A Phase IV, Multisite Study of the Treatment of Chronic Hepatitis C Virus Infection Genotype 1 in a Real World Large Health Maintenance Organization: An Evaluation of Real World Sustained Virological Response and Patient Reported Outcomes

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABT-450	NS3/NS4A (non-structural protease inhibitor)
ABT-450/r	Ritonavir (pharmacokinetic enhancer)
ABT-267	Ombitasvir (NS5A inhibitor)
ABT-333	Dasabuvir (NS5B non-nucleoside polymerase inhibitor)
AE	Adverse Event
ALT	Alanine aminotransferase (also SGPT)
ANCOVA	Analysis of Covariance
ANOVA	Analysis Of Variance
Anti-HIV Ab	Anti-Human Immunodeficiency Virus Antibody
APRI	Aspartate aminotransferase to Platelet Ratio Index
AUC	Area Under the Curve
β-hCG	βeta-human Chorionic Gonadotropin
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
CRO	Contract Research Organization
CYP	Cytochrome P450
CYP2C8	Cytochrome P450 2C8
CYP3A	Cytochrome P450 3A
DAA	Direct-Acting Antiviral
DMC	Data Monitoring Committee
dL	Deciliter
DNA	Deoxyribonucleic Acid
FDA	Food and Drug Administration (United States)
FSH	Follicle-Stimulating Hormone
ECG	Electrocardiogram
FibroScan	A non-invasive ultrasound procedure
eRVR	Extended Rapid Virologic Response
GCP	Good Clinical Practice
g/dl	gram/deciliter
Gr	Grade
Hb	Hemoglobin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HCVAb	Hepatitis C Virus Antibody
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
HT	Height
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IND	Investigational New Drug (Application)
INR	International Normalized Ratio (of prothrombin time)

IRB	Institutional Review Board
IU	International Unit
IWRS	Interactive Web Response System
kg	kilogram
KPSC	Kaiser Permanente Southern California
L	Liter
LLOQ	Lower Limit of Quantification
mg	milligram
min	minute
mL	milliliter
N	Number
NDC	National Drug Code
P	Pulse Rate
PBO	Placebo
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PK	Pharmacokinetic
pegIFN	pegylated-interferon
PRO	Patient Reported Outcomes
RBV	Ribavirin
RNA	Ribonucleic Acid
SCPMG	Southern California Permanente Medical Group
SD	Standard Deviation
SOC	Standard Of Care
SOP	Standard Operating Procedure
SVR	Sustained Virologic Response
SVR4	Sustained Virologic Response at 4 Weeks after treatment completion
SVR12	Sustained Virologic Response at 12 Weeks after treatment completion
TSH	Thyroid Stimulating Hormone
WT	Weight (body)
ULN	Upper Limit of Normal

PROTOCOL SUMMARY

Title	A Phase IV, Multisite Study of the Treatment of Chronic Hepatitis C Virus Infection Genotype 1 in a Real World Large Health Maintenance Organization: An Evaluation of Real World Sustained Virological Response and Patient Reported Outcomes
Short Title	Real World Study: Genotype 1 Chronic HCV Treatment and Evaluation of Real World SVR and PROs
Protocol Number	IRB 10568
Study Phase	Phase IV
Study Site(s)	Multiple Kaiser Permanente Southern California Medical Centers
Number of Subjects	200
Study Arms	Two study arms • Genotype 1a: VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir) + RBV (ribavirin) • Genotype 1b: VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir)
Indication	Treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection
Primary Objective	The primary objective of this open label study is to evaluate the rate of sustained virological response rate 12 weeks after completion of treatment (SVR12) with VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir), with or without ribavirin in a large real world setting.
Overview of Study Design	This is a Phase IV, open-label, multi-center study to evaluate the real world sustained virological response rate, subject adherence, and subject reported outcomes during and after treatment of non-cirrhotic genotype 1 chronic hepatitis C subjects aged 18 years and older, with the AbbVie 3 direct-acting antiviral (3-DAA) regimen of VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir), with or without ribavirin. Subjects may be treatment-naïve or treatment experienced with pegylated-interferon based regimens excluding regimens with direct-acting antiviral agents.
Investigational Product Administration	VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir)VIEKIRA PAK is ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets. Ombitasvir, paritaprevir, ritonavir fixed dose combination tablet includes a hepatitis C virus NS5A inhibitor (ombitasvir), a hepatitis C virus NS3/4A protease inhibitor (paritaprevir), and a CYP3A inhibitor (ritonavir) that inhibits CYP3A mediated metabolism of paritaprevir, thereby providing increased plasma concentration of paritaprevir. Dasabuvir is a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor, which is supplied as separate tablets in the copackage. Both tablets are for oral administration. VIEKIRA PAK is dispensed in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs. Each child resistant daily dose pack contains four tablets: two 12.5/75/50 mg ombitasvir, paritaprevir, ritonavir

	tablets and two 250 mg dasabuvir tablets, and indicates which tablets need to be taken in the morning and evening. The NDC number is NDC 0074-3093-28. VIEKIRA PAK: • Two ombitasvir, paritaprevir, ritonavir tablets once daily (in the morning) with a meal without regard to fat or calorie content and • One dasabuvir tablet twice daily (morning and evening) with a meal without regard to fat or calorie content. <u>Ribavirin</u> Ribavirin is a synthetic nucleoside analogue (purine analogue). The chemical name of ribavirin is 1-β-D-ribofuranosyl-1*H* -1,2,4-triazole-3-carboxamide. Ribavirin capsules USP, 200 mg are white, opaque, hard gelatin capsules imprinted (in blue) RIBAVIRIN over 200 mg on cap and GG 608 on body. RBV (ribavirin): Dosage is based on weight and adjusted for renal impairment subjects. • If subject weighs less than or equal to 75 kg, 1000 mg daily in two divided doses with food. • If subject weighs greater than 75 kg, 1200 mg daily in two divided doses with food.
Eligibility Criteria	<u>Inclusion Criteria</u> 1. Male or female at least 18 years of age at time of screening. 2. Subject voluntarily signed the Informed Consent Form for the study. 3. Subject is able to adhere to study visit/ procedure schedule and protocol requirements 4. Subject, if female must not use estrogen-containing hormonal contraception including oral, injectable, implantable, patch and ring varieties during study drug treatment 5. Subject, if female must meet at least one of the following: • Subject of childbearing potential must agree to either o practice 2 effective contraceptive methods for study duration, starting at the Screening Visit through 30 days after stopping study drug if not receiving ribavirin, 7 months/or as directed by ribavirin label if receiving ribavirin o practice total abstinence from sexual intercourse (minimum 1 complete menstrual cycle) o Sexually active with female partner only • Postmenopausal defined as age appropriate amenorrhea for ≥ 2 years prior to screening and post-menopausal state confirmed by follicle-stimulating hormone (FSH) level • Surgically sterile defined as bilateral tubal ligation or bilateral oophorectomy or hysterectomy • Has male sexual partner with vasectomy

	6. Subject, if male, who is not surgically sterile and is sexually active with female partner of childbearing potential must agree to practice 2 effective contraceptive methods for study duration, starting at Screening through 30 days after stopping study drug if not receiving ribavirin, 7 months/or as directed by ribavirin label if receiving ribavirin 7. Subject must have at least one of the following indicators of chronic hepatitis C virus infection prior to study enrollment: • Positive anti-HCV antibody or HCV RNA > 10,000 IU/mL at least 6 months before screening, and positive for HCV RNA at the time of screening • HCV RNA > 10,000 IU/mL at screening and liver biopsy consistent with chronic HCV infection • Credible evidence of chronic hepatitis C as per the investigator and HCV RNA > 10,000 IU/mL at the time of screening. 8. Subject has a screening laboratory result indicating HCV genotype 1-infection. Historical genotype within 6 months of screening may be used at the discretion of the investigator. <u>Exclusion Criteria</u> 1. Subject declined to sign the Informed Consent Form for the study. 2. Subject, if female is pregnant or is breastfeeding, or if male, with female partner who is currently pregnant. 3. Subject has positive test result for hepatitis B surface antigen or confirmed positive anti-HIV antibody test 4. Subject received study contraindicated medications including but not limited to those listed in Table 5, or medications contraindicated for ritonavir or ribavirin per FDA label prior to study drug administration and unwilling to discontinue prior to starting the study drug. For those that receive ribavirin, contraindicated medications must be discontinued at least 2 weeks or 10 half-lives prior to study drug administration, whichever is longer. 5. Use of known strong inducers of cytochrome P450 3A (CYP3A) or strong inducers of cytochrome P450 2C8 (CYP2C8) or strong inhibitors of CYP2C8 within 2 weeks of the respective medication/supplement prior to initial dose of study drug (see Table 5). 6. Clinically significant abnormalities or co-morbidities, other than HCV infection that in opinion of the investigator makes subject unsuitable for this study or drug regimen 7. Current enrollment in another interventional clinical study or prior or current use of any investigational or commercially available anti-HCV agents other than interferon or ribavirin including previous exposure to ABT450 (paritaprevir) , ABT-267 (ombitasvir) or ABT-333 (dasabuvir) or receipt of any investigational product within 6 weeks prior to study drug administration 8. Prior treatment of chronic HCV infection with a direct acting antiviral agent(s): telaprevir, boceprevir, sofosbuvir, simeprevir, or other direct acting antiviral

	9. History of solid organ transplant 10. Screening laboratory analyses shows any of the following abnormal laboratory results: • Glomerular filtration rate < 30 mL/min as estimated by the Cockcroft-Gault equation • Hemoglobin < 12 gram per deciliter for male • Hemoglobin < 11 gram per deciliter for female 11. Evidence of cirrhosis, documented by one of the following: • Liver biopsy histologic diagnosis: Metavir Score > 3 (includes 3 - 4 or 3/4) or Ishak score > 4 • In the absence of liver biopsy: a FibroScan score ≥ 12.5 kPa • In the absence of a FibroScan: an APRI score > 1.5 • In the judgment of the investigator clinical findings are consistent with cirrhosis. In general, a non-cirrhotic result from a Fibroscan will supersede evidence of cirrhosis based on APRI and a liver biopsy not showing cirrhosis will supersede both Fibroscan and APRI 12. History of liver decompensation: ascites noted on a physical exam, imaging or other test; variceal bleeding; hepatic encephalopathy 13. Confirmed presence of hepatocellular carcinoma indicated on computed tomography, magnetic resonance, or other imaging techniques within 3 months prior to screening 14. HCV genotype performed during screening indicates infection with any genotype other than genotype 1 15. Recent history of drug or alcohol abuse that could, in the opinion of the investigator, affect adherence to the study protocol
Study Endpoint	The primary efficacy endpoint is to assess SVR12 in two subgroups of HCV (genotype 1a or 1b). The simple percentage of subjects achieving SVR12 will be calculated and a two-sided 95% confidence interval of the percentage will be computed based on Wilson's score method. We cannot know a priori how the 200 patients will be split into the two subgroups, but we expect each group to have approximately 100 patients (presumably between 80 and 120). Assuming a subgroup size of 100 each, the lower bound of the 95% confidence interval will be within 7 percentage points of the observed SVR12 rate. Once the groups are fixed, the actual lower bound of the 95% confidence interval can be computed. The observed SVR12 rate and confidence interval will be discussed in the context of results from randomized clinical trials, such as the SAPPHIRE-I/II trials and PEARL-II/III/IV trials described in the Background section. While formal statistical inference comparing results of this study to those of the randomized clinical trials will not be conducted, the point estimates and confidence intervals will be compared to assess the degree to which results from the real world setting are similar to or different from those in the randomized clinical trial setting.

	Results by prior treatment experience and response may be summarized if appropriate, based on the number of subjects enrolled in each subgroup. No subgroup sample size targets have been established.
Statistical Methods	This is an open label, non-randomized, study with two study arms. Descriptive statistics will be used to describe the observed sustained virological response rate and patient adherence to the treatment regimen. The primary analysis, to evaluate SVR12, will occur after all subjects have completed or prematurely discontinued the study. The intent-to-treat population will consist of all enrolled subjects in this study. The primary efficacy analysis on clinical outcomes will be performed on all subjects in the intent-to-treat population. The modified intent-to-treat population will include all who receive at least one dose of study drug. No data will be imputed for any efficacy or safety analyses except for analyses of the HCV RNA endpoints. HCV RNA values will be selected for the SVR_{12} analysis based on the defined visit. The visit window for analysis of SVR4 is post-treatment days 2-56, and the visit window for analysis of SVR12 is post-treatment days 57-168. The latest available value within each window will be used to define the SVR 4 or SVR12 result.

1 BACKGROUND AND HYPOTHESIS

Hepatitis C viral (HCV) infection is a global health problem. 170 million individuals are chronically infected worldwide and at risk of developing liver cirrhosis, hepatocellular carcinoma, or both.[1] Cirrhosis develops after prolonged hepatitis C virus infection.[2] Complications of cirrhosis include hepatic decompensation (ascites; encephalopathy; variceal hemorrhage; hepato-renal syndrome or hepatic synthetic dysfunction) and hepatocellular carcinoma, which ensues at a rate of about 3% per year.[3-6] Without liver transplantation, decompensated cirrhosis leads to death in 50% to 72% of patients after 5 years.[7] As a result of the high prevalence of hepatitis C virus (HCV) infection and resultant complications, HCV is the leading indication for liver transplantation in the United States and the world as a whole.[8]

Treatment of hepatitis C virus-infected patients could reduce the risk of cirrhosis, decompensation, cancer, and liver-related deaths. Among patients treated with pegylated interferon and ribavirin therapy, achieving a sustained virologic response (SVR) was associated with significant reduction in all-cause death compared to subjects who did not achieve sustained virologic response (5-year mortality rate in HCV genotype 1-infected patients: 6.7% versus 14.4%, respectively).[9]

In addition, the 5-year occurrence of the composite clinical events of death, liver failure, and hepatocellular carcinoma were significantly lower in hepatitis C virus-infected patients with advanced fibrosis or cirrhosis who achieved sustained virologic response versus those without sustained virologic response (9.2% versus 28.2%, respectively).[10] Patients with sustained virologic response following treatment with pegylated interferon with or without ribavirin have also shown improvement in liver histology and a reduction in liver-related death in several studies.[11-13]

Moreover, patients with compensated cirrhosis who achieve sustained virologic response essentially eliminate their subsequent risk of decompensation, may achieve histologic regression, and decrease their risk of hepatocellular carcinoma by two-thirds.[14-16] In patients with advanced fibrosis and cirrhosis, viral suppression by more than 4 $\log_{10}$ with pegylated interferon and ribavirin was associated with marked reduction in death/liver transplantation, and in liver-related morbidity and death.[17]

Combinations of direct-acting antiviral (DAA) agents targeting different steps of viral replication have the potential to significantly improve hepatitis C virus treatment, compared to the current interferon-containing regimens for HCV genotype 1 infection. Combination DAA allows for increased/sustained virologic response rates, elimination of interferon as a component of therapy, increased safety, and tolerability of treatment, shortened duration of therapy and simplifying the treatment algorithm.

Wider application of direct-acting antiviral agent therapy and better responses with combination direct-acting antiviral agent regimen(s) could significantly reduce the public health burden of this disease.

AbbVie's interferon-free regimen for the treatment of chronic hepatitis C virus genotype 1 infection includes three direct-acting antiviral agents targeting different steps in hepatitis C virus

replication: ABT-450 is a nonstructural protein 3/nonstructural protein 4A (NS3/NS4A) protease inhibitor co-administered with a pharmacokinetic (PK) enhancer, ritonavir (ABT-450/r); an NS5A inhibitor ABT-267 (ombitasvir) and ABT-333 (dasabuvir) an NS5B non-nucleoside polymerase inhibitor.

The three direct-acting antiviral (3-DAA) agents regimen has been studied with and without ribavirin in over 2,300 patients in Phase 3 trials across a variety of patient populations including those with compensated cirrhosis. Based on Phase 3 data, the regimen with or without ribavirin appears to be safe, well tolerated, and efficacious in treatment-naïve and treatment-experienced hepatitis C virus genotype 1-infected subjects including those with compensated cirrhosis. The overall efficacy results (intent-to-treat) from the Phase 3 studies are listed in Table 1.

Table 1 - Combined SVR 12 Rates (Intent-to-treat, missing = failure) from Phase 3 Studies by Subpopulation of Subtype, Prior Treatment History, and Presence or Absence of Cirrhosis

Subpopulation	3-DAA 12 Weeks SVR_{12}	3-DAA + RBV 12 Weeks SVR_{12}	3-DAA + RBV 24 Weeks SVR_{12}	
Genotype 1b non-cirrhotics				
Naïve	99.0	98.9	--	
Null	100	94.4	--	
Partial	100	98.1	--	
Relapser	100	98.5	--	
Genotype 1a non-cirrhotics				
Naïve	90.2	95.7	--	
Null	--	95.4	--	
Partial	--	100	--	
Relapser	--	94.0	--	
Genotype 1b cirrhotics				
Naïve	--	100	100	
Null	--	100	100	
Partial	--	85.7*	100	
Relapser	--	100	100	
Genotype 1a cirrhotics				
Naïve	--	92.4		
Null	--	80.0	92.9	92.9
Partial	--	100	100	
Relapser	--	93.3	100	

DDA = Direct-Acting Antiviral; * Based on N = 7; 6/7 achieved SVR

The data outlined in Table 1 (above) and Table 2 (below) are based on the following studies:

1.1 Phase 3 Placebo-Controlled Studies: SAPPHIRE-I and SAPPHIRE-II

Study SAPPHIRE-I and SAPPHIRE-II are randomized, placebo-controlled studies that assessed the safety and efficacy of 12 weeks of therapy with three direct-acting antiviral (3-DAA) agents and ribavirin in hepatitis C virus (HCV) genotype 1-infected treatment-naïve subjects (Study SAPPHIRE-I) and prior pegylated-interferon/ribavirin non-responders (Study SAPPHIRE-II) without cirrhosis. Subjects received 3-DAA agents and ribavirin (RBV) for 12 weeks of treatment. Subjects randomized to the placebo arm received placebo for 12 weeks, after which they received open-label 3-DAA agents and RBV for 12 weeks. In Study SAPPHIRE-I 631 subjects were randomized and received at least one dose of study drug, of which 67.7% had HCV genotype 1a and 32.3% had HCV genotype 1b. The SVR_{12} rate for treatment-naïve subjects receiving 3-DAA agents and ribavirin for 12 weeks was 96.2%. Virologic failure was noted in 7/322 (2.2%) genotype 1a subjects (on treatment virologic failure: n = 1; relapse: n = 6) and 1/151 (0.7%) genotype 1b subjects (relapse).

In Study SAPHIRE-II, a total of 394 subjects were randomized and received at least one dose of study drug, of which 58.4% had hepatitis C virus (HCV) genotype 1a, 41.4% had HCV genotype 1b, 49.0% were prior pegylated-interferon/ribavirin null responders, 21.9/% were prior pegylated-interferon/ribavirin partial responders, and 29.2% were prior pegylated-interferon/ribavirin relapsers. The SVR_{12} rate for treatment-experienced subjects receiving three direct-acting antiviral (3-DAA) agents and ribavirin for 12 weeks was 96.3%. Virologic failure (all relapse) was noted in 5/173 (2.9%) genotype 1a subjects and 2/123 (1.6%) genotype 1b subjects.

1.2 Phase 3 Regimen-Controlled Studies: (3DAA ± RBV): Studies PEARL-II, PEARL-III, PEARL-IV, and M14-002

Studies PEARL-II, PEARL-III, and PEARL-IV are randomized, regimen-controlled trials that assessed the safety and efficacy of 12 weeks of treatment with three direct-acting antiviral agents with or without ribavirin. Studies PEARL-III and PEARL-IV are ribavirin placebo-controlled studies, while Study PEARL-II is an open-label study. The patient population was different in each of the three studies. Study PEARL-II enrolled genotype 1b-infected subjects with prior non-response to pegylated-interferon/ribavirin, Study PEARL-III enrolled genotype 1b-infected subjects who were treatment-naïve, and Study PEARL-IV enrolled genotype 1a-infected subjects who were treatment-naïve. All three studies excluded subjects with cirrhosis. In Study PEARL-II, a total of 186 subjects were randomized and received at least one dose of study drug, of which 34.9% were prior pegylated-interferon/ribavirin (pegIFN/RBV) null responders, 28.5% were prior pegIFN/RBV partial responders, and 36.6% were pegIFN/RBV relapsers. The SVR_{12} rates were 96.6% in the three direct-acting agents with ribavirin arm and 100% in the three direct-acting antiviral agents without ribavirin arm. The difference in SVR_{12} rates between the two regimens met the protocol-specified criteria for noninferiority. Hence, the three direct-acting antivirals (3-DAA) regimen without ribavirin demonstrated noninferiority compared to the (3-DAA) agents and ribavirin. No subject in either arm experienced on treatment virologic failure or post-treatment relapse.

In the PEARL-III study, 419 subjects were randomized and received at least one dose of study drug. The SVR_{12} rates for treatment-naïve subjects with HCV genotype 1b-infection, who received either 3-DAA with, or without ribavirin for 12 weeks were 99.5% and 99.0%, respectively. The difference in SVR_{12} rates between the two regimens in this study also met the protocol-specified criteria for noninferiority. One of the 419 treated subjects in the three direct-acting antiviral agents and ribavirin arm experienced on-treatment virologic failure.

In Study M14-002, 305 subjects were randomized and received at least one dose of study drug. The SVR_{12} rates for treatment-naïve subjects with HCV genotype 1a-infection who received three direct-acting antiviral agents either with or without ribavirin for 12 weeks in Study PEARL-IV were 97.0% and 90.2%, respectively. The SVR_{12} rate in the 3-DAA arm did not achieve noninferiority to the 3-DAA and ribavirin arm. Virologic failure was noted in 2/100 (2.0%) subjects (on treatment virologic failure: n = 1; relapse: n = 1) in the ribavirin-containing regimen and 16/205 (7.8%) subjects (on treatment virologic failure: n = 6; relapse: n = 10) in the ribavirin-free regimen. The difference between arms demonstrates that ribavirin contributes to the efficacy in genotype 1a-infected patients and suggests that three direct-acting antiviral agents and ribavirin is the optimal regimen for these patients.

1.3 Phase 3 Study in Cirrhotics: Study TURQUOISE-II

Study TURQUOISE-II is a randomized, multicenter, open-label trial in treatment-naïve subjects or subjects previously treated with pegylated-interferon/ribavirin with chronic hepatitis C virus genotype 1-infection with compensated cirrhosis (Child-Pugh A, score l$\leq$ 6). The three direct-acting antiviral agents and ribavirin were administered for either 12 or 24 weeks of treatment.

A total of 380 subjects were randomized and received at least one dose of study drug, of which 68.7% had hepatitis C virus genotype 1a, 31.3% had hepatitis C virus genotype 1b, 42.1% were treatment-naïve, 36.1% were prior pegylated-interferon/ribavirin (pegIFN/RBV) null responders, 8.2% were prior pegIFN/RBV partial responders, and 13.7% were prior pegIFN/RBV relapsers.

The SVR_{12} rates for subjects with compensated cirrhosis treated with three direct-acting antiviral agents and ribavirin for 12 or 24 weeks were 91.8% and 95.9%, respectively. Virologic failure was noted in 13/208 (6.3%) subjects (on treatment virologic failure: n = 1; relapse: n = 12) receiving the 12 week regimen and 4/172 (2.3%) subjects (on treatment virologic failure: n = 3; relapse: n = 1) receiving the 24 week regimen.

Analyses of subgroups suggest that the overall difference in SVR_{12} rates was driven largely by a lower SVR_{12} rate among genotype 1a prior null responders who received 12 weeks of treatment, while other subgroups had comparable response rates when treated for 12 or 24 weeks.

1.4 Integrated Safety Results

A summary of treatment-emergent adverse events from the combined analyses of data from the Phase 3 studies is presented in Table 2. A majority of subjects experienced at least one event, but most subjects experienced events that were mild in severity. Rates of severe adverse events and adverse events leading to discontinuation were low across studies but numerically higher in the study of subjects with cirrhosis.

Table 2: Overview of Treatment-Emergent Adverse Events (AE)

	Placebo-Controlled		Regimen-Controlled		Cirrhotics	
	12-Week 3-DAA + RBV	12-Week PBO	12-Week 3-DAA + RBV	12-Week 3-DAA	12-Week 3-DAA + RBV	24-Week 3-DAA + RBV
Events, %	N = 770	N = 255	N = 401	N = 509	N = 208	N = 172
Subjects ≥ 1 AE	89.0	76.9	82.8	75.0	91.8	90.7
Severe AE	3.5	0.4	1.0	1.2	6.7	7.6
Grade 3 or 4 AE	3.9	0.8	3.0	2.0	7.7	8.1
Serious AE	2.1	0.4	2.2	1.4	6.3	4.7
AE leading to discontinuation	0.8	0.4	0.5	0.4	1.9	2.3
Deaths	0.1[a]	0	0	0	0	0

DDA = Direct-Acting Antiviral; PBO: Placebo; [a]Lung Cancer

The most common adverse events regardless of causality are listed in Table 3. Adverse events that occurred at ≥ 5% incidence in the 3-DAA and RBV regimen versus the placebo were considered to be adverse drug reactions related to the study treatment. These include fatigue, nausea, pruritus, insomnia, asthenia, and anemia. The frequency of these events was generally lower in the arm treated without ribavirin. In general, rates of adverse events were similar in patients with cirrhosis versus those without.

Table 3: Treatment-Emergent Adverse Events with >/= 10% Frequency in at Least One Arm of the Analysis and Rates of Key Post-Baseline Lab Abnormalities

	Placebo-Controlled		Regimen-Controlled		Cirrhotics	
	12-Week 3-DAA + RBV	12-Week PBO	12-Week 3-DAA + RBV	12-Week 3-DAA	12-Week 3-DAA + RBV	24-Week 3-DAA + RBV
Treatment-emergent Adverse Events, %	N = 770	N = 255	N = 401	N = 509	N = 208	N = 172
Headache	34.3	29.8	24.4	25.1	27.9	30.8
Fatigue	34.2	26.3	29.9	26.5	32.7	46.5

	Placebo-Controlled		Regimen-Controlled		Cirrhotics	
	12-Week 3-DAA + RBV	12-Week PBO	12-Week 3-DAA + RBV	12-Week 3-DAA	12-Week 3-DAA + RBV	24-Week 3-DAA + RBV
Nausea	22.3	14.9	15.7	8.4	17.8	20.3
Pruritus	15.7	4.3	12.0	6.1	18.3	19.2
Insomnia	14.0	7.5	12.2	5.1	15.4	18.0
Diarrhea	13.5	9.0	8.7	11.4	14.4	16.9
Asthenia	13.5	6.7	9.0	3.9	13.9	12.8
Rash	10.0	5.9	6.2	3.7	11.1	14.5
Cough	8.7	5.1	6.7	4.7	11.5	11.0
Irritability	5.3	4.7	3.2	3.1	7.2	12.2
Anemia	5.3	0	7.5	0.2	7.7	10.5
Dyspnea	9.7	5.5	4.7	2.2	5.8	12.2
Laboratory Events, %	N = 765	N = 254	N = 401	N = 509	N = 208	N = 172
Hemoglobin						
< 10 g/dL (Gr 2)	5.5	0	6.2	0	7.2	11.0
< 8.0 g/dL (Gr 3)	0.1	0	0.5	0	1.4	0.6
ALT						
> 5 × ULN (Gr 3)	1.2	3.9	0.7	0.2	2.9	0
Bilirubin						
> 3 × ULN (Gr 3)	2.6	0	5.7	0.4	13.5	5.2

DDA = Direct-Acting Antiviral; PBO: placebo; Percentages of laboratory events based on the number of subjects with at least one post-baseline value

Transient elevations in total (predominantly indirect) bilirubin may occur due to ABT-450 inhibition of the bilirubin transporters OATP1B1 and OATP1B3, and ribavirin-induced hemolysis. The elevations generally peaked by weeks 1 - 2, declined through the end of treatment, and returned to within the normal range by four weeks post-treatment. Rates of hyperbilirubinemia were lower in subjects treated with three direct-acting antiviral (3-DAA) agents without ribavirin compared to 3-DAA with ribavirin. The rates and degree of hyperbilirubinemia were higher in patients with cirrhosis, but the temporal pattern of elevation followed by resolution was similar and few were symptomatic (jaundice). Rates of ≥ Grade 2 hemoglobin reductions were 6% among subjects without cirrhosis who received the 3-DAA and ribavirin regimen for 12 weeks, and 7% and 11% among subjects with cirrhosis who received the 3-DAA and ribavirin regimen for 12 and 24 weeks, respectively. Grade 3 hemoglobin values were rare. The decline in hemoglobin was largely managed with ribavirin dose reductions; use of hematologic growth factors and blood transfusion were rare. The

anemia reported in the clinical trials was primarily observed when the 3-DAA regimen was administered with ribavirin.

Transient asymptomatic post-baseline serum alanine aminotransferase (ALT) elevations of > 5 times upper limit of normal (ULN) occurred at a frequency of 1% across active treatment arms and were evaluated by an external hepatic panel. The serum (ALT) elevations were asymptomatic, usually occurred within the first four weeks of treatment and typically declined with ongoing treatment. A disproportionate number of the cases were in women on concurrent systemic estrogen-containing therapy (i.e. contraceptives or hormone replacement) and discontinuation of the hormonal therapy with continuation or brief interruption of the direct-acting antiviral regimen led to resolution in ALT elevation. Concomitant use of systemic estrogen-containing medications is a risk factor for these post-baseline elevations in serum alanine aminotransferase. No serum ALT elevations > 5 times ULN were observed in subjects receiving progestin only, or in subjects receiving topical vaginal estrogen preparations. Among the cases of serum ALT elevation, considered related to the direct-acting antiviral regimen, none resulted in hepatic dysfunction and they generally resolved or improved with ongoing treatment. All cases had resolved completely in the post-treatment follow-up.

ABT-450/ritonavir, ABT-267 (ombitasvir) (and its major, inactive human metabolites) and ABT-333 (dasabuvir) had no effects on embryo-fetal development in rodent and/or non-rodent species at maximal feasible exposures that provided area under the curve (AUC) multiples at least 4-fold higher than exposures at the recommended clinical doses. Clinical studies in women who are pregnant have not been conducted.

In summary, the three direct-acting antiviral (3-DAA) agents regimen, with or without ribavirin, was well tolerated with a low discontinuation rate. Adverse events were typically mild, and many of the adverse events and laboratory abnormalities observed were attributable to the presence of ribavirin.

Transient, asymptomatic serum alanine aminotransferase (ALT) elevations were observed at a low rate, were not associated with hepatic dysfunction, and generally resolved with ongoing treatment.

1.5 Study Risks versus Benefits

ABT-450/ritonavir, ABT-267 (ombitasvir) and ABT-333 (dasabuvir) with or without ribavirin have been well tolerated in the Phase 3 studies. Adverse events that are known, and those not previously described, may occur with the direct-acting antivirals or ribavirin as detailed in the informed consent for this study. In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures.

Risks associated with ABT-450/ritonavir/ABT-267 (ombitasvir) and ABT-333 (dasabuvir) co-administered with or without ribavirin, including the risks of toxicity and virologic failure, appear limited and manageable based on the results from the Phase 3 studies. Given the potential high rate of cure in hepatitis C virus genotype 1-infected subjects, the risk-benefit comparison is favorable.

This study will evaluate outcomes with ABT-450/ritonavir/ABT-267 (ombitasvir) and ABT-333 (dasabuvir) with or without ribavirin for treatment-naïve and interferon/ribavirin treatment-experienced adults with chronic HCV genotype 1-infection without cirrhosis in a real world setting. A non-cirrhotic population will be evaluated as this is a group that is not considered of highest priority according to current national practice guidelines and therefore, largely unstudied in a large real world population.

Until recently, the treatment of genotype 1 chronic HCV infection involved complicated interferon-containing regimens associated with many side effects. Due to adverse events and patient dropout, outcomes in real world settings during and after treatment with these regimens have been inferior to those seen in controlled clinical trials. The cure rate (sustained virological response) and the effectiveness of treatment has been reported to be low in real world settings using interferon-based treatment regimens. In a Veterans Administration study by Kramer et al, only 39.9% of genotype 1 patients who completed treatment and only 23.6% of those who initiated treatment achieved sustained virological response. Importantly, treatment effectiveness (defined as the proportion of the viremic cohort who achieved sustained virological response) was very low at only 3.5%.[18]

FDA Approval

On December 19, 2014, the FDA Approved ABT-450/ritonavir, ABT-267 (ombitasvir) and ABT-333 (dasabuvir) as VIEKIRA PAK™ (ombitasvir, paritaprevir, and ritonavir tablets, 12.5 mg/ 75 mg/ 50 mg; dasabuvir tablets, 250 mg), co-packaged for oral use with or without ribavirin for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.

1.6 Hypothesis

Since the new treatment regimens do not cause the adverse events associated with the prior therapy, our hypothesis is that treatment with the VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir) with or without ribavirin will result in excellent outcomes in the real world setting and that the outcomes will be similar to those seen in the registration trials.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this open label study is to evaluate the rate of sustained virological response rate 12 weeks after completion of treatment (SVR12) with VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir), with or without ribavirin in a large real world setting.

2.2 Secondary Objective

The secondary objectives of the study are as follows:

- To evaluate sustained virological response rate 4 weeks after completion of treatment (SVR4) with VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir), with or without ribavirin in a large real world setting
- To evaluate patient adherence with VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir), with or without ribavirin in a real world setting

3 STUDY DESIGN

3.1 Description of the Study

This is a Phase IV, open-label, multi-center study to evaluate the real world sustained virological response rate, subject adherence, and subject reported outcomes during and after treatment of non-cirrhotic genotype 1 chronic hepatitis C subjects aged 18 years and older, with the AbbVie 3 direct-acting antiviral (3-DAA) regimen of VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir), with or without ribavirin. Subjects may be treatment-naïve or treatment experienced with pegylated-interferon based regimens excluding regimens with direct-acting antiviral agents.

The study will be conducted at multiple KPSC Medical Centers and will screen approximately 275 subjects with an estimated 33% screen failure rate to enroll 200 subjects.

3.2 Subject Population

Subjects will be considered treatment-naïve if they have never received any antiviral treatment for HCV infection.

Subjects will be considered treatment-experienced if they have received prior interferon-based therapy (including interferon or pegylated-interferon monotherapy; interferon and ribavirin; or pegylated-interferon and ribavirin). Treatment-experienced subjects with prior use of HCV DAA(s) are excluded from study participation.

Subjects with documentation available to classify prior response to interferon and ribavirin, or pegylated-interferon and ribavirin treatment will be categorized as one of the following:

- **Null-responder:** did not achieve a 1 $\log_{10}$ IU/mL reduction in HCV RNA by week 4 or a 2 $\log_{10}$ IU/mL reduction in HCV RNA by week 12 during a prior interferon and ribavirin, or pegylated-interferon and ribavirin treatment course
- **Partial-responder:** achieved at least a 2 $\log_{10}$ IU/mL reduction in HCV RNA by week 12 during a prior interferon and ribavirin or pegylated-interferon and ribavirin treatment course, but failed to achieve HCV RNA undetectable at the end of treatment
- **Relapser:** achieved undetectable HCV RNA at end of a prior interferon and ribavirin or pegylated-interferon and ribavirin treatment course, but HCV RNA was detectable following therapy completion

Subjects with a less well-characterized IFN-based treatment experience, including those subjects with incomplete HCV RNA and treatment date documentation, will be categorized as one of the following:

- **Relapse/breakthrough:** achieved at least one documented result of HCV RNA undetectable during a prior IFN and RBV ribavirin, or pegIFN and RBV treatment course
- **Non-responder:** did not achieve a documented result of HCV RNA undetectable or HCV RNA was detected at the end of treatment during a prior IFN and RBV, or pegIFN and RBV treatment course with insufficient data available to categorize as a breakthrough, partial or null responder
- **Interferon intolerant:** did not meet any of the above definitions of treatment-failure and discontinued IFN and RBV, or pegIFN and RBV therapy due to IFN intolerability
- **Interferon experienced-other:** Includes IFN, or pegIFN and RBV monotherapy; IFN and RBV, or pegIFN and RBV experienced subjects; Includes subjects who do not have adequate documentation of response. Subjects receiving interferon or peginterferon monotherapy must be categorized as 'Interferon experienced-other'.

3.3 Treatment Arms

Subjects who meet all eligibility criteria and provide written informed consent will be enrolled in the study and assigned to one of two treatment groups.

Genotype 1a: VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir) + RBV (ribavirin)
Genotype 1b: VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir)

See Section 4.4 for more information.

3.4 Study Duration

Study Discontinuation

Southern California Permanente Medical Group (SCPMG) reserves the right to terminate this study at any time due to the incidence or severity of adverse events in this study that indicate a potential health hazard to subject or partner.

4 STUDY PRODUCT INFORMATION

For complete information on VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir), refer to the VIEKIRA PAK Package Insert version 12/2014. Select information from the document is available below.

For complete information on ribavirin, refer to the Ribavirin Package Insert version 08/2011. Select information from the document is available below.

4.1 Description

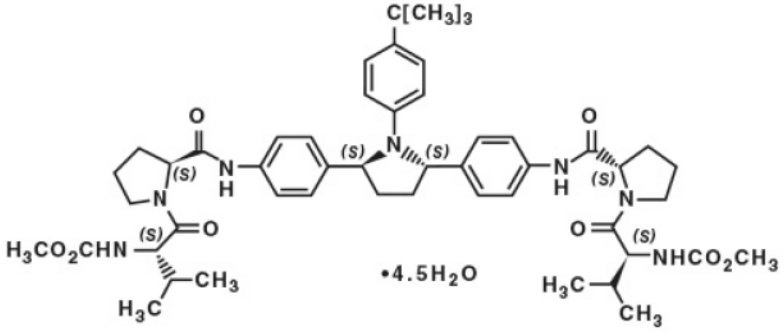
4.1.1 VIEKIRA PAK (ombitasvir, paritaprevir/r, dasubuvir)

VIEKIRA PAK is ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets.

Ombitasvir, paritaprevir, ritonavir fixed dose combination tablet includes a hepatitis C virus NS5A inhibitor (ombitasvir), a hepatitis C virus NS3/4A protease inhibitor (paritaprevir), and a CYP3A inhibitor (ritonavir) that inhibits CYP3A mediated metabolism of paritaprevir, thereby providing increased plasma concentration of paritaprevir. Dasabuvir is a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor, which is supplied as separate tablets in the copackage. Both tablets are for oral administration.

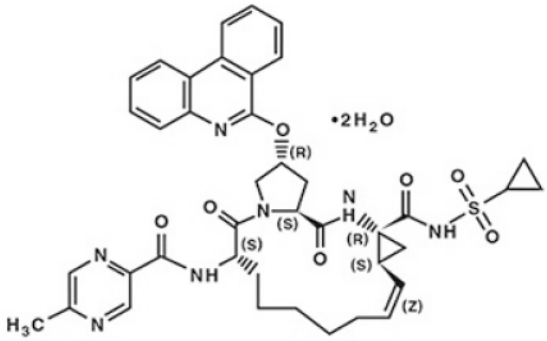
Ombitasvir

The chemical name of ombitasvir is Dimethyl ([(2*S*,5*S*)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate. The molecular formula is $C_{50}H_{67}N_7O_8 \cdot 4.5H_2O$ (hydrate) and the molecular weight for the drug substance is 975.20 (hydrate). The drug substance is white to light yellow to light pink powder, and is practically insoluble in aqueous buffers but is soluble in ethanol. Ombitasvir has the following molecular structure:



Paritaprevir

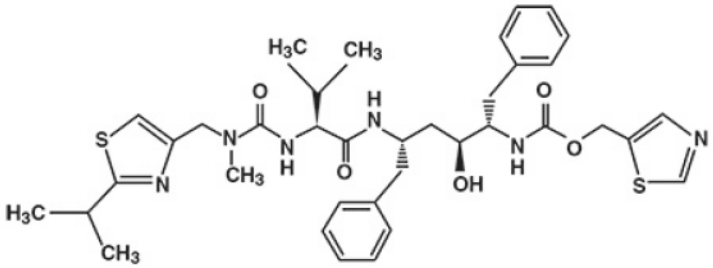
The chemical name of paritaprevir is (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14a(5H)-carboxamide dihydrate. The molecular formula is $C_{40}H_{43}N_7O_7S \cdot 2H_2O$ (dihydrate) and the molecular weight for the drug substance is 801.91 (dihydrate). The drug substance is white to off-white powder with very low water solubility. Paritaprevir has the following molecular structure:



Ritonavir

The chemical name of ritonavir is [5S-(5R*,8R*,10R*,11R*)]10-Hydroxy-2-methyl-5-(1-methyethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid,5-thiazolylmethyl ester. The molecular formula is $C_{37}H_{48}N_6O_5S_2$

and the molecular weight for the drug substance is 720.95. The drug substance is white to off white to light tan powder practically insoluble in water and freely soluble in methanol and ethanol. Ritonavir has the following molecular structure:

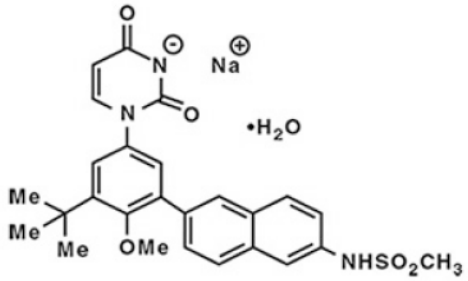


Ombitasvir, Paritaprevir, Ritonavir Fixed-Dose Combination Tablets

Ombitasvir, paritaprevir, and ritonavir film-coated tablets are co-formulated immediate release tablets. The tablet contains copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate Type I, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica, sodium stearyl fumarate, polyvinyl alcohol, polyethylene glycol 3350/macrogol 3350, talc, titanium dioxide, and iron oxide red. The strength for the tablet is 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir.

Dasabuvir

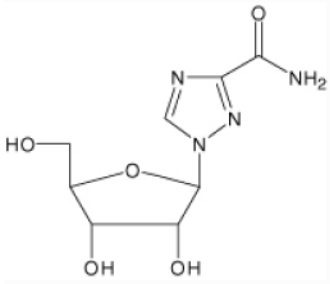
The chemical name of dasabuvir is Sodium 3-(3-*tert*-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1). The molecular formula is $C_{26}H_{26}N_3O_5S{\bullet}Na{\bullet}H_2O$ (salt, hydrate) and the molecular weight of the drug substance is 533.57 (salt, hydrate). The drug substance is white to pale yellow to pink powder, slightly soluble in water and very slightly soluble in methanol and isopropyl alcohol. Dasabuvir has the following molecular structure:



Dasabuvir is formulated as a 250 mg film-coated, immediate release tablet containing microcrystalline cellulose (D50-100 um), microcrystalline cellulose (D50-50 um), lactose monohydrate, copovidone, croscarmellose sodium, colloidal silicon dioxide/anhydrous colloidal silica, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350/macrogol 3350, talc, and iron oxide yellow, iron oxide red and iron oxide black. Each tablet contains 270.3 mg dasabuvir sodium monohydrate equivalent to 250 mg dasabuvir.

4.1.2 Ribavirin

Ribavirin is a synthetic nucleoside analogue (purine analogue). The chemical name of ribavirin is 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide and has the following structural formula:



Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The empirical formula is $C_8 H_{12} N_4 O_5$ and the molecular weight is 244.21.

Ribavirin capsules USP consist of a white powder in a white, opaque, gelatin capsule. Each capsule, for oral administration, contains 200 mg ribavirin. In addition, each capsule contains the following inactive ingredients: corn starch, croscarmellose sodium, hypromellose, magnesium stearate, mannitol and povidone. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of FD&C Blue #2 aluminum lake, propylene glycol, shellac and titanium dioxide.

4.2 Acquisition and Accountability

VIEKIRA PAK is manufactured by AbbVie Inc., North Chicago, IL 60064. Ribavirin is manufactured by Sandoz, Inc., Broomfield, CO 80020.

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

4.3 Formulation, Packaging, Labeling, and Storage

4.3.1 VIEKIRA PAK

VIEKIRA PAK is dispensed in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs. Each child resistant daily dose pack contains four tablets: two 12.5/75/50 mg ombitasvir, paritaprevir, ritonavir tablets and two 250 mg dasabuvir tablets, and indicates which tablets need to be taken in the morning and evening. The NDC number is NDC 0074-3093-28.

Ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets are pink-colored, film-coated, oblong biconvex shaped, debossed with "AV1" on one side. Dasabuvir 250 mg tablets are beige-colored, film-coated, oval-shaped, debossed with "AV2" on one side.
Store at or below 30°C (86°F).

4.3.2 Ribavirin

Ribavirin capsules USP, 200 mg are white, opaque, hard gelatin capsules imprinted (in blue) RIBAVIRIN over 200 mg on cap and GG 608 on body. Dispense in a tight container as defined in the USP. Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)

4.4 Dosage and Administration

Subjects who meet all eligibility criteria, and provide written informed consent will be enrolled in the study and assigned to either genotype 1a or genotype 1b treatment group and be administered the study drug as below:

Table 4. Treatment Regimen, Dosing and Duration per Arm

Treatment Arm	Treatment	Duration
Genotype 1a	**VIEKIRA PAK + (RBV) ribavirin**	**12 weeks**
	VIEKIRA PAK: • Two ombitasvir, paritaprevir, ritonavir tablets once daily (in the morning) with a meal without regard to fat or calorie content) and • One dasabuvir tablet twice daily (morning and evening) with a meal without regard to fat or calorie content. RBV (ribavirin): Dosage is based on weight and adjusted for renal impairment subjects. • If subject weighs less than or equal to 75 kg, 1000 mg daily in two divided doses with food. • If subject weighs greater than 75 kg, 1200 mg daily in two divided doses with food. Study drugs should be dosed together (e.g. VIEKIRA PAK with RBV in the morning with food, and dasabuvir with RBV in the evening with food).	
Genotype 1b	**VIEKIRA PAK**	**12 weeks**
	VIEKIRA PAK: • Two ombitasvir, paritaprevir, ritonavir tablets once daily (in the morning) with a meal without regard to fat or calorie content) and • One dasabuvir tablet twice daily (morning and evening) with a meal without regard to fat or calorie content.	

4.5 Dose Modification

VIEKIRA PAK will not be dose-modified.
Ribavirin will be adjusted for renal impairment subjects. Ribavirin will be dose-modified for decreases in hemoglobin or decreased glomerular filtration rate as per the package insert or per the clinical judgment of the investigator.

4.6 Toxicity and Safety Information

4.6.1 VIEKIRA PAK

ALT Elevations: Discontinue ethinyl estradiol-containing medications prior to starting VIEKIRA PAK (alternative contraceptive methods are recommended).

In subjects receiving VIEKIRA PAK with ribavirin, the most commonly reported adverse reactions (greater than 10% of subjects) were fatigue, nausea, pruritus, other skin reactions, insomnia and asthenia. In subjects receiving VIEKIRA PAK without ribavirin, the most

commonly reported adverse reactions (greater than or equal to 5% of subjects) were nausea, pruritus and insomnia. Refer to the VIEKIRA PAK Package Insert for more information.

4.6.2 Ribavirin

The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin.

Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days, and so it may persist in nonplasma compartments for as long as 6 months. Therefore, ribavirin therapy is contraindicated in women, who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post-treatment follow-up period.
Refer to the Ribavirin Package Insert for more information.

4.7 Prohibited Medication

Estrogen-containing hormonal contraceptives, including oral, injectable, implantable, patch and ring varieties, may not be used during study drug treatment.

Participants must not receive contraindicated medication prior to study drug administration including, but not limited to those listed in Table 4, or medications contraindicated for ritonavir or ribavirin per FDA label. For those that receive ribavirin, contraindicated medications must be discontinued at least 2 weeks or 10 half-lives prior to study drug administration, whichever is longer.

Table 5. Medications Contraindicated for Use with Study Drug Regimen

Alfuzosin Astemizole Carbamazepine Dihydroergotamine Efavirenz Ergotamine Ergonovine	Estrogen-containing Medications for Systemic Use Fusidic Acid Gemfibrozil Lovastatin Methylergonovine Midazolam (oral) Phenobarbital	Phenytoin Pimozide Rifampin Sildenafil** Simvastatin St. John's Wort Terfenadine Triazolam

* Not all medications contraindicated with VIEKIRA PAK, ritonavir, and ribavirin are listed above. Refer to the most current package inserts or product labeling for each drug for a complete list of contraindicated medications.
** When used for the treatment of pulmonary arterial hypertension

5 SELECTION OF SUBJECTS

5.1 Inclusion Criteria

To participate in this study the subject must **meet all** of the following inclusion criteria:

1. Male or female at least 18 years of age at time of screening.
2. Subject voluntarily signed the Informed Consent Form for the study.
3. Subject is able to adhere to study visit/ procedure schedule and protocol requirements
4. Subject, if female must not use estrogen-containing hormonal contraception including oral, injectable, implantable, patch and ring varieties during study drug treatment
5. Subject, if female must meet at least one of the following:
   - Subject of childbearing potential must agree to either
     - practice 2 effective contraceptive methods[1] for study duration, starting Screening through 30 days after stopping study drug if not receiving ribavirin, 6 months/or as directed by ribavirin label if receiving ribavirin
     - practice total abstinence from sexual intercourse (minimum 1 complete menstrual cycle)
     - be sexually active with female partner only
   - Postmenopausal defined as age appropriate amenorrhea for $\geq$ 2 years prior to screening and post-menopausal state confirmed by follicle-stimulating hormone (FSH) level
   - Surgically sterile defined as bilateral tubal ligation or bilateral oophorectomy or hysterectomy
   - Has male sexual partner with vasectomy
6. Subject, if male, who is not surgically sterile and is sexually active with female partner of childbearing potential must agree to practice 2 effective contraceptive methods[2] for study duration, starting at Screening through 30 days after stopping study drug if not receiving ribavirin, 7 months/or as directed by ribavirin label if receiving ribavirin
7. Subject must have at least one of the following indicators of chronic hepatitis C virus infection prior to study enrollment:
   - Positive anti-HCV antibody or HCV RNA > 10,000 IU/mL at least 6 months before screening, and positive for HCV RNA at the time of screening
   - HCV RNA > 10,000 IU/mL at screening and liver biopsy consistent with chronic HCV infection
   - Credible evidence of chronic hepatitis C as per the investigator and HCV RNA > 10,000 IU/mL at the time of screening.
8. Subject has a screening laboratory result indicating HCV genotype 1-infection. Historical genotype within 6 months of screening may be used at the discretion of the investigator.

[1] Effective contraceptive methods outlined in informed consent form, subject information sheet, and other subject documents
[2] Effective contraceptive methods outlined in informed consent form, subject information sheet, and other subject documents

5.2 Exclusion Criteria

To participate in this study the subject must **not meet any** of the following exclusion criteria:

1. Subject declined to sign the Informed Consent Form for the study.
2. Subject, if female is pregnant or is breastfeeding, or if male, with a partner who is currently pregnant.
3. Subject has positive test result for hepatitis B surface antigen or confirmed positive anti-HIV antibody test
4. Subject received study contraindicated medications including but not limited to those listed in Table 5, or medications contraindicated for ritonavir or ribavirin per FDA label prior to the study drug administration and unwilling to discontinue prior to starting the study drug. For those that receive ribavirin, contraindicated medications must be discontinued at least 2 weeks or 10 half-lives prior to study drug administration, whichever is longer.
5. Use of known strong inducers of cytochrome P450 3A (CYP3A) or strong inducers of cytochrome P450 2C8 (CYP2C8) or strong inhibitors of CYP2C8 within 2 weeks of the respective medication/supplement prior to initial dose of study drug (see Table 5).
6. Clinically significant abnormalities or co-morbidities, other than HCV infection that in opinion of the investigator makes subject unsuitable for this study or drug regimen
7. Current enrollment in another interventional clinical study or prior or current use of any investigational or commercially available anti-HCV agents other than interferon or ribavirin including previous exposure to ABT450 (paritaprevir), ABT-267 (ombitasvir) or ABT-333 (dasabuvir) or receipt of any investigational product within 6 weeks prior to study drug administration
8. Prior treatment of chronic HCV infection with a direct acting antiviral agent(s): telaprevir, boceprevir, sofosbuvir, simeprevir, or other direct acting antiviral
9. History of solid organ transplant
10. Screening laboratory analyses shows any of the following abnormal laboratory results:
    - Glomerular filtration rate < 30 mL/min as estimated by the Cockcroft-Gault equation[19]
    - Hemoglobin < 12 gram per deciliter for male
    - Hemoglobin < 11 gram per deciliter for female
11. Evidence of cirrhosis, documented by one of the following:
    - Liver biopsy histologic diagnosis: Metavir Score > 3 (includes 3 - 4 or 3/4) or Ishak score > 4
    - In the absence of liver biopsy: a FibroScan score $\geq$ 12.5 kPa
    - In the absence of a FibroScan: an APRI score > 1.5
    - In the judgment of the investigator clinical findings are consistent with cirrhosis. In general, a non-cirrhotic result from a Fibroscan will supersede evidence of cirrhosis based on APRI and a liver biopsy not showing cirrhosis will superseded both Fibroscan and APRI.
12. History of liver decompensation: ascites noted on a physical exam, imaging or other test; variceal bleeding; hepatic encephalopathy

13. Confirmed presence of hepatocellular carcinoma indicated on computed tomography, magnetic resonance, or other imaging techniques within 3 months prior to screening
14. HCV genotype performed during screening indicates infection with any genotype other than genotype 1
15. Recent history of active drug or alcohol abuse that could, in the opinion of the investigator, affect adherence to the study protocol

6 STUDY ASSESSMENTS

The study procedures to be performed are outlined in Appendix A: Study Visit/ Procedures Table and discussed in detail in this section. All study data will be recorded in the subject's source documentation and appropriate case report form(s).

6.1 Study Procedures

6.1.1 Informed Consent

The study and the associated risks and benefits of participating in the study will be outlined in detail by the investigator. Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. Details regarding the informed consent process and documentation are provided in Section 13.1.

6.1.2 Eligibility Review

An eligibility review will be documented at Screening and confirmed at Baseline/Day 1.

6.1.3 Medical History

A review of medical history will be done at screening and baseline (before treatment).

6.1.4 Complete Physical Examination

A complete physical examination will be conducted at the Screening Visit. The physical examination performed at the screening visit will serve as the baseline physical examination for clinical assessment.

Additional physical exam(s) may be performed at the discretion of investigator per standard of care. If available, data related to changes from baseline, adverse events, and participant follow-up resulting from the symptom-directed physical exam will be documented as appropriate.

6.1.5 Liver Fibrosis Assessment

Liver fibrosis assessment is comprised of aspartate aminotransferase to platelet ratio index (APRI), liver FibroScan, liver biopsy, and/or clinical finding consistent with cirrhosis.

6.1.6 Vital Signs, Weight, and Height

Body temperature, blood pressure, pulse, body weight, and height will be measured at the screening visit. Optional, obtain vital signs (temperature, blood pressure, pulse), weight and height at the Baseline Visit may be done at the discretion of the investigator for Ribavirin dosing calculations.

6.1.7 Pregnancy Test

Pregnancy tests are not required for female subjects with documented prior bilateral tubal ligation, bilateral oophorectomy, or hysterectomy, or for subjects who are confirmed to be postmenopausal. Confirmation of post-menopausal status measured by follicle-stimulating hormone (FSH) will be obtained at the screening visit only for all female subjects.

For females of childbearing potential:

- A serum pregnancy test will be performed at the screening visit only and sent to the local laboratory for analysis.
- Pregnancy testing will be performed on site during the study visits as specified in Appendix A: Study Visit/ Procedures Table regardless of treatment regimen. If a urine pregnancy result is positive, a confirmatory serum human chorionic gonadotropin (β-hCG) test will be collected and sent to the local lab for processing.
- Subjects that receive a ribavirin-containing regimen will have pregnancy tests performed in accordance with the protocol while participating in the study. Otherwise, subjects are recommended to have monthly pregnancy test throughout the treatment period and for a minimum of 7 months after the discontinuation of ribavirin, or according to the FDA approved ribavirin label and/or standard of care.

For females of childbearing potential, and males with a female partner of child-bearing potential:

- Upon completion of the study, subjects will be counseled regarding pregnancy at their last study visit with instructions to contact their healthcare provider right away in the event that they or their female partner becomes pregnant.

For subjects with positive pregnancy test during the course of the study, refer to Section 6.3.4.

6.1.8 Clinical Laboratory Samples

The following laboratory samples will be obtained as outlined in Appendix A. Laboratory samples will be managed, processed, and resulted in accordance with KPSC standards.

6.1.8.1 Hepatitis and HIV Screen

Hepatitis B surface antigen (HBsAg), anti-hepatitis C antibody (anti-HCV Ab), and anti-human immunodeficiency virus antibody (anti-HIV Ab) will be performed at screening. A positive anti-HIV Ab test result must be confirmed. The site will report these results per local regulations, if necessary.

6.1.8.2 Hepatitis C Virus Genotype and Subtype

Plasma samples for HCV genotype and subtype will be collected at screening. Historical HCV genotype and subtype within 6 months of the Screening Visit is permitted and may be substituted for the screening plasma sample collection at the discretion of the investigator. Genotype and subtype will be assessed using the standard assay per Kaiser Permanente regional laboratory.

6.1.8.3 Hepatitis C Virus RNA

Plasma samples for HCV RNA levels will be collected as indicated in Appendix A: Study Visit/ Procedures Table. Plasma HCV RNA levels will be determined using the standard assay per Kaiser Permanente laboratory.

6.1.8.4 Safety Monitoring Labs

CBC with differential, creatinine, and liver panel lab tests (total bilirubin, alanine aminotransferase (ALT), and alkaline phosphatase levels (AlkPhos)) will be performed as indicated in Appendix A: Study Visit/ Procedures Table.

6.1.8.5 Additional Labs

At the discretion of the treating investigator, additional laboratory tests may be ordered with the study labs. If available, results from the following labs will also be collected in the study: coagulation panel (PT, PTT), INR, reticulocyte count, direct bilirubin, and electrolytes.

Consistent with standard practice, clinically significant laboratory tests must be repeated and monitored to a satisfactory clinical resolution.

6.1.9 Concomitant Medication Assessment

Subject's use of concomitant medications, prescription and over-the-counter including vitamins and herbal supplements, administered from the time of signing the consent through 30 days after last dose of study drug administration will be collected. The investigator or authorized designee should review concomitant medication label(s) and assess for potential drug interactions.

6.1.10 Adverse Event (AE) Assessment

Clinical outcome events that occur during the treatment period through post-treatment week 12 will be recorded and documented in the case report form as an AE or Serious Adverse Event (SAE). Refer to Section 9 Assessment of Safety for more information.

6.1.11 Study Drug Dispensing

Study drugs will be dispensed at the visits as indicated Appendix A. At each visit, any remaining study drug from the previous visit will be re-dispensed to the subject.

Subjects receiving ribavirin will be provided with the Ribavirin Medication Guide at their Baseline Visit.

6.1.12 Study Drug Accountability/ Compliance Review

At each visit noted in Appendix A, study drug dispensation and administration reconciliation will be recorded according to the number(s) of: VIEKIRA PAK™ and ribavirin tablets (if applicable) available at each study visit. Study drug dosing will be reviewed at each study visit. Subject adherence to study protocol and study drug treatment will be monitored each visit.

6.2 STUDY VISITS

6.2.1 Screening Visit Procedures (- 28 days to Baseline/Day 1) (Visit 1)

The following assessments/procedures will be performed in-clinic:

- Obtain signed informed consent
- Eligibility review
- Complete medical history
- Complete physical examination
- Liver fibrosis assessment
- Obtain vital signs (temperature, blood pressure, pulse), weight and height
- Obtain Pregnancy Test, serum β-hCG[1]
- Obtain HCV Genotype and Subtype[2]
- Obtain the following labs. Note: Laboratory results obtained within three (3) months of Screening Visit may be used at the discretion of the investigator.
  - HBsAg and anti-HCV Ab
  - Anti-HIV Ab
  - HCV RNA
  - CBC with differential
  - Creatinine
  - Liver panel (ALT, Alkaline Phosphatase, Total Bilirubin), AST and Direct Bilirubin
  - Additional labs as determined by the investigator
- Review concomitant medications

6.2.2 Baseline/Day 1 Procedures (Visit 2)

The following assessments/procedures will be performed in-clinic:

- Confirm inclusion and exclusion criteria to determine eligibility
- Review Medical History

[1] Pregnancy test not required for female subject with documented bilateral tubal ligation, bilateral oophorectomy, or hysterectomy, or for postmenopausal subjects as confirmed by FSH test
[2] Medical record documentation of HCV genotype and subtype within the last 6 months may be substituted for the screening plasma sample collection

- Optional, obtain vital signs (temperature, blood pressure, pulse), weight and height at the discretion of the investigator
- Pregnancy Test, Serum or Urine
- Additional labs as determined by the investigator
- Review concomitant medications
- Review for AEs
- Study Enrollment/Treatment assignment
- Dispense study drug by providing the subject with a ne two week supply of Viekira Pak, and if applicable, provide subject with the Ribavirin Medication Guide. Subjects should be instructed to have their first dose same day that they can take a full day course of the study drug (e.g. subject seen in the afternoon should be instructed to take their first dose the next day)
- Study drug accountability

6.2.3 Treatment Period

Treatment visits should be based on the subject's Baseline Visit date.

If a subject discontinues or withdraws from the study during the treatment period, he/she should be encouraged to complete the End of Treatment (EOT) Procedures (Section 6.2.3.3) and the Early Termination Visit (Section 6.2.4.2) within 14 days of the last study treatment dose. In the event that subject is unable to complete the visit(s) but willing to provide survival status, the study site staff should contact the subject within 14 days to collect the information.

6.2.3.1 Week 2 (Visit 3)

The following assessments/procedures will be performed in-clinic:

- Obtain labs:
  - HCV RNA
  - CBC with differential, only required for subjects receiving ribavirin (Genotype 1a)
  - Creatinine
  - Liver panel (ALT, Alkaline Phosphatase, Total Bilirubin), AST and Direct Bilirubin
  - Additional labs as determined by the investigator
- Review concomitant medications
- Review for AEs
- Dispense study drug by providing the subject with a new two week supply of Viekira Pak and re-dispensing the remaining RBV
- Study drug accountability

6.2.3.2 Week 4 (Visit 4) and Week 8 (Visit 5)

The following assessments/procedures will be performed in-clinic:

- Pregnancy Test, Serum or Urine
- Obtain labs:
  - CBC with differential
  - Creatinine
  - Liver panel (ALT, Alkaline Phosphatase, Total Bilirubin), AST and Direct Bilirubin
  - Additional labs as determined by the investigator
- Review concomitant medications
- Review for AEs
- Dispense study drug
- Study drug accountability

6.2.3.3 Week 12 (Visit 6) - End of Treatment (EOT) Procedures

The following assessments/procedures will be performed in-clinic:

- Pregnancy Test, Serum or Urine
- Obtain labs:
  - HCV RNA
  - CBC with differential
  - Creatinine
  - Liver panel (ALT, Alkaline Phosphatase, Total Bilirubin), AST and Direct Bilirubin
  - Additional labs as determined by the investigator
- Review concomitant medications
- Review for AEs
- Study drug accountability

6.2.4 Post-Treatment (PT) Period

Post-treatment visits should be based on the subject's last dose of the study drug.

If a subject discontinues or withdraws from the study during the post-treatment period, he/she should be encouraged to complete the Early Termination Visit (Section 6.2.4.2) except when the reason for discontinuation is confirmed virologic failure as described in Section 6.3.3. If a subject is unable to complete the Early Termination visit but willing to provide survival status, the study site staff should contact the subject to collect the information.

6.2.4.1 Post-Treatment (PT) Week 4 (Visit 7)

The following assessments/procedures will be performed either in-clinic, or remotely by phone with labs collected at the subject's nearest laboratory facility:

- Pregnancy Test, Serum or Urine
- Obtain labs:

- HCV RNA
- CBC with differential
- Creatinine
- Liver panel (ALT, Alkaline Phosphatase, Total Bilirubin), AST and Direct Bilirubin
- Additional labs as determined by the investigator

- Review concomitant medications
- Review for AEs

6.2.4.2 Post-Treatment (PT) Week 12 (Visit 8) - End of Study/ Early Termination (ET)

The End of Study Post-Treatment Week 12 visit will be completed at the conclusion of the post-treatment period.

Early Termination Visit should be completed when a subject discontinues or withdraws from the study during either the Treatment or Post-treatment, except when the reason for discontinuation is confirmed virologic failure (Section 6.3.3).

If a subject discontinues or withdraws from the study during the treatment period, he/she should be encouraged to complete the End of Treatment (EOT) Procedures (Section 6.2.3.3) and the Early Termination Visit (Section 6.2.4.2) within 14 days of the last study treatment dose. In the event that subject is unable to complete the visit(s) but willing to provide survival status, the study site staff should contact the subject within 14 days to collect the information.

If a subject discontinues or withdraws from the study during the post-treatment period, he/she should be encouraged to complete the Early Termination Visit (Section 6.2.4.2) except when the reason for discontinuation is confirmed virologic failure as described in Section 6.3.3. If a subject is unable to complete the Early Termination visit but willing to provide survival status, the study site staff should contact the subject to collect the information.

The following assessments/procedures will be performed in-clinic, or remotely by phone with labs collected at the subject's nearest laboratory facility:

- Pregnancy Test, Serum or Urine
- Obtain labs:
  - HCV RNA
  - CBC with differential
  - Creatinine
  - Liver panel (ALT, Alkaline Phosphatase, Total Bilirubin), AST and Direct Bilirubin
  - Additional labs as determined by the investigator
- Review concomitant medications
- Review for AEs

6.2.4.3 Unscheduled Visits and Labs

Unscheduled visits and labs may be done as determined by the investigator to protect the safety of the subject, such as in the case of AEs.

6.2.4.4 Unscheduled Drug Dispensing

Unscheduled drug dispensing to prevent treatment interruption requires prior approval from the Sponsor-Investigator or designee.

6.3 Subject Discontinuation

6.3.1 Subject Initiated Discontinuation

Each subject has the right to withdraw from the study at any time for any reason. Subjects who discontinue from the study regardless of cause should be encouraged to complete the Early Termination Visit within 14 days of the last treatment dose. Ideally for study drug discontinuation, this should occur on the day of study drug discontinuation, and prior to the initiation of any other anti-hepatitis C virus therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition.

In the event that subject is unable to complete the visit but willing to provide survival status, the study site staff should contact the patient within 14 days of the last study dose to collect the information.

Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment. The last dose of any study drug and reason for discontinuation from the treatment period will be recorded in the case report form.

Withdrawal of consent for the study will be documented in the subject's study records and reported to the PI and/or designee.

6.3.2 Investigator Initiated Discontinuation

The investigator may also discontinue a subject from the study at any time for the following reasons:

- Subject or subject's partner experiences AE or toxicity from the study drug that warrants discontinuation, or
- Subject is noncompliant (e.g. missed treatment doses, or missed visits) with the protocol, or
- If a subject has an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range at the time of study drug discontinuation, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or AE is resolved.

6.3.3 Discontinuation of Subjects Meeting Virologic Failure Criteria

The following criteria will be considered evidence of virologic failure:

- Confirmed increase from nadir in HCV RNA, defined as two consecutive HCV RNA measurements > 1 log10 IU/mL above nadir, at any time point during treatment
- Confirmed HCV RNA ≥ lower limit of quantification, defined as two consecutive HCV RNA measurements ≥ lower limit of quantification, at any point **after** HCV RNA less than lower limit of quantification

Confirmatory testing for the above criteria should be completed. Subjects receiving study drug treatment should remain on treatment until the virologic failure has been confirmed.

- ➢ If any of the above criteria are confirmed for subjects during study drug treatment, the subject will discontinue treatment.
- ➢ If any of the above criteria are confirmed for subjects during the post-treatment phase of the study, the subject will be discontinued from the study.

6.3.4 Pregnancy

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the treatment period, the administration of ribavirin (if applicable) to that subject must be discontinued immediately. The investigator is also encouraged to report the pregnancy information to the voluntary ribavirin pregnancy registry, if applicable.

Direct-acting antiviral agents may be continued at the Sponsor-investigator's discretion after discussion with the subject, if the benefit of continuing direct acting antiviral agents is felt to outweigh the potential risk. Subjects will be monitored for sustained virological response in the post-treatment period per protocol.

7 DATA COLLECTION AND MONITORING

7.1 Data Management and Record Keeping

The data will be collected and reported on paper case report forms and/or in electronic medical record. Each site will be responsible for data entry into system. In the event of discrepant data, research personnel at each site will resolve items. KPSC will be responsible for the data management of this study, including quality checking of the data by conducting an internal audit review.

7.2 Data Monitoring Plan

Remote and on-site monitoring visits will be conducted at each site in accordance with the study monitoring plan that includes at a minimum, a review of signed ICFs, review of subject eligibility, AE reporting and data integrity. Visits will occur approximately during the screening period, after start of study treatment, and at the end of study.

Monitoring visits will be performed by a Kaiser Permanente employee approved by the Department of Research & Evaluation. In addition, this employee will have been trained and met criteria under applicable KPSC Clinical Trials Standard Operating Procedures.

During the monitoring visits, any finding that pose as an actual or potential risk to the health, safety, welfare, or privacy of a research participant or the integrity of the study may be disclosed to the KPSC IRB by the monitor.

Investigators will permit national and local health authorities, KPSC IRB, KPSC Research & Evaluation, U.S. FDA, Department of Health and Human Services, along with other governmental agencies with responsibilities for the safety of drugs and studies.

7.3 Data Safety Monitoring Board (DSMB)

There will be no Data Safety Monitoring Board (DSMB) for this clinical trial since the study drugs used in this study is FDA approved and is being used in accordance to the approved indication. Additionally, all study procedures are considered standard of care.

7.4 Retention of Study Record

Records and documents pertaining to the conduct of this study, including Informed Consent Forms, case report forms, Patient Reported Outcome data, drug accountability logs, IRB submissions, approvals and correspondence, and any regulatory documents, must be retained by the Sponsor-Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant Federal or local regulations, whichever is longer. After this time period, study documents may be destroyed per local regulations after receipt of written approval by the Sponsor-Investigator and KPSC Research & Evaluation. Written notification must be provided to the Sponsor-Investigator and KPSC Research & Evaluation prior to moving records to another location or when transferring any records to another party.

8 STATISTICAL CONSIDERATIONS

This is an open label, non-randomized, study with one study arm. Descriptive statistics will be used to describe the observed sustained virological response rate and patient adherence to the treatment regimen. The primary analysis, to evaluate SVR12, will occur after all subjects have completed or prematurely discontinued the study.

The intent-to-treat population will consist of all enrolled subjects in this study. The primary efficacy analysis on clinical outcomes will be performed on all subjects in the intent-to-treat population. The modified intent-to-treat population will include all who receive at least one dose of study drug.

No data will be imputed for any efficacy or safety analyses except for analyses of the HCV RNA endpoints.

HCV RNA values will be selected for the SVR4 and SVR12 analysis based on the defined visit windows. The visit window for analysis of SVR4 is post-treatment days 2-56, and the visit window for analysis of SVR12 is post-treatment days 57-168. The latest available value within each window will be used to define the SVR 4 or SVR12 result.

8.1 Demographics

Demographics and baseline characteristics will be summarized for all subjects in the intent to treat population. Demographics include age, weight, height, and body mass index, and the frequency of gender, race, and ethnicity.

Baseline characteristics will include:

- HCV genotype 1 subtype (1a, 1b); interferon treatment history (treatment-naïve [interferon-eligible, interferon-ineligible] or interferon-based treatment experienced [null responder, partial responder, relapse, prior relapse/breakthrough, prior nonresponder, interferon intolerant and interferon experienced-other]);
- Baseline HCV RNA levels [(continuous) ≤ 800,000 IU/ or > 800,000 IU/mL], baseline.

Summary statistics (number, mean, median, standard deviation and range) will be generated for continuous variables for example, age, and body mass index. The number and percentage of subjects will be presented for categorical variables for example, gender, and race.

8.2 Safety Outcome Measures

The following safety evaluations will be analyzed during the study: AEs monitoring, and laboratory test assessments. Potential AEs that will be captured include those most commonly reported in the registration trials including headache, fatigue, nausea, pruritus, insomnia, diarrhea, asthenia, rash, cough, irritability, anemia and dyspnea.

All subjects who receive at least one dose of study drug will be included in the safety analyses.

8.3 Efficacy Analysis

The primary efficacy analysis on clinical outcomes will be performed on all subjects in the intent to treat population. All other efficacy analyses will be performed on the modified intent to treat population

8.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is to assess SVR12 in two subgroups of HCV (genotype 1a or 1b). The simple percentage of subjects achieving SVR12 will be calculated and a two-sided 95% confidence interval of the percentage will be computed based on Wilson's score method. We cannot know a priori how the 200 patients will be split into the two subgroups, but we expect each group to have approximately 100 patients (presumably between 80 and 120). Assuming a subgroup size of 100 each, the lower bound of the 95% confidence interval will

be within 7 percentage points of the observed SVR12 rate. Once the groups are fixed, the actual lower bound of the 95% confidence interval can be computed.

The observed SVR12 rate and confidence interval will be discussed in the context of results from randomized clinical trials, such as the SAPPHIRE-I/II trials and PEARL-II/III/IV trials described in the Background section. While formal statistical inference comparing results of this study to those of the randomized clinical trials will not be conducted, the point estimates and confidence intervals will be compared to assess the degree to which results from the real world setting are similar to or different from those in the randomized clinical trial setting. Results by prior treatment experience and response may be summarized if appropriate, based on the number of subjects enrolled in each subgroup. No subgroup sample size targets have been established.

8.3.2 Secondary Efficacy Endpoint

The secondary efficacy endpoints are:

- To assess SVR4. The simple percentage of subjects achieving SVR4 will be calculated and a two-sided 95% confidence interval of the percentage will be computed based on Wilson's score method.
- Patient adherence with the VIEKIRA PAK regimen will be evaluated by review of study drug returned for drug reconciliation and/or compilation of patient reported compliance information.

9 ASSESSMENT OF SAFETY

9.1 Safety Parameter and Definitions

9.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable experience associated with the use of a medical product in a subject and includes the following:

- AE not previously observed in the subject during the protocol-specified AE reporting period, limited to signs or symptoms associated with Genotype 1 Chronic Hepatitis C and effects of study drug
- Complications that occur as a result of protocol-mandated activities
- AEs that occur prior to study treatment assignment that are related to a protocol-mandated activity
- Pre-existing medical conditions determined by investigator to have worsened in frequency or severity during the protocol-specified AE reporting period

9.1.2 Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is any adverse event that is any of the following:

- Fatal

- Life-threatening
- Requires initial or prolonged hospitalization
- Disability or permanent damage
- A congenital anomaly/birth defect in a neonate/infant that is suspect to exposure to a medical product prior to conception or during pregnancy
- A significant medical event determined by the investigator that may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

9.1.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs, However, in the event that the abnormalities require medical or surgical intervention, or lead to interruption, modification or discontinuation of either of the investigational drug, they must be recorded as an AE, and if applicable as an SAE. When reporting the AE, the event should be based on the syndrome or diagnosis, and not the lab result.

9.2 Methods and Timing for Capturing Safety Parameters

The investigator is responsible for ensuring that all potential AEs (defined in Section 9.1.1) or SAEs (defined in Section 9.1.2) that occurred after subject provides written informed consent, but prior to initiation of study medication that are caused by protocol-mandated interventions will be collected and reported.

After initiation of study treatment, all AE and SAE probably related or possibly related to the study treatment or study-related procedures will be collected and reported until the end of study visit, or Early Termination.

9.2.1 Timing of Adverse Event (AE) Reporting

All AEs occurring after the initiation of study treatment that are considered expected, and possibly or definitely related to the study (e.g. treatment) must be documented, and subsequently reported to the Sponsor-Investigator or designee at the end of the subject's participation in the study.

All AEs that are considered unanticipated, and possibly or definitely related to the study (e.g. treatment) must be reported to the Sponsor-Investigator or designee within 72 hours.

All unanticipated SAEs considered possibly or definitely related to the study (e.g. treatment) must be reported to the Sponsor-Investigator or designee within 24 hours of discovery.

Any AEs identified as occurring prior to the study treatment will be considered as part of the subject's medical history.

9.2.1 Reportable Adverse Event (AE) or Serious Adverse Event (SAE)

All reportable AEs or SAE will be recorded in source documents and reported to IRB per reporting guidelines. Additionally, any AEs that meet the criteria for MedWatch reporting will be submitted accordingly.

9.2.2 Assessment of Serious, Severity, Causality and Unexpectedness

Investigators are required to assess all AEs occurring after the initiation of study treatment for seriousness, severity, and causality as defined below.

Serious refers to events that pose a threat to a subject's life or vital functions and is based on subject or event outcome or action criteria. An AE that does not meet any criteria for serious, as defined in Section 9.1.2 should be regarded as "non-serious" AE.

Severity refers to intensity of an AE as "mild," "moderate," or "severe":

- *Mild*: Symptom(s) that do not interfere with subject's usual social and functional activities
- *Moderate*: Symptom(s) that interfere to some extent with subject's usual social and functional activities
- *Severe*: Symptom(s) that interfere significantly with subject's usual social and functional activities

Causality refers to a reasonable possibility that the AE is related to the study medication or study-related procedure. If AE is not related to study medication or study-related procedure, investigators will assess the most likely cause of AE.

Unexpected refers to whether or not the AE is described as a risk in the package insert or investigator's brochure for the study drug(s), the protocol or in the informed consent form.

10 ADMINISTRATIVE STRUCTURE

This study is a collaborative effort between AbbVie Inc. and Southern California Permanente Medical Group (SCPMG) with Sponsor-Investigator, Lisa Nyberg, MD as the Principal Investigator. Multiple KPSC Medical Centers will be participating in the study with a lead site investigator delegated by the PI to supervise local activities.

Data collected in this study will be managed in accordance to the signed contract.

11 REGISTRATION GUIDELINE

11.1 No randomization

11.2 Forms and Records for Registration

A screening number will be assigned for each subject that signs the study informed consent. Once deemed eligible, the subject will be assigned a unique study ID that will be used to identify the subject for registration and enrollment.

12 BIOHAZARD CONTAINMENT

Biohazard materials will be discarded according to standard guidelines.

13 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full compliance with the KPSC IRB, International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), principles of the Declaration of Helsinki, and applicable United States Food and Drug Administration (FDA), state, and local laws, policies, and guidelines.

13.1 Informed Consent

The Informed Consent Form (ICF) will contain all the required elements for informed consent as indicated in 21 CFR Part 50.25, and will be approved by KPSC IRB prior to distribution to prospective subjects. Written informed consent will be obtained in accordance to 21 CFR Part 50 and KPSC IRB applicable requirements.

The study ICF and Privacy Rule Authorization Form, will be signed and dated by the subject or the subject's legally authorized representative before participating in any study procedures. A copy of the signed Informed Consent Form and Privacy Rule Authorization Form, and a copy of the Experimental Subject's Bill of Rights will be provided to the subject or the subject's legally authorized representative. The investigator will document the informed consent process in the subject's medical record.

All original signed ICFs will be maintained at the site with the subject's study chart, and available for study monitoring at any time.

Non-English Speaking Subject

In the case that a non-English speaking subject is eligible in the study, the informed consent process will involve the use of the KPSC IRB-approved Short Form as described in 21 CFR 50.27(2). Every effort will be made to have subsequent informed consents translated in the subject's language.

13.2 Institutional Review Board (IRB)

This study protocol, the Informed Consent Forms, any information intended for distribution to subjects, and any relevant supporting information will be submitted to KPSC IRB by the Principal Investigator and reviewed and approved by KPSC IRB prior to initiation of the study.

The Principal Investigator is responsible for submitting all reportable events as defined by KPSC IRB SOP 502 to KPSC IRB within the appropriate reporting periods.

13.3 Confidentiality

KPSC maintains confidentiality standards by coding each subject in the study with a subject identification number. As a result, subjects' name and medical record number are removed from data sets, and subject is identified by subject identification number.

Results of this study may be published or presented at scientific conference or committee meetings as aggregated data.

13.4 Conflict of Interest

All investigators involved in this study that has a conflict of interest with this study must provide information about this conflict to KPSC IRB for review.

14 PROTOCOL SIGNATURE PAGE

The study will be conducted in compliance with the protocol, International Conference on Harmonization, Good Clinical Practice guidelines and applicable regulatory requirements.

I have read and understand the protocol and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I will personally conduct the study as described.

I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I understand that all information concerning the study supplied to me in connection with this study and not previously published is considered confidential information.

I am aware that this protocol must be approved by the KPSC IRB. I understand that any changes to the protocol must be approved by the KPSC IRB. I attest that I have read, understood, and agree to abide by all conditions, instructions and restrictions contained in the above protocol.

Lisa M. Nyberg, MD, MPH	Kaiser Permanente San Diego
Sponsor-Investigator Name (print name)	Study Site
Signature on file	03/01/2016
Sponsor-Investigator Signature	Date

APPENDIX A: STUDY VISIT/ PROCEDURES TABLE

	Screening	Treatment Period					Post-Treatment (PT)	
	-28 Days	Baseline Day 1	Week 2	Week 4	Week 8	EOT[1]/ Week 12	PT[2] Week 4	PT Week 12/ ET[3]
Visit Window			± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5days
Visit	1	2	3	4	5	6	7	8
Informed Consent	X							
Eligibility Review	X	X						
Medical History	X	X						
Complete Physical Exam	X							
Liver fibrosis assessment[4]	X							
Vital Signs[5], Weight and Height	X	X[6]						
Pregnancy test[7]	X	X		X	X	X	X	X
HBsAg, anti-HCV Ab	X[8]							
Anti-HIV Ab	X[8]							
HCV Genotype and Subtype[9]	X							
HCV RNA Samples	X[8]		X			X	X	X

[1] EOT = End of Treatment. See 6.2.33 Week 12 (Visit 6) – End of Treatment (EOT) Procedures
[2] PT = Post Treatment, can be done in-clinic or remotely by phone with labs collected at the subject's nearest laboratory facility
[3] ET = Early Termination. See 6.2.4.2 Post-Treatment (PT) Week 12 (Visit 8) – End of Study/ Early Termination (ET).
[4] Liver fibrosis assessment: aspartate aminotransferase to platelet ratio index (APRI); Liver FibroScan; Liver Biopsy, and/or clinical finding consistent with cirrhosis
[5] Blood Pressure, Pulse and Temperature
[6] Optional assessment at the discretion of the investigator
[7] Pregnancy test is not required for female subject with documented bilateral tubal ligation, bilateral oophorectomy, or hysterectomy, or for postmenopausal subjects as confirmed by FSH test. Serum pregnancy test at screening; urine or serum pregnancy test at subsequent visits
[8] Laboratory results obtained within three (3) months of the Screening Visit may be used at the discretion of the investigator
[9] Historical HCV genotype and subtype within 6 months of the Screening Visit is permitted with medical record documentation at the discretion of the investigator

	Screening	Treatment Period					Post-Treatment (PT)	
	-28 Days	Baseline Day 1	Week 2	Week 4	Week 8	EOT[1]/ Week 12	PT[2] Week 4	PT Week 12/ ET[3]
Visit Window			± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5days
Visit	1	2	3	4	5	6	7	8
CBC with differential	X[8]		X[10]	X	X	X	X	X
Creatinine	X[8]		X	X	X	X	X	X
Liver panel[11], AST, Direct Bilirubin	X[8]		X	X	X	X	X	X
Additional labs as determined by the investigator[12]	X[8]	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X
Enrollment/treatment assignment		X						
Study Drug Dispense		X[13]	X[14]	X	X			
Ribavirin Medication Guide[15]		X						
Study Drug Accountability		X	X	X	X	X		

[10] Only required for subjects receiving ribavirin (Genotype 1a)
[11] ALT, Alkaline Phosphatase, and Total Bilirubin
[12] Consider Coagulation Panel (PT, PTT); INR, Reticulocyte Count; Direct Bilirubin, Electrolytes
[13] Subject is dispensed a new two week supply of Viekira Pak and one bottle of RBV
[14] Subject is dispensed a new two week supply of Viekira Pak and re-dispensed their remaining RBV
[15] Applicable only to subjects receiving Ribavirin as part of their study treatment.

APPENDIX B: REFERENCES

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APPENDIX C: SITE LEAD INVESTIGATOR SIGNATURE PAGE

The study will be conducted in compliance with the protocol, International Conference on Harmonization, Good Clinical Practice guidelines and applicable regulatory requirements.

I have read and understand the protocol and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I will personally conduct the study as described.

I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I understand that all information concerning the study supplied to me in connection with this study and not previously published is considered confidential information.

I am aware that this protocol must be approved by the KPSC IRB. I understand that any changes to the protocol must be approved in writing by the Primary Investigator and approved by the KPSC IRB. I attest that I have read, understood, and agree to abide by all conditions, instructions and restrictions contained in the above protocol.

Site Lead Investigator Name (print name)	Study Site
Site Lead Investigator Signature	Date

APPENDIX D: PROTOCOL HISTORY/ SUMMARY OF PROTOCOL CHANGES

Original Protocol version 1.0 dated 07Jan2015	
Protocol Amendment 01 version 1.0 dated 27Jan2015	▪ Revised to remove use of Short-Form-36 version 2 questionnaire
Protocol Amendment 02 version 1.0 dated 22May2015	▪ Increase in the screening period from 2 weeks to 28 days
Protocol Amendment 03 version 1.0 dated 10Aug2015	▪ Increase in the number of subjects to 200 enrolled ▪ Updated inclusion and exclusion criteria ▪ Clarifications regarding study procedures including vital signs, weight, and height, pregnancy test, hepatitis C virus genotype and subtype, adverse event assessment, and drug dispensing ▪ Revised adverse event reporting timelines
Protocol Amendment 04 version 1.0 dated 18Dec2015	▪ Eligibility criteria revised for clarification ▪ Study procedures were revised to allow use of serum pregnancy test in lieu of urine pregnancy test and for Post-treatment Visits to occur remotely ▪ Description of the study visits were updated to provide guidance in scheduling visits Treatment Period and the Post-treatment Period of the study, and to clarify the necessary steps for subjects who meet virologic failure during the course of the study.

Protocol Amendment 05 version 1.0	
Major Changes	Rationale
5.1 Inclusion Criteria 7. Subject must have at least one of the following indicators of chronic hepatitis C virus infection prior to study enrollment: • Positive anti-HCV antibody or HCV RNA > 10,000 IU/mL at least 6 months before screening, and positive for HCV RNA at the time of screening • HCV RNA > 10,000 IU/mL at screening and liver biopsy consistent with chronic HCV infection • Credible evidence of chronic hepatitis C as per the investigator and HCV RNA > 10,000 IU/mL at the time of screening	To allow new members with Kaiser Foundation Health Plan who have credible medical history of chronic HCV as per the investigator but only have one HCV RNA value available due to their new status with Kaiser Permanente.

Protocol Amendment 05 version 1.0	
Major Changes	Rationale
5.2 Exclusion Criteria 11. Evidence of cirrhosis, documented by one of the following: • Liver biopsy histologic diagnosis: Metavir Score > 3 (includes 3 - 4 or 3/4) or Ishak score > 4 • In the absence of liver biopsy: a FibroScan score ≥ 12.5 kPa ~~or~~ • In the absence of a FibroScan: an APRI score > 1.5 • In the judgment of the investigator clinical findings are consistent with cirrhosis. In general, a non-cirrhotic result from a Fibroscan will supersede evidence of cirrhosis based on APRI and a liver biopsy not showing cirrhosis will supersede both Fibroscan and APRI.	To confirm that for the study, a Fibroscan result will take precedence over an APRI score when determining cirrhosis.
6.2 STUDY VISITS **6.2.1Screening Visit Procedures (- 28 days to Baseline/Day 1) (Visit 1)** The following assessments/procedures will be performed in-clinic: • Obtain Pregnancy Test, serum β-hCG[1] • Obtain HCV Genotype and Subtype[2] • Obtain the following labs. Note: Laboratory results obtained within three (3) months of Screening Visit may be used at the discretion of the investigator. o HBsAg and anti-HCV Ab o Anti-HIV Ab o HCV RNA o CBC with differential o Creatinine o Liver panel (ALT, Alkaline Phosphatase, Total Bilirubin), AST and Direct Bilirubin o Additional labs as determined by the investigator	To minimize/eliminate the number of labs and lab copay cost for potential subjects with laboratory results available within three (3) months of Screening Visit.

[1] Pregnancy test not required for female subject with documented bilateral tubal ligation, bilateral oophorectomy, or hysterectomy, or for postmenopausal subjects as confirmed by FSH test
[2] Medical record documentation of HCV genotype and subtype within the last 6 months may be substituted for the screening plasma sample collection

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