronic HCV infection achieve sustained virological response (SVR) by conventional IFN or peginterferon monotherapy.[16-18] In addition 18-30% of patients receiving IFN-based monotherapy prematurely discontinued treatment due to adverse events (AEs). Although the addition of ribavirin to IFN further improves the SVR rate in HCV-infected patients with normal renal function, ribavirin has been considered contraindicated to treat HCV-infected hemodialysis patients because of concern for life-threatening hemolytic anemia. Recently, pilot studies have indicated the feasibility of adding low-dose ribavirin (200 mg three times per week to daily 400 mg, adjusted to achieve a target concentration of 10-15 μmol/L), to IFN for treatment of HCV-infected hemodialysis patients.[19-28] Generally, the SVR rate and the premature

discontinuation rate due to null-response, severe anemia, and/or heart failure for combination therapy are 56% and 22%, respectively.[29] Based on these small-scale studies, low-dose ribavirin (daily 200 mg) was approved in August 2011 by the U.S. Food and Drug Administration to treat HCV-infected hemodialysis patients.[30] Two recent well-conducted randomized control studies to compare the efficacy and safety of combination therapy with peginterferon alfa-2a (135 μg/week) plus low-dose ribavirin (RBV) (200 mg/day) or monotherapy with peginterferon (135 μg/week) for 48 and 24 weeks in treatment-naïve HCV GT-1 and GT-2 infected individuals receiving hemodialysis showed that the SVR rates of combination therapy groups were greater than those of monotherapy groups (64% versus 34%, $p < 0.001$ for HCV GT-1; 74% versus 44%, $p < 0.001$ for HCV GT-2), respectively.[31,32] Although the SVR rate of combination therapy with peginterferon plus low-dose ribavirin is higher than that of peginterferon monotherapy. About 70-75% of these patients experienced clinically significant anemia which needed high dose of erythropoiesis stimulating agents (ESAs) to keep the hemoglobin level within the safety range. Although telaprevir (TVR)-based triple therapy has been used to treat 4 HCV-1 patients receiving hemodialysis who were not responsive to prior peginterferon plus RBV with good efficacy, the added on-treatment adverse events (AEs) and the pill burden precluded the widespread use of this agent.[33,34]

1.3 Clinical experience of IFN-free therapy by ombitasvir/paritaprevir/ritonavir plus dasabuvir in HCV GT-1 patients

The recent introduction of IFN-free direct acting antiviral agents (DAAs) has made a paradigm shift with regard to the medical treatment for HCV-infected individuals, based on the excellent efficacy and safety in ordinary patients. Among the various IFN-free DAA regimens, treatment with ombitasvir/paritaprevir/ritonavir plus dasabuvir (PrOD) has been approved in 2014 to treat patients with chronic HCV GT-1 infection. Treatment with PrOD plus weight-based ribavirin for 12 weeks achieved an SVR_{12} rate of 96.2% and 96.3% in treatment-naïve and treatment-experienced non-cirrhotic HCV GT-1 patients, respectively (SAPPHIRE-I and SAPPHIRE-II).[35,36] Furthermore, the

SVR_{12} rates in those with GT-1a and GT-1b were 95.3% and 98.0% in treatment-naïve patents, and 96.0% and 96.7% in treatment-experienced patients, respectively. Among treatment-experienced HCV-1 patients, the SVR rates of PrOD plus RBV were comparable in those with various prior treatment responses by peginterferon plus RBV (relapse: 95.3%; partial response: 100%, null response: 95.2%).[36] Among treatment-naïve and treatment-experienced compensated cirrhotic HCV GT-1 patients, treatment with PrOD plus RBV for 12 or 24 weeks achieved and SVR rate of 91.8% and 95.%, respectively (TURQUOISE-II).[37] The SVR_{12} rates in HCV GT-1b cirrhotic patients were similar in those receiving 12 and 24 weeks of treatment (98.5% versus 100%); the SVR_{12} rate in HCV GT-1a cirrhotic patients receiving 24 week of treatment was greater than those receiving 12 weeks of treatment (94.2% versus 88.6%), particularly for prior non-responders to peginterferon plus RBV (92.9% versus 80%).[37] The PEARL-III and PEARL-IV studies compared the SVR_{12} rates in treatment-naïve non-cirrhotic HCV GT-1b and HCV GT-1a patients receiving PrOD with/without RBV for 12 weeks.[37] The SVR_{12} rate of PrOD without RBV was similar to that of PrOD with RBV in HCV GT-1b patients (99.0% versus 99.5%). However, the SVR_{12} rate in HCV GT-1a patients receiving PrOD with RBV was marginally higher than those receiving PrOD without RBV (97.0% versus 90.2%).[38] The PEARL-II study further confirmed that in treatment-experienced non-cirrhotic HCV GT-1b patients, treatment with PrOD without RBV for 12 weeks had comparable SVR12 rate to PrOD with RBV therapy (100% versus 96.6%).[39] In TURQUOISE-III study, PrOD without RBV for 12 weeks achieved an SVR_{12} rate of 100% in treatment-naïve and treatment-experienced compensated cirrhotic HCV GT-1b patients.[40] With regard to safety, PrOD with/without RBV showed excellent safety profiles with few patients experiencing serious adverse events (SAEs) and prematurely treatment discontinuation. The constitutional AEs in patients receiving PrOD based treatment showed were slightly higher than those receiving placebo. Furthermore, most of these symptoms were mild in grades. About 5% of the non-cirrhotic patients and about 8% of the cirrhotic patients receiving PrOD plus RBV had an on-treatment hemoglobin level of < 10 g/dL; and none of the non-cirrhotic patients and about 2% of the compensated

cirrhotic patients receiving PrOD had an on-treatment hemoglobin level of < 10 g/dL, respectively.[35-40] In addition, the on-treatment AST/ALT elevation of more than 5 times the upper limit of normal (ULN) were 0.6%-1.7% and 0.5% in non-cirrhotic patients receiving PrOD with and without RBV; and were 2.9% and 2.0% in compensated cirrhotic patients receiving PrOD with and without RBV, respectively. The on-treatment total bilirubin elevation of more than 3 times ULN were 2.4%-5.7% and 0.5% in non-cirrhotic patients receiving PrOD with and without RBV; 13.5% and 0% in compensated cirrhotic patients receiving PrOD with and without RBV, respectively.[35-40] Based on the above evidence, treatment with PrOD for 12 weeks is recommended for treatment-naïve and treatment-experienced HCV GT-1b patients, regardless of cirrhosis or not. Treatment with PrOD plus RBV for 12 weeks is recommended for HCV GT-1a patients, except for compensated cirrhotic HCV GT-1a null responders to prior therapy where treatment with PrOD plus RBV for 24 weeks is recommended.

1.4 Clinical experience of IFN-free therapy by ombitasvir/paritaprevir/ritonavir plus dasabuvir in HCV GT-1 patients with severe renal impairment or end-stage renal disease (ESRD)

The pharmacokinetic (PK) study of ombitasvir, paritaprevir, ritonavir, and dasabuvir was evaluated in 24 subjects with normal renal function, and with mild, moderate or severe renal impairment (each arm 6 patients). Compared to subjects with normal renal function, the area under the curves (AUCs) in subjects with mild renal impairment were comparable for ombitasvir, 20% higher for paritaprevir and dasabuvir, and 42% higher for ritonavir; the AUCs in subjects with moderate renal impairment were comparable for ombitasvir, 37% higher for paritaprevir and dasabuvir, and 80% higher for ritonavir; the AUCs in subjects with severe renal impairment were comparable for ombitasvir, 50% higher for paritaprevir and dasabuvir, and 114% higher for ritonavir.[41] All patients were well tolerated for PrOD treatment except for mild AEs, including nausea, myalgia, and catheter-site erythema, encountered in 1 subject with moderate renal impairment. Based on the PK study, the changes of the drug exposure were not clinically relevant and the doses of PrOD do

not require adjustment.

The phase 3b RUBY-I study evaluated the safety and efficacy of PrOD with RBV and PrOD without RBV for 12 weeks in 13 and 7 HCV GT-1a and HCV GT-1b treatment-naïve non-cirrhotic patients with severe renal impairment or ESRD.[42] The interim safety analysis showed that no patients had study drug discontinuation, no treatment-related serious adverse events (SAEs) and no clinically significant changes in markers of liver or kidney function. With regard to efficacy, 14 of the 20 patients completed 12 weeks of treatment and all of them achieved end-of-treatment virologic response (EOTVR). Ten patients (8 in GT-1a and 2 in GT-1b) completed post-treatment follow-up for 4 weeks and all achieved SVR_4. Furthermore, 2 HCV GT-1a patients completed post-treatment follow-up for 12 weeks and all achieved SVR_{12}.

1.5 Rationale of the study design

Although peginterferon monotherapy and combination therapy with peginterferon plus low-dose RBV for 24-48 weeks have been evaluated in many studies, the efficacy for the treatment regimens were only modest (SVR rate about 60%). In addition, the on-treatment AEs and SAEs by IFN-based therapies were frequently encountered in HCV-infected patients receiving hemodialysis. Of note was the pronounced on-treatment hemoglobin level decrease in patients receiving combination therapy by peginterferon plus low-dose RBV, necessitating significant RBV dose reduction and high-dose erythrocyte stimulating agent (ESA) support.

By receiving IFN-free DAA therapies, HCV-infected patients have excellent SVR rates, low on-treatment SAE and AE rates, shorter treatment duration, and low pill burdens. The PK study of ombitasvir, paritaprevir, ritonavir and dasabuvir proves the excellent safety profiles and dose adjustment are not needed for PrOD regimen in subjects with various degrees of renal impairment. The interim analysis of RUBY-I study showed the excellent on-treatment and off-therapy antiviral effects in HCV GT-1a and GT-1b infected patients receiving PrOD plus low-dose RBV and PrOD, respectively. However, all the patients enrolled in the RUBY-I study were treatment-naïve and were non-cirrhotic. Furthermore, only 7 patients in the RUBY-I study

were HCV GT-1b patients. Based on the excellent safety and efficacy profiles of PrOD treatment for HCV GT-1b infected patients with normal renal function, we aim to evaluate the safety and efficacy of PrOD for 12 weeks in treatment-naïve and treatment-experienced HCV GT-1b non-cirrhotic patients receiving hemodialysis.

2. STUDY DESIGN

2.1 Study population

We will conduct a phase 3b, multicenter, open-label trial at 9 academic centers in Taiwan. Treatment-naïve and treatment-experienced HCV GT-1b non-cirrhotic patients who receive maintenance hemodialysis due to ESRD and who are 20-70 years old are consecutively enrolled in the study. The protocol will be approved by Central Institutional Review Board (C-IRB) of Taiwan and will be conducted in accordance with the principles of Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. Each patient provides written informed consent before enrollment.

2.1.1 Inclusion criteria

[1] Ages of 20 to 70 yeas

[2] Male or female

[3] Body mass index (BMI) 18.5-35.0 kg/m^2

[4] Chronic HCV infection, defined as patients who meet as least one of the two following criteria

- Anti-HCV antibody (Abbott HCV enzyme immunoassay [EIA] 2.0, Abbott Laboratories, Abbott Park, Illinois, USA) or HCV RNA > 1,000 IU/mL for at least 6 months before screening
- Positive HCV RNA > 1,0000 IU/mL (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL) at the time of screening with a liver biopsy consistent with chronic HCV infection

[5] HCV GT-1b infection (Abbott RealTi*me* HCV genotyping II, Abbott Molecular Inc. Illinois, USA)

[6] Treatment-naïve or treatment-experienced (including patients who relapsed, who had virological breakthrough, or who were null-responsive to IFN-based therapies)

[7] HCV RNA > 10,000 IU/mL at screening

[8] Absence of cirrhosis with documented results of one of the following criteria:

- Liver biopsy within 24 months prior to or during screening demonstration the absence of cirrhosis, e.g. METAVIR score ≤ 3 or Ishak score ≤ 4.
- A screening transient elastography (Fibroscan) result of < 12.5 kPa
- A screening Fibrosis Index Based on 4 markers (FIB-4) of ≤ 1.45 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) of ≤ 2
- Subjects with non-qualifying FIB-4/APRI or Fibroscan result may only be enrolled if they have a qualifying liver biopsy within 24 months prior to or during screening

[9] Estimated glomerular filtration (eGFR) rate < 15 mL/min/1.73m^2 as assessed by modified of diet in renal disease (MDRD) equation, and receiving regular hemodialysis

2.1.2 Exclusion criteria

[1] HCV infection other than HCV GT-1b

[2] HBV or HIV coinfection

[3] Presence of cirrhosis (Child-Puge class A, B or C)

[4] Any primary cause of liver disease other than chronic HCV infection, including but not limited to the following

- Hemochromatosis
- Alfa-1 antitrypsin deficiency
- Wilson's disease
- Autoimmune hepatitis
- Alcoholic liver disease
- Drug-induced hepatitis

[5] Screening laboratory analyses showing any of the following results

- Hemoglobin (Hb) level < 10 g/dL
- Absolute neutrophil count (ANC) < 1,500 cells/μL
- Platelet count < 60,000 cells/mm^3
- International normalized ratio (INR) > 2.0
- Albumin (Alb) < 2.8 g/dL
- Bilirubin (Bil) > 3.0 mg/dL
- Alanine aminotransferase (ALT) > 5X upper limit of normal (ULN)
- Aspartate aminotransferase (AST) > 5X upper limit of normal (ULN)

- Serum alfa-fetoprotein (AFP) > 100 ng/mL

[6] Presence of hepatocellular carcinoma (HCC) on imaging studies such as computed tomography (CT) scan or magnetic resonance imaging (MRI)

[7] History of malignancy (except cutaneous melanoma) within 5 years at the screening

[8] Organ transplantation other than cornea and hair (prior renal transplantation with graft failure not included)

[9] Prior exposure to investigational agents for HCV (direct acting antiviral agents, host-targeting agents, or therapeutic vaccines)

[10] Pregnancy

[11] Unwilling to have contraception during the study period

[12] Unwilling to provide informed consent

2.1.3 Definition of the criteria

[1] Stage of the hepatic fibrosis: diagnosis of the hepatic fibrosis by one of the following methods

- Liver biopsy: graded by METAVIR fibrosis score F0-F4.
- Fibroscan score: F0 (≤ 6 KPa), F1 (6.1 to 7.0 KPa), F2 (7.1 to 9.4 KPa), F3 (9.5 to 12.5KPa), F4 (≥ 12.5 KPa).
- Subjects with a non-qualifying Fibroscan results (including failure to measure [zero valid measurement], unreliable measurement [less than 10 valid measurement, a successful rate of less than 60% or the interquartile range more than 30% of the median FibroScan score]) are suggested to receive liver biopsy to confirm the severity of hepatic fibrosis. Liver biopsy is not optional and is not compulsive.

[2] Compensated cirrhosis: cirrhotic patients with Child-Pugh score of < 7 (See below Table).

[3] Decompensated cirrhosis: cirrhotic patients with Child-Pugh score of ≥ 7 (See Table below).

Parameter	Points assigned for Observed Findings		
	1	2	3

Total bilirubin (mg/dL)	< 2	2-3	> 3
Serum albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time (INR)	< 1.7	1.7-2.3	> 2.3
Ascites[1]	None	Mild	Moderate to severe
Hepatic encephalopathy[2]	Grade 0	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory

[1] Mild = ascites detectable only by ultrasound examination; moderate to severe = ascites manifested by moderate symmetrical distention of the abdomen

[2] Grade 0 = normal consciousness, personality, neurological examination, electroencephalogram; grade I = restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, triphasic wave (5 Hz); grade II = lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic wave; grade III = somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower triphasic wave; grade IV = unarousable coma, no personality/behavior, decerebrate, slow delta wave (2-3 Hz)

[4] Definition of treatment-experienced patients

- Relapser: patients receiving IFN-based therapy (IFN or peginterferon with/without RBV) for the treatment of HCV and with undetectable HCV RNA at or after the end of treatment, but subsequently having detectable HCV RNA within 24 weeks of off-therapy follow-up.
- Viral breakthrough: patients receiving IFN-based therapy (IFN or peginterferon with/without RBV) for the treatment of HCV and with on-treatment undetectable HCV RNA, but subsequently having detectable HCV RNA with ongoing treatment.
- Null responder: patients receiving at least 12 weeks of IFN-based therapy (IFN or peginterferon with/without RBV) for the treatment of HCV and failing to achieve at least 2 log HCV RNA decline from the baseline to week 12 of therapy, or with continuous detectable HCV RNA after 24 weeks of treatment.
- Intolerance: patients who discontinue IFN-based therapy (IFN or peginterferon with/without RBV) during the treatment for HCV due to intolerance to any of the components of the IFN-based therapy.

2.1.4 Prior or concomitant HCV therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, traditional medicines, and/or herbal medicines) taken by the subjects from the timing of signing the informed consent through the treatment period and 28 days after the study drugs are stopped, must be recorded in the case report form (CRF) along with the reason for use, date(s) of administration including the start and end dates, and dosage information (including route, dosage and frequency). The investigators should review all concomitant medications for any potential drug-drug interactions (DDIs).

2.1.4.1 Prior therapy

Treatment-naïve patients must not have prior or current use of the investigational or commercially available agents for HCV, including IFN, peginterferon, telaprevir, boceprevir, asunaprevir, daclatasvir, PrOD, sofosbuvir, ledipasvir, simeprevir or RBV.

Treatment-experienced patients must have previously received IFN-based therapy, including IFN or peginterferon monotherapy, or combination therapy with IFN/peginterferon plus RBV and failed treatment. These patients should have documentation of the types and duration of prior therapy, as well as the type of treatment failure and/or the reason for premature treatment discontinuation due to intolerance.

2.1.4.2 Concomitant therapy

The investigator should confirm than concomitant medications can be administered with PrOD. Some medications may require dose adjustment due to potential for DDIs. The investigator should also review the label(s) for the concomitant medication(s) for additional information.

The use of hepatic protective medications, such as milk thistle, ursodeoxycholic acid, glycyrrhizin acid, SAM, Sho-saiko-to etc., is

allowed, provided that the drug does not meet any other exclusion criteria. The dose of these drugs should be kept stable while the subjects are during the PrOD treatment.

During the post-treatment period, the investigator should reassess concomitant medications and subjects may resume previously prohibited medications or revert to pre-study doses 2 weeks following the last dose of the study drugs, if applicable.

2.1.4.3 Prohibited therapy

The prohibited therapy in subjects receiving PrOD therapy is listed below:

Alfuzocin	Etravirine	Propafenone
Aliskiren	Flecamide	Propoxyphene
Amiodarone	Flurazepam	Quetiapine
Astemizole	Fusidic acid	Quinidine
Atorvastatin	Gemfibrozil	Rifabutin
Bepredil	Hormone contraceptives	Rifampin
Carbamazepine	Lovastatin	Saquinavir
Cisapride	Lopinavir	Sildenafil
Clorazepate	Midazolam	Simvastatin
Clozapine	Nevirapine	St. John's Wort
Diazepam	Pethidine	Terfenadine
Efavirenz	Phenobarbital	Trizolam
Elvitegravir/cobicstat	Phenytoin	Voriconazole
Encainide Ergot Derivatives	Pimozide	
Estazolam	Piroxicam	

2.1.4.4 Concomitant therapy requiring dosage adjustment, altered timing or additional monitoring

The concomitant therapy than requires dosage adjustment, altered timing, or additional monitoring in subjects receiving PrOD therapy is listed below:

Amlodipine	Doxazocin	Risperidone
Amitriptyline	Enalapril	Rouvastatin
Aripiprazole	Ezetimibe	Sertraline
Bisoprolol	Flupentixol	Sirolimus
Chlorpromazine	Fluvastatin	Tacrolimus
Candesartan	Haloperidol	Trazodone
Clopidogrel	Mycophenolate	Venlafaxine
Cyclosporine	Olanzapine	Verapamil
Dabigatran	Pitavastatin	Vernakalant
Digoxin	Pravastatin	

In addition to the medications listed above, the use of known strong inducers of cytochrome P3A (CYP3A) or strong inhibitors of CYP2C8 are prohibited within 2 weeks or within 10 half-lives, whichever is longer, prior to the initial dose of PrOD and through the first 2 weeks after the subjects has completed PrOD in the treatment period.

Refer to the ritonavir labeling for a list of prohibited medications. Anti-HCV medications other than those specified in the protocol will not be allowed during the treatment period.

Management of hematological toxicity, including leukopenia, and thrombocytopenia, by hematological growth factor is not allowed. The ESA can be allowed during the treatment period for renal anemia. However, the Sponsor will not reimburse the expense of ESA usage.

2.2 Intervention

2.2.1 Identity of investigational drugs

Investigational Drugs	Manufacturer	Route of Administration	Dosage Form	Strength
Ombitasvir/paritaprevir/	Abbvie	Oral	Tablet	12.5 mg/75mg

ritonavir				/50mg
Dasabuvir	Abbvie	Oral	Tablet	250 mg

2.2.2 Packing and labeling

Ombitasvir/paritaprevir/ritonavir will be supplied in bottles containing 64 tablets. Dasabuvir will be supplied in bottles containing 64 tablets. Each bottle will be labeled as required by local requirement.

2.2.3 Storage and disposition of investigational drugs

Investigational Drugs	Storage Condition
Ombitasvir/paritaprevir/ritonavir	15° to 25°C (59°F to 77°F)
Dasabuvir	15° to 25°C (59°F to 77°F)

The investigational drugs are for investigational use only and must be used within the context of the study. The study drugs supplied for this study must be maintained under adequate security and stored under appropriate conditions specified on the label until dispensed for subject use or returned to the Sponsor.

2.2.4 Shipment of the investigational drugs

A supply of investigational drugs will be sent to the each clinical pharmacology department of each participating center by the Sponsor following the approval of the site by the Department Ministry of Health and Welfare, Executive Yuan, Taiwan. Because this is an open-label trial, all the study medications are supplied with an open-code.

2.2.5 Blinding

This is an open-label study.

2.2.6 Dispensing of the investigational drugs

Ombitasvir/paritaprevir/ritonavir and dasabuvir are taken Per Os (PO) with food to increase the bioavailability. Subjects should comply with

the investigators' instructions and receive adequate dosage of the study drugs to secure the efficacy and safety. Furthermore, if the subject misses the scheduling timing for the study drugs, he/she should replace the dose within 12 hours; otherwise he/she should not receive the study drugs and be considered as missed dosage.

2.2.7 Dosage and duration of interventional drugs

[1] Ombitasvir/paritaprevir/ritonavir (12.5 mg/75mg/50mg per tablet) will be dosed 2 tablets QD.

[2] Dasabuvir (250 mg per tablet) will be dosed 1 tablet BID.

[3] All study drugs should be dosed together and administered with food i.e., the AM dose of ombitasvir/paritaprevir/ritonavir and dasabuvir should be taken together with food and the PM dose of dasabuvir should be taken with food.

2.2.8 Dosage adjustment

The dosage and dosing frequency adjustments of the study drugs are generally not allowed. The study drugs can be discontinued under protocol-defined conditions.

2.2.9 Treatment compliance

The investigator or his/her designated and qualified representatives will administer and dispense investigational drugs for subjects enrolled in this study. The study drugs must not be dispensed for reasons other than that described in the protocol. Furthermore, all study drugs will be dispensed to subjects by study-site personnel under the instruction of the investigator.

At the start of the study, each subject should be instructed the importance of the dosing adherence to the assigned treatment regimen with regard to virologic responses and potential development of resistance associated variants (RAVs). Subjects will receive investigational drugs from Day 1 visit to the EOT. In addition, subjects will be instructed to return all bottles of investigational drugs to the site

staff at the appropriate visits. During the on-treatment visits, the site staff will inspect the content of the bottles and record the status of each one as well as the exact number of remaining tablets of investigational drugs.

Investigational drugs should not be interrupted for toxicity management or any other reason for more than 7 consecutive days. If investigational drugs must be interrupted for more than 7 consecutive days, the investigator should note the attributed reason in case report form (CRF), and should consider discontinue the subject.

2.2.10 Drug accountability

The investigator or his/her designated and qualified representatives will verify that the investigational drug supplies are well received and in the correct amount. An overall accountability of the investigational drugs will be performed and verified by Abbvie monitor throughout the treatment period. Final accountability will be verified by the monitor at the end of the study drug treatment at each site.

During the study, should the subject misplace or damage the investigational drug bottle, the investigator should contact the study coordinator as well as Abbvie for the replacement of the drugs. An explanation of the reason of the misplaced or damaged study drug(s) should be documented in CRF. Upon completion of or discontinuation from the treatment period, all original investigational drug bottles should be counted and returned to the Sponsor or destroyed at site.

The site will maintain the records of the study drugs including the amount of drugs received, and return as well as disposal.

2.3 Objective

2.3.1 Primary objectives

[1] Sustained virological response (SVR_{12}): HCV RNA level < LLOQ 12 weeks after the completion of therapy (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL)

[2] Treatment-emergent adverse event (AE)-related withdrawal rate

2.3.2 Secondary objectives

[1] Sustained virological response (SVR_{24}): HCV RNA level < LLOQ 24 weeks after the completion of therapy (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL)

[2] Rapid virological response (RVR): HCV RNA level < LLOQ at week 4 of treatment (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL)

[3] End-of-treatment virological response (EOTVR): HCV RNA level < LLOQ at end of treatment (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL)

[4] Fibrosis Index Based on 4 markers (FIB-4): changes of FIB-4 before treatment and at the end-of-follow-up

[5] FibroScan: changes of liver stiffness before treatment and at the end-of-follow-up

2.3.3 Outcome measures

[1] Efficacy: sustained virologic response (SVR_{12}), defined as HCV RNA < LLOQ 12 weeks after the completion of therapy (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL) for subjects who receive at least one dose of the study medications.

[2] Safety: treatment-emergent AE-related withdrawal rate for subjects who receive at least one dose of the study drugs.

2.4 Study schedule

2.4.1 Study windows and rounding principles

The time windows allowed in the study are listed below and should be followed unless otherwise specified in this protocol.

Timeframe	Allowable Windows

Screening visit	0
Rescreening visit	± 28 days
Treatment visits	± 2 days
Follow-up visits	± 7 days
End of follow-up visit	± 14 days
Extended follow-up visit	± 14 days

Data for the analyses will be rounded following the standard mathematical or scientific principles where values < 5 will be round down whereas values ≥ 5 will be round up to the next significant digit.

2.4.2 Screening visit

At the screening visit, subjects who provide signed and dated written informed consent will undergo the study procedure identified in Section 2.5 associated with the screening visit. The investigator will evaluate whether the subject meets all of the eligibility criteria during the period from the screening visit through the start of the treatment period. Subjects who meet all eligibility criteria with the exception of non-evaluable FibroScan should undergo a liver biopsy. Liver biopsy should be performed during the screening period if all the inclusion criteria and one of the exclusion criteria are met. The screening visit will be conducted up to 28 days before the start of the drug treatment. Subjects who fail to fulfill initial screening can have another rescreening which would be spanned within 28 days of the first screening. The study is designed to enroll 35 treatment-naïve and 15 treatment-experienced eligible subjects to meet the scientific objectives. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects undergoing screening will not be enrolled.

2.4.3 Rescreening visit

Subjects who meet all eligibility criteria with the exception of up to 3 exclusionary laboratory parameters may rescreen once within the 28-day screening period. However, subjects with any of the following

exclusionary values will not be allowed to rescreen:

[1] Positive hepatitis B surface antigen

[2] Positive HIV antibody

[3] Confirmed pregnancy

Subjects who fail to enroll within 28 days of screening, regardless of the reason for falling outside the 28-day screening window, may be allowed to rescreen only once. These subjects must be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary at the first screening attempt.

2.4.4 Treatment visit

After meeting the eligibility criteria, 35 treatment-naïve and 15 treatment-experienced patients will be enrolled and assigned to 12 weeks of PrOD treatment. Subjects will receive instructions about the investigational drugs and the dosing schedule at the week 0 (i.e. day 1/baseline) visit. Ombitasvir/paritaprevir/ritonavir will be dosed orally daily and dasabuvir will be dosed orally twice daily as described in Section 2.2.7. All subjects will continue to return to the site on an outpatient basis up to 12 weeks for the study procedures. Sites should ensure that subjects adhere to the study visits listed in the flow chart. Subjects who cannot complete the study visits should ensure they do not run out of the investigational drugs prior to the next study visit. Compliance is critical to ensure adequate drug exposure. Safety and tolerability of the treatment will be assessed throughout the study. Laboratory tests will include hematology, biochemistry, coagulation profiles, virological, serological test, and urinalysis when appropriate. Blood samples for the RAVs will be collected as detailed in flow chart. Virologic failure criteria will be evaluated and applied by the investigator as detailed in Section 2.5.4.3. Subjects who prematurely discontinue from the treatment should return for a treatment discontinuation visit and undergo the study procedures as described (See Section 4.2).

2.4.5 Follow-up visit

All subjects who receive at least one of investigational drugs after treatment visits and either complete treatment or prematurely discontinue treatment will be monitored in the post-treatment follow-up for safety, efficacy and the emergence and persistence of RAVs for additional 24 weeks following the last dose of investigational drugs. The post-treatment follow-up will begin the day following the last dose of investigational drugs. Subjects with HCV RNA <LOD at the EOT (i.e. end-of-treatment virologic response, EOTVR) and who have a confirmed HCV RNA ≥ LOD at any point in the post-treatment follow-up till 12 weeks after the completion of therapy will be considered to have relapsed.

2.4.6 End of follow-up visit

Subjects should return to the site for the end of follow-up visit at week 12 off-therapy. If the subject prematurely discontinues treatment, then he/she should have all end of follow-up visit during the last site visit. The site staff should contact the subjects who fail to receive end of follow-up visit whining 7 days to confirm the availability of efficacy and safety endpoints.

2.4.7 Extended follow-up visit

Subjects are suggested return to the site for the extended follow-up visit at week 24 off-therapy. If the subject prematurely discontinues treatment, then he/she should have all end of follow-up visit during the last site visit.

2.5 Study procedures/evaluations (See summary Table at the end of the section)

The study procedures are outlined and discussed in detail in this section with the exception of assessment of concomitant medications (See Section 2.1.4.2), monitoring of treatment compliance (See Section 2.2.9), and collection of adverse event (AE) information (Section 3). All study data will be recorded in the subject's source documentation and then the appropriate CRF.

2.5.1 Informed consent

Written informed consent will be obtained from the subject before any study procedures are commenced.

2.5.2 Demographics, baseline values, medical history

Demographics and baseline characteristics including the age, gender, race, and medical history will be obtained from each patient who provides written informed consent. The medical history will be obtained by consulting the subjects. If there is uncertainty with regard to the subject's medical history, he/she may be requested to provide the related medical records from the primary care physicians or other health-care providers, if appropriate. Methods of contraception, if applicable, should also be documented in the source documents.

2.5.3 Clinical evaluations

2.5.3.1 Vital signs, weight, height

Vital signs will include ear temperature, pulse rate (PR), respiratory rate (RR) and blood pressure (BP). The subject should wear lightweight clothing and no shoes during weighing. Height will only be measured at screening visit, and the subject will not wear shoes.

2.5.3.2 Physical examination

The site investigators will perform the physical examination for each subject at the defined clinic visits. The complete physical examination will include examination of all pertinent body systems (head & neck, chest, heart, abdomen, genitourinary, extremities, skin, and nervous system). Furthermore, the site investigators should document the specific changes from previous medical status.

2.5.3.3 Adverse events

The site investigators are responsible for the detection and documentation of any event meeting the criteria and definition of adverse events (AEs) or serious adverse events (SAEs). All AEs and SAEs should be recorded by a pre-specific checklist in the source documents. The severity of all constitutional AEs is graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Furthermore, the site investigators should assess the causality between the allocated treatment and the AEs or SAEs.

2.5.4 Laboratory evaluations

2.5.4.1 Routine laboratory panels

Hematology, coagulation profile, biochemistry, serology and urinalysis panels performed at the assigned visits will be shown below.

Classification	Item
Hematology	Hemoglobin (Hb), hematocrit (HCT), white blood cell count (WBC), platelet count (PLT), differential WBC count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell count (RBC)
Coagulation profile	Prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR)
Biochemistry	Albumin (ALB), total bilirubin (T-BIL), direct bilirubin (D-BIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutaryl transpeptidase (γ-GT), blood urea nitrogen (BUN), creatinine (CRE), sodium (NA), potassium (K), chloride (CL), calcium (Ca), inorganic phosphorus (P), magnesium (Mg), uric acid (UA), fasting glucose (GLUAC), glycated hemoglobin (HbA1c), triglyceride (TG), cholesterol (CHO), low density lipoprotein (LDL), high

	density lipoprotein (HDL), iron (FE), total iron binding capacity (TIBC), ferritin
Serology	Hepatitis B virus surface antigen (HBsAg), hepatitis B virus surface antigen antibody(anti-HBs), hepatitis B core antigen antibody (anti-HBc), hepatitis C virus antibody (Anti-HCV), human immunodeficiency virus antibody (Anti-HIV), alfa-fetoprotein (AFP)
Pregnancy test	Urine or serum beta human chorionic gonadotropin (β-HCG)

Fibrosis index based on 4 markers (FIB-4): an index to assess the severity of fibrosis stages by using age, platelet count, AST, and ALT levels. The formula of FIB-4 is shown as below:

$$\textbf{FIB-4} = \frac{\text{Age (years)} \times \text{AST (IU/L)}}{\text{Platelet count } (10^9 \text{ cells/L}) \times \text{ALT (IU/L)}^{1/2}}$$

FIB-4 ≤ 1.45 denotes a fibrosis stage of < F3

FIB-4 > 3.25 denotes a fibrosis stage of ≥ F3

2.5.4.2 Human genetic analysis

Human genetic study will be performed by testing the single nucleotide polymorphism (SNP) at the locus of rs8099917 for interleukin 28B (IL28B) gene (ABI TaqMan allelic discrimination kit and ABI7900HT Sequence Detection System, Applied Biosystems, Life Technologies Corporation, Grand Island, NY) at screening visit. Subjects who do not have available but who can be reached before the trial completion will be required to perform this genetic study.

2.5.4.3 Virology analyses

Virology analyses performed at the assigned site visits are shown below.

Classification	Item
Virology	Hepatitis C virus RNA (HCV RNA)
Virology	Hepatitis C virus genotype (HCV genotype)
Virology	Resistance associated variants (RAVs)

[1] HCV RNA will be tested by Cobas TaqMan HCV Test v2.0 (Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL)

[2] HCV genotype will be tested by Abbott RealTi*me* HCV genotype II (Abbott Molecular Inc. Illinois, USA)

[3] RAV analysis: specific instruction for preparation and storage of samples will be provided by the central laboratory, and RAVs will be performed by population-based sequencing at sites of interest for HCV NS regions

The virological responses during treatment and virologic outcome are listed below:

Parameter	Definition
Very rapid virologic response (vRVR)	HCV RNA < LLOQ at week 2 of treatment
Rapid virologic response (RVR)	HCV RNA < LLOQ at week 4 of treatment
End-of-treatment virologic response (EOTVR)	HCV RNA < LLOQ at the end of treatment (EOT)
Sustained virologic response (SVR_4)	HCV RNA < LLOQ 4 weeks after the completion of treatment
Sustained virologic response (SVR_{12})	HCV RNA < LLOQ 12 weeks after the completion of treatment
Sustained virologic response (SVR_{24})	HCV RNA < LLOQ 24 weeks after the completion of treatment
Virologic failure	Failure to achieve SVR
Relapse	HCV RNA < LLOQ at the end-of-treatment, but becoming detectable after the cessation of treatment
Null-response	Failure to achieve HCV RNA < LLOQ by week

	6
Viral breakthrough	HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurement ≥ LOD) at any time point after HCV RNA < LLOQ during treatment Increased from nadir HCV RNA (defined as 2 consecutive HCV RNA measurement of > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment
Non virologic failure	Subjects who fail to achieve SVR and who cannot be categorized to relapse, null response or viral breakthrough

Except for subjects with relapse or subjects who meet the non virologic failure, those who meet the criteria for viral breakthrough or viral null-response should discontinue study treatment.

2.5.4.4 Abdominal ultrasonography

Gray-scale abdominal ultrasonography (US) will be recorded at the time points of screening visit, and EOT and EOF.

2.5.4.5 Electrocardiogram (ECG)

Resting 12-lead ECG will be recorded at the time points of screening visit, day 1 of treatment, EOT, EOF and the extended follow-up.

2.5.4.6 FibroScan and liver biopsy

FibroScan is required at the screening visit for all subjects who are willing to participate in the study. Subjects with a non-qualifying Fibroscan results (including failure to measure [zero valid measurement], unreliable measurement [less than 10 valid measurement, a successful rate of less than 60% or the

interquartile range more than 30% of the median FibroScan score]) are suggested to receive liver biopsy to confirm the severity of hepatic fibrosis. Liver biopsy is not optional and is not compulsive. Follow-up Fibroscan will be performed at EOT and EOF for all subjects who participate in the study, even if the subject with non-qualifying FibroScan evaluation at the screening visit. Furthermore, liver biopsy to stage the severity of hepatic fibrosis at EOF is also optional.

2.5.4.7 Archive serum sample

Archive serum samples will be collected at the study visits. Archive serum samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, viral load, safety/efficacy assessment, HCV gene sequencing, HCV resistance testing, and other possible predictors for treatment responses.

The preparation, transport, and storage of the archive serum samples will be provided by the central laboratory.

Summary Tables for Study Procedures/Evaluations

Study Visit	0	1	2	3	4	5	6	7	8	9	10	11	12
Procedure	Screening	Treatment							EOT	Follow-up		EOF	Extended follow-up
Study Week	-4 to -1	Day 1	1	2	4	6	8	10	12	16	20	24	36
Informed Consent	X												
Inclusion/Exclusion	X												
Demographic (age, gender, race)	X												
Height	X												
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X												
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	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			
Abdominal US	X								X			X	
12-lead ECG	X	X							X			X	X
Pregnancy test	X	X			X		X		X	X			
FibroScan or Liver biopsy	X								X			X	

Study Visit	0	1	2	3	4	5	6	7	8	9	10	11	12
Procedure	Screening	Treatment							EOT	Follow-up		EOF	Extended follow-up
Study Week	-4 to -1	Day 1	1	2	4	6	8	10	12	16	20	24	36
Complete blood count	X	X	X	X	X	X	X	X	X	X	X	X	X
PT/aPTT	X	X							X			X	X
Alb	X	X							X			X	X
T-Bil/D-Bil	X	X	X	X	X	X	X	X	X	X	X	X	X
AST/ALT	X	X	X	X	X	X	X	X	X	X	X	X	X
ALP/r-GT	X	X	X	X	X	X	X	X	X	X	X	X	X
BUN/Cre	X	X							X			X	X
Na/K/Cl/Ca/P/Mg	X	X			X		X		X			X	X
Uric acid	X	X			X		X		X			X	X
GluAC	X	X			X		X		X			X	X
HbA1c	X	X							X			X	X
TG/T-CHO/HDL/LDL	X	X			X		X		X			X	X
Fe/TIBC/ferritin	X	X							X			X	X
AFP	X	X							X			X	X
Anti-HCV	X	X							X			X	X
HBsAg/anti-HBs/anti-HBc/anti-HIV	X												
HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV genotype	X												
Resistant variants	X	X	X	X	X	X	X	X	X	X	X	X	X

Archive serum sample	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

3. ADVERSE EVENT MANAGEMENT & REPORTING

3.1 Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory tests), symptom, or disease temporally associated with the use of a medicinal or investigational product, whether or not the event is considered causally related to the use of the product.

An AE can result from the use of drugs stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a subject's pre-existing health status is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in treatment discontinuation or drug dosage reduction, necessitate additional medical intervention, and/or if the practitioner/investigator considers them to be an AE.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE even if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been planned prior to the study, and then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

3.2 Serious adverse event

A serious adverse event (SAE) is any adverse event occurring for treated patients during the study period that will results in any of the following outcomes:

[1] Death

[2] Life-threatening (subject at immediate risk of death)

[3] In-patients hospitalization or prolongation of existing hospitalization

[4] Congenital anomaly or birth defect

[5] Persistent or significant disability or incapacity

[6] Important medical event requiring medical or surgical intervention to prevent serious outcome

For SAEs with the outcome of death, the date and the cause of death will be recorded on the appropriate CRF.

3.3 Reporting and classification procedures

All constitutional and laboratory AEs of the study are graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, which can be available by visiting the following website (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). If the subject experiences the same AE with more than one grade of intensity, the highest grade of intensity should be recorded in CRF. In addition to grade the severity, the investigator should also determine the causal-relationship between each AE or SAEs and the administered investigational drug(s). When assessing the relationship to the investigational drug(s), the most conservative evaluation should be adopted.

If a SAE occurs during the study period, the investigator should immediately notify the Data Monitor and Safety Board (DMSB), Institutional Review Board (IRB)/Ethics Committee (EC), and local regulatory authorities. The site investigator must complete a SAE Report Form and is responsible to report the event to the regulatory authorities mentioned above by faxing the required documents.

3.3.1 Severity of adverse event

The investigator will use the following definition to grade the severity of each AE:

Severity*	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3	Severe or medically significant but not immediate life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

* Not all grades are appropriate for all AEs. Therefore, some AEs are listed in CTCAE v.4.0 with fewer than five options for Grade selection.

3.3.2 Relationship to investigational drug

The investigator will use the following definition to assess the relationship of the AE to the use of PrOD

Relationship	Definition
Reasonable possibility	An AE where there is evidence to suggest a causal relationship between the study drug and the AE
No reasonable possibility	An AE where there is no evidence to suggest a causal relationship between the study drug and the AE

For causality assessments, events assessed as having a reasonable possibility of being related to the investigational drug will be considered “associated”. Events assessed as having no reasonable possibility of being related to the investigational drug will be considered “not associated”. An AE will be considered to be associated to the investigational drug if the investigator has not reported a causality or deemed it not assessable.

3.3.3 Pregnancy

Subjects and their partners should avoid pregnancy and males should avoid sperm donation throughout the course of the study, starting with study day 1 and for 28 days after the EOT by PrOD.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected for pregnancies occurring up to 28 days after the EOT by PrOD.

Subjects who discontinue investigational drugs due to pregnancy will be monitored for SVR in post-treatment period.

Pregnancy in a study subject is not considered an AE. However, the

medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE.

3.3.4 Toxicity management

For the purpose of medical management, all AEs and laboratory abnormalities that occurring during the study must be evaluated by the investigator. Toxicity is deemed “clinically significant” based on the judgement of the investigator. Laboratory abnormalities will be managed as deemed clinically appropriate by the investigator until resolved.

The investigator should avoid interruption investigational drugs for > 7 consecutive days. The investigator should ensure that the study drug interruptions and the associated AEs are promptly entered into appropriate CRF.

3.3.4.1 Grade 1 or 2 adverse events and laboratory abnormalities

Subjects who develop Grade 1 or 2 AEs or laboratory abnormalities may continue investigational drugs with follow-up per study protocol and in accordance with local standard of care. (See Appendix A)

3.3.4.2 Grade 3, or higher adverse events and laboratory abnormalities

[1] Grade 3, or higher adverse events (severe or serious adverse events)

If a subject experiences a severe or serious AE that the investigator considers to be a reasonable possibility of relationship to the study drug, investigator should assess whether the AE can be managed medically without interruption of study drug, or whether study drug should be interrupted until it improves, or study drugs should be permanently discontinued. If study drugs are interrupted and restarted and the AE recurs, then study drug should be permanently discontinued.

If a subject experiences a severe or serious AE that is considered unrelated (no reasonable possibility) to the study drugs, it is not necessary to interrupt study drugs unless an interruption is required because of the nature of the event (e.g. unable to take oral medications). If an

interruption is required, it should not exceed 7 days.

The investigator should ensure that all SAEs are reported to DMSB, IRB/EC, local regulatory authorities and the Sponsor within 24 hours of awareness. SAE follow-up information, including associated dose interruption or discontinuation, must also be reported to these institutes within 24 hours of awareness and the information should be promptly recorded in CRF.

[2] Grade 3, or higher laboratory abnormalities (See Appendix A)

With the exception of Grade 3 or higher abnormalities of total bilirubin, uric acid, phosphorous, total cholesterol, triglyceride, or glucose (in subjects with a diagnosis of diabetes mellitus), if the subject a Grade 3 or higher laboratory parameter during the treatment period, the abnormal laboratory test should be repeated. If the Grade 3 or higher abnormality is confirmed, the investigator should assess whether the abnormality can be managed medically without interruption of the study drugs, or whether study drugs should be interrupted or permanently discontinued and the laboratory parameter followed until it improves. If study drugs are interrupted and restarted and the abnormality recurs, then study drugs should be permanently discontinued.

Elevations of serum AST or ALT should be managed according to the guidance in Section 3.3.4.3. Grade 3 or higher abnormalities of total bilirubin, uric acid, phosphorus, total cholesterol, triglyceride, or glucose (in subjects with a diagnosis of diabetes mellitus) should be managed medically as appropriate and do not require conformation or study drug interruption unless deemed necessary by the investigator.

3.3.4.3 Management of transaminase elevations

Transient asymptomatic Grade 3 or higher ALT elevations have been observed in approximately 1% of subjects receiving paritaprevir/ritonavir-containing regimens. If a subject

experiences an increase in ALT > 10X ULN, or to > 5X ULN which was increased from previous measurement, the subject should have a confirmatory ALT measurement performed in a timely fashion. If the ALT increase in confirmed, the management guideline should be followed (See Table "Management of Confirmed ALT Elevations"). Subject using an estrogen-containing product should discontinue use of that product.

Management of Confirmed ALT Elevations	
ALT ≥ 20X ULN	• Permanently discontinue study drugs. • Manage the subject as medically appropriate.
ALT ≥ 10X ULN or ALT ≥ 5X ULN and increased from previous measurement with symptoms and signs of hepatitis present	• If using and estrogen-containing product: discontinue estrogen-containing product and repeat ALT testing, preferably within 1 week. • Repeat ALT, AST, T-Bil, D-Bil, ALP, and INR, preferably within 1 week • Evaluate for alterative etiology of ALT elevation: update medical history and concomitant medications CRF (if applicable), and obtain appropriate testing as appropriate. • Manage the subject as medically appropriate. • Permanently discontinue study drugs for any of the following: ALT level increase to 20X ULN, increasing D-Bil, increasing INR, or new symptoms/signs of hepatitis.
ALT ≥ 5X ULN and increased from previous measurement, but < 10X ULN and without symptoms or signs of hepatitis	• Continue study drugs. • As soon as possible, measure ALT, AST, T-Bil, D-Bil, ALP and INR. Repeat liver chemistry as indicated until resolution. Evaluate for alternative etiology of ALT elevation: update medical history and concomitant medications CRF (if applicable), and obtain additional testing as appropriate. • Manage the subject as medically appropriate. • Permanently discontinue study drugs for any of the following: ALT level increase to 20X ULN, increasing D-Bil, increasing INR, or new

	symptoms/signs of hepatitis.

4. DOSE INTERRUPTION, DISCONTINUATION RULES

4.1 Dose interruption

If a subject cannot take his/her study drugs according to protocol specific day due to AE, the subject should be treated for the event when appropriate. In addition, the subject should return to the clinic as soon as possible to receive the scheduled dosing within the timeframe (See Section 2.4.1). If the subject fails to receive the assigned study drugs within the timeframe, he/she should skip this dosing and return to the clinic for the next protocol specific dosing day. If an interruption is required, it should not exceed 7 days.

4.2 Dose discontinuation

Subjects who meet the one of the following criteria will be discontinued from the study

[1] Serious adverse events (SAEs)

[2] Subjectively wish to discontinue further treatment

[3] Pregnancy

[4] Null response to treatment

[5] Viral breakthrough under treatment

[6] Subject's non-compliance with the protocol

At any time, if the site investigator thinks that the study is no longer in the best interest for the patient, then the patients should be discontinued for further treatment.

4.3 Subject withdrawal and replacement

Subjects may withdrawal from the trials at any time for any reasons. Any subjects who are withdrawn from the trials are encouraged to receive off-therapy study visits to assess the efficacy and safety. The timing and reasons for treatment withdrawal should be documented by investigator in the CRF.

Eligible subjects who are scheduled for treatment but who do not receive any study drugs will be replaced and will not be considered in the analyses of efficacy and safety endpoints. Subjects who receive at least one dose of the study drugs and who prematurely discontinue treatment will not be replaced.

5. PROTOCOL DEVIATION

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with EC and local regulatory authorities, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the Sponsor and the study coordinator. Any significant protocol deviations affecting the subject eligibility and/or safety must be reviewed and/or approved by IRB/EC and local regulatory authorities, as applicable, prior to implementation.

6. STATISTICAL CONSIDERATION

6.1 Sample size determination

[1] Treatment-naïve HCV GT1b patients:

Based on the assumption that the SVR rate of treatment-naïve HCV GT-1b patients who receive 48 weeks of peginterferon alfa-2a plus low – dose RBV group is 64%, we estimate that a total of 35 patients would provide 90% power to detect an absolute increase in SVR with PrOD therapy of 30% points or more (2-sided alpha = 0.05).[31]

[2] Treatment-experienced HCV GT-1b patients:

It is not designed to evaluate formal statistical hypotheses, and no sample size calculation performed because of the lack of SVR rate data by peginterferon alfa-2a plus low-dose RBV retreatment. The estimated sample size in treatment-experienced subjects is 15.

[3] Estimated timeframe for completing the enrollment: 24 weeks

6.2 Definition of primary endpoints

[1] Primary efficacy endpoint: SVR_{12} rate, defined as subjects with serum HCV RNA <LOD 12 weeks after the cessation of treatment by a sensitive HCV RNA test (Abbott RealTi*me* HCV, Limit of detection (LOD): 12 IU/mL; Abbott Park, Illinois, USA) divided by total enrolled subjects in each arm for subjects who receive at least one dose of the study medication.

[2] Primary safety endpoint: adverse event (AE)-related withdrawal rate for subjects who receive at least one dose of the study medication.

6.3 Analyses for primary efficacy endpoint

The efficacy endpoint is SVR_{12}, and subjects who do not meet the criteria for SVR are considered not to achieve SVR_{12}. The clinical scenarios for subjects who fail to achieve SVR_{12} include: virologic failure, including relapse, null-response, viral breakthrough, and non virologic failure (See Section 2.5.4.3).

Subjects who are categorized as null-response or viral breakthrough are considered non-SVR regardless of the availability of the end of follow-up HCV RNA data.

Subjects (except null-response and viral breakthrough) are considered failure to achieve SVR_{12} even if they do not have available end of follow-up HCV RNA data.

To test the hypothesis that the SVR_{12} rate of treatment-naïve patients who receive PrOD for 12 weeks is superior to those who receive peginterferon plus low-dose RBV for 48 weeks, the percentages of subjects with SVR12 in patients will be calculated with a 2-sided 95% confidence interval (CI) using Wilson score method, and the lower confidence bound will be compared to the defined threshold. The lower confidence bound must be greater than 64% in order for the regimen to be considered superior.

6.4 Analysis for primary safety endpoint

The safety endpoint is treatment-emergent adverse event (AE)-related withdrawal rate for subjects who receive at least one dose of the study medication. The proportions of AE-related withdrawal rate in the study are reported by number (percentage) as appropriate. We will not report the P value because the estimated sample sizes in this trial are aimed to detect the differences of efficacy endpoint, rather than the differences of safety endpoint.

6.5 Sensitivity analysis for the primary efficacy endpoint

In addition to presenting the primary efficacy endpoint (SVR_{12}), SVR_{12} will be presented using the following other methods to impute missing post-treatment virologic results:

[1] Imputing any missing HCV RNA values in the SVR_{12} window by carrying forward the last non-missing (post-baseline) HCV RNA value prior to the SVR_{12} window

[2] Imputing as any missing HCV RNA values in the SVR_{12} window but exclude the subjects who are categorized as “prematurely discontinue study drugs with no no-treatment virologic failure” and “missing follow-up data in the post-treatment period”

6.6 Subgroup analyses

The SVR_{12} will be presented in percentage with 2-sided 95% CI in the following subgroups:

[1] Age (< 55 versus ≥ 55 yeas)

[2] Sex (male versus female)

[3] BMI (< 25 versus ≥ 25 kg/m^2)

[4] Baseline HCV RNA level (< 800,000 versus ≥ 800,000 IU/mL)

[5] IL28B genotype rs8099917 (TT versus non-TT)

[6] Fibrosis stage (< F2 versus ≥ F2) by FibroScan and/or liver biopsy

6.7 Additional efficacy endpoint

[1] SVR_{24}: HCV RNA level < LLOQ 24 weeks after the completion of therapy (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL)

[2] Rapid virological response (RVR): HCV RNA level < LLOQ) at week 4 of treatment(Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL)

[3] End-of-treatment virological response (EOTVR): HCV RNA level < LLOQ at the end of treatment (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, low limit of quantification (LLOQ): 25 IU/mL)

[4] Fibrosis index based on 4 markers (FIB-4): changes of FIB-4 before treatment and at the end-of-follow-up

[5] FibroScan: changes of liver stiffness before treatment and at the end-of-follow-up

6.8 Resistance analyses

Only samples with an HCV RNA level of ≥ 1,000 IU/mL will undergo population sequence analysis in order to allow accurate assessment of the product amplification. For subjects who experience virologic failure, the sample closest in time after with an HCV RNA level of ≥ 1,000 IU/mL will be used if the HCV RNA level at the time of failure is < 1,000 IU/mL. The prototype reference strain with its associated GenBank Accession ID for sequence analyses is 1b-Con1 (AJ238799)

For PrOD treatment, resistance-associated signature amino acid variants will be identified as appropriate. Amino acid positions where RAVs have been identified *in vitro* and/or *in vivo* in HCV GT-1b are shown:

Direct Acting Antiviral	**Amino Acid Position for HCV GT-1b RAVs**
Paritaprevir (NS3)	56, 155, 156, 168
Ombitasvir (NS5A)	28, 29, 30, 31, 32, 58, 93
Dasabuvir (NS5B)	316, 368, 411, 414, 445, 448, 453, 553, 556, 558, 559

The following definition will be used in the resistance analyses:

[1] Baseline sample: sample collected before the first dose of PrOD.

[2] Baseline variant: a variant (by population sequencing) in a baseline sample determined by comparison of the amino acid sequence of the baseline sample to the appropriate prototypic reference amino acid sequence for a given target at the NS3, NS5A and NS5B region.

[3] Post-baseline variant by population sequencing: an amino acid variant in a post-baseline time point sample that is not detected at baseline in the subject and is detectable by population sequencing.

[4] Emerged variant by population sequencing: a post-baseline variant that is observed in 2 or more subjects of the same subgenotype by population sequencing.

[5] Linked variant by population sequencing: 2 or more signature or emerged amino acid variants identified within a sample by population sequencing where at least one of the variants is at a signature position, and no mixture amino acids is detected at either position.

For those samples to be evaluated, a listing by subject of all baseline variants relative to the prototypic reference sequence at signature resistance-associated amino acid positions will be provided for each target of PrOD regimen. Furthermore, the HCV amino acid sequence at post-baseline time points with an HCV RNA level of ≥ 1,000 IU/mL that are analyzed will be compared to the baseline and prototypic reference amino acid sequences. A listing by subject and time point of all post-baseline variants relative to the baseline amino acid sequences will be provided for paritaprevir (NS3),

ombitasvir (NS5A) and dasabuvir (NS5B). In addition, a listing by subject and time point of all post-baseline variants at signature resistance-associated amino acid positions relative to the prototypic reference amino acid sequences will be provided. Furthermore, the number and percentage of subjects with emerged variants by amino acid position and variant within a DAA target as compared to baseline will be summarized.

The number and percentage of subjects with linked variants by population sequencing within paritaprevir, ombitasvir and dasabuvir will be summarized. In addition to a listing of linked variants by subject and time point will be provided for each DAA target.

The persistence of resistance-associated substitutions that emerged for paritaprevir, ombitasvir, and dasabuvir will be assessed by population sequencing at selected post-treatment time point. Listing by subject and time point of all post-treatment variants relative to the baseline amino acid sequence will be provided for each DAA target.

6.9 Adverse events

The number and percentage of subjects with treatment-emergent AEs after initiation of study drugs through 28 days after the last dose of study drugs will be tabulated and provided according to definition provided by CTCAE, version 4.0. In addition, the number and percentage of subjects with SAEs ad the number and the number of percentage of subjects with treatment-emergent AEs leading to treatment discontinuation will also be provided.

Subjects with more than one AE defined by CTCAE, version 4.0, will be counted only once for that term using the most severe incidence for the severity rating table and the most related for the relationship to study drug table.

6.10 Clinical laboratory data

Clinical laboratory tests will be summarized in each study visit. The baseline value will be the last measurement prior to the initial dose of study drug. Laboratory data values collected during the treatment period will be categorized as low, normal, or high based on reference ranges of the

laboratory used in this study. The number and percentage of subjects who experience post-baseline changes during treatment in clinical laboratory values from low/normal to high and high/normal to low based in the normal range will be summarized.

Additional analyses will be performed if useful and appropriate.

7. STUDY ADMINISTRATION

7.1 Regulatory and ethical consideration

7.1.1 Institutional review board/ethics committee approval

It is the investigator's responsibility to ensure that the protocol is reviewed and approved by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC). The investigator must also submit the informed consent form, any other written documents for the subject, and all advertisements that may be used for subject recruitment to the IRB/EC for review and approval before commencing study-specific activities. If there would be any protocol amendment during the study, it is the investigator's responsibility to submit the related documents to IRB/EC and ensure to obtain IRB/EC approval before implementation of any amended procedures. It is also the investigator's responsibility to submit any SAE report, regular progress report to IRB/EC, and receive scheduled or un-scheduled monitoring from IRB/EC.

7.1.2 Ethical conduct of the study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principle that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified as followed:

[1] Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying IRB/EC, local regulatory authorities, and the Sponsor, except when necessary to protect the safety, rights or welfare of subjects

[2] Personally conducting or supervising the described investigation(s)

[3] Informing all subjects that the drugs are being used for investigational purposes and complying with the requirements

relating to informed consent and IRB/EC review and approval of the protocol and amendments

[4] Reporting adverse experiences that occur in the course of the investigation(s) to the principle investigator, IRB/EC, local regulatory authorities, and the Sponsor

[5] Reading the safety information in the protocol, including the instructions for use and the potential risks and side effects of the investigational product(s)

[6] Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments

[7] Maintaining adequate and accurate records of the conduct during the study, making those records available for inspection by IRB/EC, local regulatory authorities, and the Sponsor

[8] Maintaining records demonstrating that an EC reviews and approves the initial clinical investigation and all amendments

[9] Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals and/or directly to the IRB/EC, local regulatory authorities and the Sponsor

[10] Following the protocol and not make any changes in the research without IRB/EC approval, except where necessary to eliminate the apparent immediate hazards to human subjects

7.1.3 Subject informed consent

Before enrollment, the subject must provide written informed consent form to the investigator in accordance to ethical regulations. A copy of the informed consent form will be given to the subject and the original one will be placed in the subject's medical record. The International Conference on Harmonization (ICH) required elements and Health Insurance Portability and Accountability Act (HIPAA) authorization in language that is readable an understandable to the subject.

7.2 Data collection

7.2.1 Source documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, evaluation checklist, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media and/or X-rays. Data collected during the study must be recorded by the investigator on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, IRB/EC audit, and regulatory inspection(s), providing direct access to source documents.

7.2.2 Case report forms

Case report form (CRF) must be completed for each subject screened or enrolled in this study. These forms will be used to transmit information collected during the study to the Sponsor and the local regulatory authorities, as applicable. An electronic CRF (eCRF) will be provided for the study. All data should be entered into eCRF within 3 days after the subject's visit. After the subject has completed the trial, the principle investigator in each site must review the eCRF and sign the signature page of the eCRF to confirm he/she has reviewed all the data in eCRF that are pertinent to the subject.

7.3 Record retention

The site should retain a copy of all the study records for the study subjects in a secure and accessible location for a minimum of 10 years after the completion of the study. Study records will contain the appropriate documents which are conformed to the recommendation by International Conference on Harmonization for Good Clinical Practice (ICH-GCP).

7.4 Information disclosure

7.4.1 Confidentiality

The name of each subject will be kept confidential. The subject's code number, subject's initial, and date of birth will be recorded in eCRF. All the findings in the study will be stored in electronic database. Subject will be informed that all personal information made available for inspection will be protected in strict confidence.

7.4.2 Completion of the study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and the Sponsor. Continuation of this study beyond this date must be mutually agreed upon writing by both the investigator and the Sponsor. The investigator will provide a final report to the IRB/EC following completion of the study, and will forward a copy of this report to the Sponsor.

7.4.3 Publication policy

The investigators are intended to publish the results in the form of interim analysis or final completion report to the conference meeting or related journals as appropriate within a reasonable period of time after completion of the study. The Sponsor will determine the timing for data disclosure when appropriate.

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9. APPENDIX

Appendix A: Grading for Laboratory Abnormalities (Adapted from CTCAE, version 4.0)

	Hematology				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hemoglobin decreased	<LLN - 10.0 g/dL <LLN - 6.2 mmol/L <LLN – 100 g/L	10.0 - 8.0 g/dL 6.2 - 4.9 mmol/L 100 – 80 g/L	8.0 – 6.5 g/dL 4.9 – 4.0 mmol/L 80 – 65 g/L	< 6.5 g/dL < 4.0 mmol/L < 65 g/L	-
White blood cell count decreased	< LLN – 3,000/mm^3 < LLN – 3.0 x 10^9/L	< 3,000 – 2,000/mm^3 < 3.0 x 10^9 – 2.0 x 10^9/L	< 2,000 – 1,000/mm^3 < 2.0 x 10^9 – 1.0 x 10^9/L	< 1,000/mm^3 < 1.0 x 10^9/L	-
Neutrophil count decreased	< LLN – 1,500/mm^3 < LLN – 1.5 x 10^9/L	< 1,500 – 1,000/mm^3 < 1.5 x 10^9 – 1.0 x 10^9/L	< 1,000 – 500/mm^3 < 1.0 x 10^9 – 0.5 x 10^9/L	< 500/mm^3 < 0.5 x 10^9/L	-
Lymphocyte count decreased	< LLN –800/mm^3 < LLN – 0.8 x 10^9/L	< 800 – 500/mm^3 < 0.8 x 10^9 – 0.5 x 10^9/L	< 500 – 200/mm^3 < 0.5 x 10^9 – 0.2 x 10^9/L	< 200/mm^3 < 0.2 x 10^9/L	-
Lymphocyte count increased	-	> 4,000 – 20,000/mm^3	> 20,000/mm^3	-	-
Platelet count decreased	< LLN – 75,000/mm^3 < LLN – 75.0 x 10^9/L	75,000 – 50,000/mm^3 75.0 x 10^9 – 50.0 x 10^9/L	50,000 – 25,000/mm^3 50.0 x 10^9 – 25.0 x 10^9/L	< 25,000/mm^3 < 25.0 x 10^9/L	-
INR increased	> 1 – 1.5 x ULN; > 1 – 1.5 times above baseline if on anticoagulation	> 1.5 – 2.5 x ULN; > 1.5 – 2.5 times above baseline if on anticoagulation	> 2.5 x ULN; > 2.5 times above baseline if on anticoagulation	-	-
Activated partial thromboplastin time prolonged	> ULN – 1.5 x ULN	> 1.5 -2.5 x ULN	> 2.5 x ULN	-	-

	Biochemistry				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Albumin, serum, low	< LLN – 3 g/dL < LLN – 30 g/L	< 3 - 2 g/dL < 30 - 20 g/L	< 2 g/dL < 20 g/L	Life-threatening consequences; urgent intervention indicated	-
Blood bilirubin increased	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 x ULN	
Alanine aminotransferase increased	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN	-
Aspartate aminotransferase increased	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN	-
Alkaline phosphatase increased	> ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN	-
r-GT increased	> ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN	-
Glucose, serum, low	< LLN – 55 mg/dL < LLN – 3.0 mmol/L	< 55 – 40 mg/dL < 3.0 – 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 – 1.7 mmol/L Hospitalization indicated	< 30 mg/dL < 1.7 mmol/L Life-threatening consequences	Death
Glucose, serum, high (fasting)	> ULN – 160 mg/dL > ULN – 8.9 mmol/L	> 160 - 250 mg/dL > 8.9 – 13.9 mmol/L	> 250 -500 mg/dL > 13.9 – 27.8 mmol/L Hospitalization indicated	> 500 mg/dL > 27.8 mmol/L Life-threatening consequences	Death
Triglyceride, high (fasting)	> 150 – 300 mg/dL	> 300 - 500 mg/dL	> 500 – 1,000 mg/dL	> 1,000 mg/dL	-

	> 1.71 -3.42 mmol/L	> 3.42 -5.7 mmol/L	> 5.7 -11.4 mmol/L	> 11.4 mmol/L	
Cholesterol, high	> ULN – 300 mg/dL > ULN – 7.75 mmol/L	> 300 - 400 mg/dL > 7.75 – 10.34 mmol/L	> 400 - 500 mg/dL > 10.34 – 12.92 mmol/L	> 500 mg/dL > 12.92 mmol/L	-
Uric acid, serum, high	> ULN – 10.0 mg/dL (0.59 mmol/L) without physiologic consequences	-	> ULN – 10.0 mg/dL (0.59 mmol/L) with physiologic consequences	> 10.0 mg/dL (> 0.59 mmol/L) Life-threatening consequences	-
Sodium, serum, high	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L Hospitalization indicated	> 160 mmol/L Life-threatening consequences	Death
Sodium, serum, low	< LLN – 130 mmol/L	-	< 130 – 120 mmol/L	< 120 mmol/L Life-threatening consequences	Death
Potassium, serum, high	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L Hospitalization indicated	> 7.0 mmol/L Life-threatening consequences	Death
Potassium, serum, low	< LLN – 3.0 mmol/L	< LLN – 3.0 mmol/L Symptomatic; intervention indicated	< 3.0 – 2.5 mmol/L Hospitalization indicated	< 2.5 mmol/L Life-threatening consequences	Death
Calcium, serum, high	> ULN – 11.5 mg/dL > ULN – 2.9 mmol/L	> 11.5 – 12.5 mg/dL > 2.9 – 3.1 mmol/L Symptomatic	> 12.5 – 13.5 mg/dL > 3.1 – 3.4 mmol/L Hospitalization indicated	> 13.5 mg/dL > 3.4 mmol/L Life-threatening	Death

				consequences	
Calcium, ionized, high	> ULN – 1.5 mmol/L	> 1.5 – 1.6 mmol/L Symptomatic	> 1.6 – 1.8 mmol/L Hospitalization indicated	> 1.8 mmol/L Life-threatening consequences	Death
Calcium, serum, low	< LLN – 8.0 mg/dL < LLN – 2.0 mmol/L	< 8.0 – 7.0 mg/dL < 2.0 – 1.75 mmol/L	< 7.0 – 6.0 mg/dL < 1.75 – 1.5 mmol/L Hospitalization indicated	< 6.0 mg/dL < 1.5 mmol/L Life-threatening consequences	Death
Calcium, ionized, low	< LLN – 1.0 mmol/L	< 1.0 – 0.9 mmol/L Symptomatic	< 0.9 – 0.8 mmol/L Hospitalization indicated	< 0.8 mmol/L Life-threatening consequences	Death
Phosphate, serum, low	< LLN – 2.5 mg/dL < LLN – 0.8 mmol/L	< 2.5 – 2.0 mg/dL < 0.8 – 0.6 mmol/L	< 2.0 – 1.0 mg/dL < 0.6 – 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L Life-threatening consequences	Death
Magnesium, serum, high	> ULN – 3.0 mg/dL > ULN – 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.30 mmol/L	> 8.0 mg/dL > 3.30 mmol/L Life-threatening consequences	Death
Magnesium, serum, low	< LLN – 1.2 mg/dL < LLN – 0.5 mmol/L	< 1.2 – 0.9 mg/dL < 0.5 – 0.4 mmol/L	< 0.9 – 0.7 mg/dL < 0.4 – 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L Life-threatening	Death

				consequences	
Lipase increased	> ULN – 1.5 x ULN	> 1.5 – 2.0 x ULN	> 2.0 – 5.0 x ULN	> 5.0 x ULN	-
Serum amylase increased	> ULN – 1.5 x ULN	> 1.5 – 2.0 x ULN	> 2.0 – 5.0 x ULN	> 5.0 x ULN	-
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	Cardiac Investigation				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Electrocardiogram QT corrected interval prolonged	QTc 450-480 ms	QTc 481-500 ms	QTc ≥ 501 ms at least two separate ECGs	QTc ≥ 501 ms and > 60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	-

LLN: lower limit of normal; ULN: upper limit of normal