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1.0 Title Page

Clinical Study Protocol B16-439

A Phase 3b, Multi-Center, Randomized, Open-Label, Pragmatic Study of Glecaprevir/Pibrentasvir (G/P) +/- Ribavirin for GT1 Subjects with Chronic Hepatitis C Previously Treated with an NS5A Inhibitor + Sofosbuvir Therapy

AbbVie Investigational Product:	Glecaprevir, Pibrentasvir	
Date:	November 20, 2018 (Applicable to sites participating in Retreatment sub-study only)	
Development Phase:	3b	
Study Design:	Main Study: Randomized open-label, multi-center study. Retreatment Sub-study: Open-Label, multi-center study	
Investigators:	Multi-center. Investigator information is on file with University of Florida.	
IND Sponsor:	David R. Nelson, MD (UF Hepatology Research at CTRB)	
Sponsor/Emergency Contact:	[redacted]	Phone: [redacted] Fax: [redacted] Mobile: [redacted]

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1. Synopsis

IND Sponsor: David R. Nelson, MD	**Protocol Number**: B16-439
Name of Study Drug: Glecaprevir (ABT-493), Pibrentasvir (ABT-530), Ribavirin (RBV), *Sofosbuvir (GS-7977)	**Phase of Development**: 3b
Name of Active Ingredient: ABT-493, ABT-530, ribavirin, *GS-7977	**Date of Protocol Synopsis**: November 20, 2018
Protocol Title: A Phase 3b, Multi-Center, Randomized, Open-Label, Pragmatic Study of Glecaprevir/Pibrentasvir (G/P) +/- Ribavirin for GT1 Subjects with Chronic Hepatitis C Previously Treated with an NS5A Inhibitor + Sofosbuvir Therapy	

Objectives: The primary objectives of this study are to: 1. Compare the efficacy (SVR_{12}) of G/P given for 12 weeks to non-cirrhotic GT1-infected subjects who are treatment-experienced with a NS5A inhibitor+SOF±RBV regimen (Arm A) vs. G/P given for 16 weeks (Arm B) 2. Compare the efficacy (SVR_{12}) of G/P plus RBV given for 12 weeks to GT1-infected subjects with compensated cirrhosis and who are treatment-experienced with a NS5A inhibitor+SOF±RBV regimen (Arm C) vs. G/P given for 16 weeks (Arm D) 3. Assess the safety and tolerability of G/P with or without RBV, in these subjects with chronic HCV GT1 infection and treatment-experienced with a NS5A inhibitor+SOF±RBV regimen.
Investigators: Multi-center
Study Sites: Approximately 35 sites.
Study Population: Main Study: Chronic HCV GT1-infected male and female adults, at least 18 years of age, without cirrhosis or with compensated cirrhosis and prior NS5A-inhibitor plus sofosbuvir ± RBV treatment experience. Retreatment sub-study: Subjects who experience virologic failure in the Main study
Number of Subjects to be Enrolled: up to 225 subjects
***Applicable to Retreatment sub-study only**

Methodology:

Main Study:

This is a Phase 3b, randomized, open-label, pragmatic, multicenter study to evaluate efficacy and safety of the fixed-dose combination tablets of glecaprevir/pibrentasvir with or without RBV in NS5A-inhibitor plus sofosbuvir ± RBV-experienced, chronic HCV GT1-infected subjects. Up to 225 subjects at approximately 35 sites will be enrolled into four study arms A, B, C and D. Up to 150 non-cirrhotic subjects will be randomized in a 2:1 ratio to Arms A and B, and up to 75 subjects with compensated cirrhosis will be randomized in a 1:1 ratio to Arms C and D. Randomization will be stratified by HCV genotype 1 subtype (1b or non-1b).

Subjects without cirrhosis will be randomized 2:1 to:

Arm A: G/P 300 mg/120 mg QD for 12 weeks

Arm B: G/P 300 mg/120 mg QD for 16 weeks

Subjects with compensated cirrhosis will be randomized 1:1 to:

Arm C: G/P 300 mg/120 mg QD + weight-based RBV BID (1000 mg or 1200 mg total daily dose) for 12 weeks

Arm D: G/P 300 mg/120 mg QD for 16 weeks

Subjects who complete or prematurely discontinue the treatment will be followed for 12 weeks to monitor HCV RNA and to evaluate efficacy and the emergence and persistence of viral variants.

Scheduled visits for subjects in the planned Treatment Period consist of Day 1, Weeks 4, 8, 12 for all subjects and Week 16 for subjects in Arms B and D. During the Post-Treatment Period, subjects will have visits at Weeks 4 and 12 following completion of the Treatment Period. Efficacy and safety data will be monitored throughout the study. These data will enable assessment of virologic stopping, futility, and treatment extension criteria as described in the protocol.

Retreatment Sub-study

Subjects who experience virologic failure in the Main study will have the option to enter the Retreatment sub-study after experiencing G/P failure and receive G/P+SOF±RBV for a total of 16 weeks. Ribavirin will be used at the discretion of the investigator, with particular consideration for a subject who may be at increased risk for ribavirin toxicity.

Subjects electing to participate in the Retreatment Sub-study will be followed for safety and efficacy according to the Main study pragmatic design procedures and Study Activities Tables (5 & 6) with exceptions as noted to screening procedures prior to re-treatment dosing. Retreatment eligibility will be determined prior to administering G/P+SOF+/-RBV based on Inclusion Criterion 1, 2, 4, 6, 7, 8, 9, and 10 and Exclusion Criterion 1, 3, 4, 6, 8, 10, 11 and 12 in Sections 5.2.1 and 5.2.2.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female at least 18 years of age at time of screening.
2. A history of previous treatment with an NS5A-inhibitor plus sofosbuvir therapy ± RBV for chronic HCV genotype 1 infection*.
3. Screening laboratory result indicating chronic HCV GT1 infection*.
4. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements and must voluntarily sign and date an informed consent.

Retreatment Sub-study

Subjects who experience virologic failure in the Main study will be considered for the Retreatment Sub-study.

*Applicable during Screening for the Main study only.

Main Exclusion:

1. History of severe, life-threatening or other significant sensitivity to any drug.
2. Female who is pregnant, planning to become pregnant during the study or breastfeeding; or male whose partner is pregnant or planning to become pregnant during the study.
3. Clinically significant abnormalities or comorbidities or recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that make the subjects an unsuitable candidate for this study in the opinion of the investigator.
4. Positive test result at Screening for hepatitis B co-infection (HBsAg positive or Hep B Core Ab -Total positive with detectable HBV DNA) or anti-human immunodeficiency virus antibody (HIV Ab) in patient without known history of HIV+ and stable HART therapy*.
5. Prior therapy with HCV PI at any time*.
6. History or presence of liver decompensation.

*Applicable during Screening for the Main study only.

Study Drug(s)	Glecaprevir/pibrentasvir 100 mg/40 mg Tablet Ribavirin 200 mg Tablet*** *Sofosbuvir 400 mg Tablet ***Ribavirin Dosage Form to be determined by dispensing pharmacy during Retreatment sub-study
Doses:	Glecaprevir Dose: 300 mg QD Pibrentasvir Dose: 120 mg QD Glecaprevir/pibrentasvir tablets: 300 mg/120 mg QD (3 tablets) Ribavirin tablets***: 1000 to 1200 mg total daily dose divided into two doses BID (5 or 6 tablets total daily dose) at the discretion of the PI * Sofosbuvir 400 mg QD
Mode of Administration:	Oral with food for glecaprevir/pibrentasvir, ribavirin, and *Sofosbuvir
Reference Therapy:	N/A
Duration of Treatment: Main Study treatment duration is 12 weeks in Arms A and C, and 16 weeks in Arms B and D. Retreatment sub-study treatment duration is 16 weeks. * For Retreatment sub-study only	
Criteria for Evaluation:	
Efficacy: Efficacy will be assessed by plasma HCV RNA levels throughout the study.	

Resistance:

The following information will be tabulated and summarized: 1) for all subjects with available samples, the polymorphisms in NS3 and NS5A (and NS5B for those subjects enrolled in the Retreatment sub-study who experience virologic failure) at baseline at resistance-associated amino acid positions relative to the appropriate prototypic reference sequence, and the impact of baseline polymorphisms on SVR_{12}; and 2) for subjects who do not achieve SVR_{12}, all post-baseline substitutions in the NS3 and NS5A (and NS5B for those subjects enrolled in the Retreatment sub-study) relative to baseline.

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests, and vital signs.

Statistical Methods:
The mITT population for the Main Study will be all subjects enrolled in the Main Study receiving at least one dose of study drug categorized according to the treatment arm in which they were actually treated, and the Evaluable Patient Population for the Retreatment sub-study (EP-RS) will be all subjects who receive at least one dose of G/P and of SOF in the Retreatment sub-study.

Efficacy:
The primary efficacy endpoints for the mITT population are the difference in SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) rates between Arm A and Arm B in non-cirrhotic subjects, and difference in SVR_{12} rates between Arm C and Arm D in cirrhotic subjects.

The difference in SVR_{12} rates will be summarized with a two-sided 95% confidence interval for the comparison between Arm A and Arm B in non-cirrhotic subjects, and for the comparison between Arm C and Arm D in cirrhotic subjects. The number and percentage of subjects achieving SVR_{12} by treatment arm according to final treatment arm assignment of subjects will also be summarized with a two-sided 95% confidence interval. The confidence interval for the difference in SVR_{12} rates will be calculated using Wilson's score method. The confidence interval for the SVR12 rates by treatment arm will be calculated using the normal approximation to the binomial distribution if the number of subjects who failed to achieve SVR12 is at least 5. If the number of subjects who failed to achieve SVR12 is less than 5, Wilson's score method will be used instead.

The secondary efficacy variables are:

1. The difference in SVR12 rates between G/P given for 12 weeks (Arm A and C combined) and G/P given for 16 weeks (Arm B and D combined);
2. The percentage of subjects with on-treatment virologic failure;
3. The percentage of subjects with post-treatment relapse.

For the Main study, the differences in the percentages of subjects with on-treatment virologic failure or post-treatment relapse for non-cirrhotic subjects (Arm A vs Arm B) and subjects with compensated cirrhosis (Arm C vs Arm D) will be summarized along with 95% Wilson score intervals. Additional efficacy endpoints and efficacy subgroup analyses will be performed.

As an additional efficacy endpoint, the percentage of retreated subjects achieving SVR_{12} will be analysed on the EP-RS population overall for the Retreatment sub-study.

DAA Resistance:

For all subjects receiving study drugs and with available samples, the polymorphisms at resistance-associated amino acid positions in the NS3 and NS5A (and NS5B for those subjects enrolled in the Retreatment sub-study who experience virologic failure) proteins at baseline identified by population sequencing or next-generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed. The impact of baseline polymorphisms on SVR_{12} will be examined.

The following resistance information will be analyzed for subjects receiving study drugs who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the amino acid substitutions in NS3 and NS5A (and NS5B for those subjects enrolled in the Retreatment sub-study who experience virologic failure) in available post-baseline samples identified by population sequencing or NGS and comparison to the baseline sequence, 2) the amino acid substitutions in NS3 and NS5A (and NS5B for those subjects enrolled in the Retreatment sub-study who experience virologic failure) in available post-baseline samples at resistance-associated positions identified by population sequencing or NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral substitutions by population sequencing or NGS.

Safety:

All subjects who receive at least one dose of study drugs will be included in the safety analyses. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by subject's final treatment arm assignment. Safety summaries will be provided by treatment group of the Main study and overall for the Retreatment sub-study. The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug) will be tabulated by primary System Organ Class (SOC). The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by grade and relationship to study drug. Change from baseline in laboratory tests to each time point of collection will be summarized by subject's final treatment arm assignment. Laboratory values that show an increase in CTCAE grade will be summarized.

1.2 List of Abbreviations, Definitions and Terms

Abbreviations

3TC	Lamivudine
Ab	Antibody
ABC	Abacvir
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
APRI	Aminotransferase/platelet ratio index
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area Under the Concentration Curve
BID	Twice Daily
BMI	Body Mass Index
BUN	Blood urea nitrogen
CCC	Clinical Coordinating Center
CKD	Chronic kidney disease
CL/F	Apparent Oral Clearance
CPK	Creatine phosphokinase
CR/CL	Creatinine clearance
CRF	Case report form
CT	Computed Tomography
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DCV	Daclatasvir
DCC	Data Coordinating Center

DNA	Deoxyribonucleic acid
EC	Ethics Committee
EDC	Electronic data capture
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
EHR	Electronic health record
EMR	Electronic medical record
EOT	End of treatment
EP	Evaluable Population
EU	European Union
FSH	Follicle stimulating hormone
FTC	Emtricitabine
GAM	Generalized additive method
GCP	Good Clinical Practice
GCSF	Granulocyte colony stimulating factor
GGT	Gamma-glutamyl transferase
GLE	Glecaprevir
G/P	Glecaprevir/Pibrentasvir fixed dose combination
GT	Genotype
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
Hemoglobin A1c	Glycated haemoglobin
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon

IL28B	Interleukin 28B
IMP	Investigational Medical Product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International units
IUD	Intrauterine device
LDV	Ledipasvir
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NGS	Next generation sequencing
NONMEM	Non-linear mixed-effect modeling
NS3	Nonstructural viral protein 3
NS4A	Nonstructural viral protein 4A
NS5A	Nonstructural viral protein 5A
NS5B	Nonstructural viral protein 5B
PCR	Polymerase Chain Reaction
PegIFN	Pegylated-interferon alfa-2a or alfa-2b
PegIFN/RBV	Combination of pegylated-interferon alfa-2a or alfa-2b and ribavirin
PI	Protease Inhibitor
PIB	Pibrentasvir
PK	Pharmacokinetic
POR	Proof of Receipt
PRS	IFN, pegIFN, RBV and/or sofosbuvir

PT	Post-Treatment
QD	Once daily
QTc	QT interval corrected for heart rate
QTcF	QTc using Fridericia's correction formula
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
EP-PCR	Reverse transcriptase PCR
RS	Retreatment sub-study
SAD	Single Ascending Dose
SAE	Serious adverse event
sAFP	Serum Alpha-Fetoprotein
SAS	Statistical Analysis System
SD	Standard Deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class/Standard of Care
SOF	Sofosbuvir
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
SVR_4	Sustained virologic response 4 weeks post dosing
SVR_{12}	Sustained virologic response 12 weeks post dosing
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
ULN	Upper limit of normal
V/F	Apparent Volume of distribution
WBC	White blood cells

Pharmacokinetic and Statistical Abbreviations

AUC	Area under the plasma concentration-time curve
AUC_{24}	AUC for the 24-hour dosing interval
β	Apparent terminal phase elimination rate constant
CL/F	Apparent oral plasma clearance
C_{max}	Maximum observed plasma concentration
C_{trough}	Pre-dose trough plasma concentration
$t_{1/2}$	Terminal phase elimination half-life
T_{max}	Time to maximum observed plasma concentration (C_{max})

Definition of Terms

Study Drug	Glecaprevir (ABT-493), pibrentasvir (ABT-530), Ribavirin (RBV), *Sofosbuvir (GS-7977)
Study Day 1	First day of study drug dosing
Treatment Period	Day 1 through last dose of study drug
Post-Treatment Period	Day after the last dose of study drug through Post-Treatment Week 12 or Post-Treatment Discontinuation
	Note: Differentiation between terms within the Main Study and Re-Treatment Substudy will be made with the use of headers throughout the protocol

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3.0 Introduction

Approximately 170 million people worldwide are chronically infected with hepatitis C virus (HCV), including approximately 4-5 million in the United States.[1-4] The majority of individuals infected progress to chronic hepatitis, which can lead to cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[5] HCV is the leading cause of HCC and indication for liver transplantation in most countries, including the United States.[5] Recently, the development of oral direct acting anti-viral therapy has been a major advance for the treatment of HCV with available combinations curing the majority of infected patients.[6,7] Despite the high sustained virologic response (SVR) rates with direct-acting antiviral agents (DAAs), there are patients who fail these combinations and there are currently limited approved retreatment options for subjects who failed an NS5A-inhibitor all-oral DAA regimen.[7-9]

Treatment failure in HCV-infected patients is often associated with host (cirrhosis) and/or viral factors, including resistant-associated substitutions.[10-12]

AbbVie recently received FDA approval for two "next generation" DAAs, glecaprevir (GLE, formerly known as ABT-493), an HCV NS3/4A protease inhibitor (PI) and pibrentasvir (PIB, formerly known as ABT-530), an NS5A inhibitor, for use in combination for the treatment of chronic HCV infection, including in subjects with chronic HCV GT1 infection who failed a prior NS5A inhibitor-containing regimen without an NS3/4A protease inhibitor.[23] GLE and PIB each have potent in vitro antiviral activity against genotypes 1 through 6[13,22] and a high genetic barrier to resistance, with no or little loss of potency against common resistant-associated substitutions[22]. Additive or synergistic in vitro anti-HCV activity has been demonstrated with the combination of GLE and PIB. GLE 100 mg and PIB 40 mg are co-formulated into a fixed-dose combination tablet herein referred to as G/P, which provides patients with a convenient once-daily (QD), fixed-dose combination treatment regimen of three tablets QD to maximize treatment compliance.

A detailed discussion of the preclinical pharmacology and toxicology, in vitro virology and

metabolism, and clinical data can be found in the Investigator's Brochure (applicable to Main Study only).[13]

3.1 Glecaprevir/Pibrentasvir (G/P)

Overview of G/P Registration Program and Supportive Studies

The G/P registration program included a broad subject population including subjects with compensated liver disease and subjects with severe renal insufficiency across all 6 major genotypes using a single dose of 300 mg/120 mg QD. Supportive Phase 2 studies used the Phase 2 formulation of separate GLE and PIB tablets, with each tablet containing 100 mg and 40 mg, respectively. Treatment arms from these supportive Phase 2 studies using the regimen selected for registration studies (GLE 300 mg plus PIB 120 mg) were pooled with arms from the registration studies for analyses of efficacy and safety. Treatment-naïve (TN) and TE subjects to any combination of pegylated IFN (pegIFN), RBV, sofosbuvir (SOF), NS5A inhibitors, or PIs were allowed in the program. In addition, the program included subjects with human immunodeficiency virus (HIV) coinfection (Study M13-590), subjects with chronic kidney disease [CKD] Stages 4 – 5, including those on hemodialysis (Study M15-462), subjects with compensated cirrhosis (Studies M14-172, M15-462, and M14-868), and subjects with or without cirrhosis who failed a previous regimen containing an NS5A inhibitor and/or an NS3/4A PI (Study M15-410).

A total of 2,376 subjects were randomized or enrolled in the registration studies or supportive Phase 2 studies to receive G/P 300 mg QD/120 mg QD. Of these, 2,369 subjects received at least 1 dose of G/P 300 mg QD/120 mg QD (**Table 1**).

Table 1. Overview of Clinical Studies by Subject Population

Genotype	Clinical Study	Summary of Study Design
TN and TE Subjects Without Cirrhosis		
GT1	M13-590	G/P 300 mg/120 mg QD for 8 (n = 351) or 12 weeks (n = 352)
	M14-867	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 34)
GT2	M15-464	G/P 300 mg/120 mg QD (n = 202) or placebo (n = 100) for 12 weeks
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 199) or 12 weeks (n = 25)
GT3	M13-594	G/P 300 mg/120 mg QD for 8 (n = 157) or 12 weeks (n = 233) or SOF 400 mg + DCV 60 mg QD for 12 weeks (n = 115) (all subjects in study were TN)
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 29; TN only), 12 weeks (n = 76), or 16 weeks (n = 22; TE only)
GT4, 5, 6	M13-583	G/P 300 mg/120 mg QD for 12 weeks (n = 121)
	M14-867	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 32)
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 58)
TN and TE Subjects with compensated Cirrhosis		
GT1, 2, 4, 5, 6	M14-172	G/P 300 mg/120 mg QD for 12 weeks (n = 146)
GT3	M14-868	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 64; TN only) or 16 weeks (n = 51; TE only)
Subjects with CKD Stages 4 – 5 With or Without compensated Cirrhosis		
GT1 – 6	M15-462	G/P 300 mg/120 mg QD for 12 weeks (n = 104)
NS5A Inhibitor and/or PI-Experienced Subjects With or Without compensated Cirrhosis		
GT1, 4	M15-410	G/P 300 mg/120 mg QD for 12 (n = 66) or 16 weeks (n = 47)

CKD = chronic kidney disease; DCV = daclatasvir; GLE = glecaprevir; GT = genotype; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; PIB = pibrentasvir; QD = once daily; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naïve

3.1.1 Efficacy

In TN or IFN, pegIFN, RBV, and/or SOF treatment-experienced (TE-PRS) subjects, the pooled overall SVR_{12} rates with G/P were > 97% across GT1, 2, 4, 5 and 6 regardless of treatment experience, treatment duration, including any degree of renal impairment, presence of cirrhosis, or HIV-1 coinfection (**Table 2**).

Among subjects with GT3 infection, the pooled SVR_{12} rates across durations were 95.2% among all subjects, 96.6% among cirrhotic subjects, and 100% among subjects with CKD Stages 4 – 5.

The SVR_{12} rates among subjects previously treated with a PI and/or NS5A inhibitor were ≥ 89.0% for GT1 and GT4.

Table 2. SVR_{12} Rates by Treatment Experience and HCV Genotype – GT1 – 6 (ITT Population, Phase 2 and 3 Analysis Set)

Genotype	TN n/N (%) 95% CI[a]	TE-PRS n/N (%) 95% CI[a]	TN + TE-PRS All[a]	TN + TE-PRS Cirrhotic n/N (%) 95% CI[b]	TN + TE-PRS CKD 4 – 5 n/N (%) 95% CI[b]	TE-NS5A and/or PIs n/N (%) 95% CI[a]	Overall n/N (%) 95% CI[a]
Phase 2 and 3 Analysis Set	1604/1640 (**97.8**) 97.1, 98.5	602/616 (**97.7**) 96.6, 98.9	2206/2256 (**97.8**) 97.2, 98.4	274/281 (**97.5**) 95.7, 99.3	102/104 (**98.1**) 95.4, 100.0	101/113 (**89.4**) 83.7, 95.1	2307/2369 (**97.4**) 96.7, 98.0
GT1	555/561 (**98.9**) 98.1, 99.8	326/328 (**99.4**) 98.5, 100.0	881/889 (**99.1**) 98.5, 99.7	98/101 (**97.0**) 93.7, 100.0	53/55 (**96.4**) 91.4, 100.0	97/109 (**89.0**) 83.1, 94.9	978/998[c] (**98.0**) 97.1, 98.8
GT2	365/369 (**98.9**) 97.9, 100.0	95/97 (**97.9**) 95.1, 100.0	460/466 (**98.7**) 97.7, 99.7	35/35 (**100**) 100.0, 100.0	16/16 (**100**) 100.0, 100.0	N/A	460/466 (**98.7**) 97.7, 99.7
GT3	499/521 (**95.8**) 94.0, 97.5	113/122 (**92.6**) 88.0, 97.3	612/643 (**95.2**) 93.5, 96.8	112/116 (**96.6**) 93.2, 99.9	11/11 (**100**) 100.0, 100.0	N/A	612/643 (**95.2**) 93.5, 96.8
GT4	119/122 (**97.5**) 94.8, 100.0	55/56 (**98.2**) 94.7, 100.0	174/178 (**97.8**) 95.6, 99.9	20/20 (**100**) 100.0, 100.0	20/20 (**100**) 100.0, 100.0	4/4 (**100**) 100.0, 100.0	178/182 (**97.8**) 95.7, 99.9
GT5	26/26 (**100**) 100.0, 100.0	6/6 (**100**) 100.0, 100.0	32/32 (**100**) 100.0, 100.0	2/2 (**100**) 100.0, 100.0	1/1 (**100**) 100.0, 100.0	N/A	32/32 (**100**) 100.0, 100.0
GT6	40/41 (**97.6**) 92.8, 100.0	7/7 (**100**) 100.0, 100.0	47/48 (**97.9**) 93.8, 100.0	7/7 (**100**) 100.0, 100.0	1/1 (**100**) 100.0, 100.0	N/A	47/48 (**97.9**) 93.8, 100.0

CI = confidence interval; CKD = chronic kidney disease; GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat; N/A = not applicable; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SVR_{12} = sustained virologic response 12 weeks post dosing; TE = treatment-experienced; TN = treatment-naïve; TE-NS5A and/or PI = TE with NS5A inhibitor and/or PI

1. CI was calculated using a stratum-weighted proportion and variance.
2. CI was calculated using the normal approximation to the binomial distribution.
3. Eleven subjects were classified by the central laboratory and treated as GT2 but included here as GT1 due to being identified as such by phylogenetic analysis; all 11 subjects achieved SVR_{12}
4. Cross reference: AbbVie, data on file.

3.1.2 Impact of Baseline Polymorphisms on Treatment Outcome

The association between baseline polymorphisms and treatment outcome in TN and TE-PRS subjects who received G/P 300 mg/120 mg QD in the registration or supportive Phase 2 studies was evaluated by conducting an integrated analysis of baseline sequence data. Next-generation sequencing (NGS) was conducted on all baseline samples at 15% detection threshold at key amino acid positions 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A.

In subjects who were TN or TE-PRS, baseline polymorphisms in NS3 were detected in 1.1% (9/845), 0.8% (3/398), 1.6% (10/613), 1.2% (2/164), 41.9% (13/31), and 2.9% (1/34) of subjects with HCV genotype 1, 2, 3, 4, 5 and 6 infection, respectively. Baseline polymorphisms in NS5A were detected in 26.8% (225/841), 79.8% (331/415), 22.1% (136/615), 49.7% (80/161), 12.9% (4/31), and 54.1% (20/37) of subjects with HCV genotype 1, 2, 3, 4, 5, and 6 infection, respectively.

The presence of baseline polymorphisms in NS3 and/or NS5A did not have an impact on SVR_{12} rates for GT1-, 2-, 4-, 5-, or 6-infected subjects.
Within GT3-infected subjects, baseline polymorphisms in NS3 and the NS5A polymorphisms at positions 24, 28, 31, 58, 92, or 93 did not have an impact on treatment outcome.

3.1.3 Amino Acid Substitutions in Subjects Experiencing Virologic Failure

Among TN and TE-PRS subjects with or without cirrhosis treated for 8, 12, or 16 weeks, 23 subjects experienced virologic failure (2 with GT1, 2 with GT2, and 19 with GT3). One GT3-infected subject experiencing virologic failure was determined to have been re-infected with GT3a virus distinct from the one present at baseline. Therefore, baseline polymorphisms and treatment-emergent substitutions were analyzed for 22 subjects experiencing virologic failure.

Among the 2 GT1-infected subjects, 1 had treatment-emergent substitutions A156V in NS3 and Q30R/L31M/H58D in NS5A, and 1 had treatment-emergent Q30R/H58D (while Y93N was present at baseline and post-treatment) in NS5A.
Among the 2 GT2-infected subjects, no treatment-emergent substitutions were observed in NS3

or NS5A; the prevalent M31 polymorphism in NS5A was present at baseline and post-treatment in both subjects.

Among the 18 GT3-infected subjects, the majority of subjects had treatment-emergent variants at the time of failure in NS3 (61.1%, 11/18) and NS5A (88.9%, 16/18). Treatment-emergent NS3 substitutions Y56H/N, Q80K/R, A156G, and Q168L/R were observed in 11 subjects, and A166S or Q168R was present at both baseline and post-treatment in 5 subjects. Treatment-emergent NS5A substitutions M28G, A30G/K, L31F, P58T, or Y93H were observed in 16 subjects, and 13 subjects had A30K (n = 9) or Y93H (n = 5) at both baseline and post-treatment.

3.1.4 Integrated Safety Results

A summary of treatment-emergent adverse events (AEs) from pooled analyses of the registration studies and supportive Phase 2 studies are presented in **Table 3**. The severity of the underlying renal disease and its associated comorbidities in patients with CKD Stages 4 and 5, the frequency and severity of the AEs in subjects enrolled Study M15-462 were expected to be higher than in subjects enrolled in the other registration studies. Therefore, the summary of adverse events reported in **Table 3** does not include the results of Study M15-462.

As shown in **Table 3**, the AEs occurring with a frequency ≥ 5% are headache, fatigue, nausea and diarrhea. The majority of subjects experienced an AE, which were mostly considered to be mild in severity by the investigator (Grade 1). Rates of AEs that were serious, led to premature study drug discontinuation or had a severity Grade ≥ 3 were low. Including data from Study M15-462, there were 7 deaths, none of which were related to study drug, and the majority occurred several months after the last dose of study drug.

Table 3. Adverse Events Reported for ≥ 5.0% of Subjects (Phase 2 and 3 Analysis Set)

	Phase 2 and 3 Analysis Set[a] (N = 2,265) n (%)	
	All Adverse Events	DAA-Related Adverse Events[b]
Any AE	1,529 (67.5)	929 (41.0)
An AE Grade ≥ 3	65 (2.9)	4 (0.2)
Any SAE	48 (2.1)	1 (< 0.1)
Discontinuation of study drug due to any AE	8 (0.4)	3 (0.1)
All deaths[c]	6 (0.3)	0
Preferred Term[d]		
Headache	410 (18.1)	298 (13.2)
Fatigue	330 (14.6)	259 (11.4)
Nausea	208 (9.2)	172 (7.6)
Diarrhea	146 (6.4)	86 (3.8)

AE = adverse event; DAA = direct-acting antiviral agent; GLE = glecaprevir; PIB = pibrentasvir; SAE = serious adverse event

a. Excludes Study M15-462.

b. DAAs = GLE, PIB, or GLE/PIB.

c. Includes non-treatment-emergent deaths. One additional death occurred in Study M15-462.

d. DAA-related AEs reported for ≥ 5.0% of subjects in the Phase 2 and 3 Analysis Set.

Cross reference: AbbVie, data on file.

Adverse events in subjects without cirrhosis (n = 1,977) were similar in type, frequency, and severity compared with subjects with cirrhosis (n = 288). The safety profile in subjects with HCV/HIV-1 co-infection (n = 33) was similar to that in HCV mono-infected subjects. Overall, the safety profile of G/P in the elderly population (≥ 65 years old, n = 328) was comparable to the safety profile in the non-elderly population (n = 2,041).

The frequency and severity of hepatic-related AEs as well as liver chemistry abnormalities evaluating potential hepatotoxicity were low across the Phase 2 and 3 studies. Liver-related safety results indicated that:

- Four subjects had post-nadir Grade 3 ALT abnormalities or Grade 2 ALT with total bilirubin ≥ 2 × ULN. None of these subjects prematurely discontinued study drug due to an ALT or bilirubin increase.
- ALT abnormalities in 3 of these 4 subjects were not clinically significant

- One subject experienced concurrent ALT > 3 × ULN (increased from nadir grade) and total bilirubin ≥ 2 × ULN in the context of multiple gallstones and was not considered to have drug-induced liver injury
- Based on exposure-response analyses, no exposure-dependent ALT increases were observed in subjects with ALT abnormalities
- Grade 3 increases in bilirubin were infrequent (0.4%) and without bilirubin-related AEs; none were associated with liver disease progression
- No subjects experienced drug-related hepatic decompensation. One subject with cirrhosis (Study M14-172) who had known esophageal varices experienced an episode of esophageal varices hemorrhage that was considered not related to study drug. Treatment was continued without clinical or laboratory signs of liver disease progression.
- A total of 6 (0.3%) subjects experienced a de novo event of HCC. In all 6 subjects, the events were considered related to subject's medical history of underlying liver disease and not to G/P.

In summary, G/P demonstrated a favorable safety profile similar across durations of 8, 12, and 16 weeks. The regimen was well tolerated across a broad and diverse population of subjects, including subjects with cirrhosis, HIV co-infection, and CKD Stage 4 or 5.
Common study drug-related AEs occurring in ≥ 5% of subjects were headache, fatigue, nausea and were mostly Grade 1 (mild) in severity. Serious AEs and AEs leading to premature study drug discontinuation were rare. There were no hematological or blood chemistry findings of concern or considered likely related to treatment. Unlike other protease inhibitors, no liver-related toxicities and no cases consistent with drug-induced liver injury were identified.

G/P+SOF+/-RBV for G/P treatment failures

AbbVie has recently evaluated the safety and efficacy of G/P+SOF+/-RBV in combination in patients who had virologic failure following G/P treatment in AbbVie's registration program. The MAGELLAN-3 study (M15-942) is ongoing and reported to date on a total of 23 subjects including 7 GT1-infected patients treated for 16 weeks with G/P+SOF+RBV; 6/7 achieved an SVR_{12} (86%). The patient who experienced virologic failure relapsed, had GT1a infection,

compensated cirrhosis, and had failed a course of LDV/SOF prior to enrolling in the AbbVie parent study MAGELLAN-1 (M15-410), where the patient experienced on-treatment failure. Overall, the 7 GT1-infected patients enrolled in MAGELLAN-3 had a median of 9 months (min: 6.7/max: 14) from time of G/P failure in the AbbVie parent study to start of retreatment in MAGELLAN-3 and all had persistent NS5A RASs at baseline prior to retreatment with G/P+SOF+RBV. Retreatment with G/P+SOF+RBV was well tolerated. There have been no serious adverse events attributed to the retreatment regimen and no Grade 3 adverse events. The most common adverse events in >10% of subjects were headache, pruritus, dizziness, irritability, fatigue, insomnia and upper respiratory tract infection. There was one grade 3 ALT elevation in a subject with an SAE of cholelithiasis that was consistent with biliary obstruction.[24]

3.2 Ledipasvir/Sofosbuvir (LDV/SOF)

LDV/SOF is a single tablet combining LDV, an NS5A inhibitor, with SOF a nucleotide analog HCV NS5B polymerase inhibitor, that was the first fixed dose combination of an all oral DAA regimen approved in the US for genotype 1 patients. In the registration clinical trials with LDV/SOF, the treatment combination resulted in high SVR rates (≥ 94%) following 8-24 weeks of treatment in treatment-naïve and pegIFN and RBV treatment-experienced subjects, irrespective of cirrhosis, yet still some patients fail this therapy.[14] Subjects with HCV genotype 1 that failed eight or twelve weeks of LDV/SOF-containing regimens that were retreated with 24 weeks of LDV/SOF had an SVR12 rate of 71% and in this population, the presence of baseline NS5A RAVs was associated with virologic failure[15]. Post-baseline NS5A and NS5B deep nucleotide sequence analysis data (assay sensitivity of 1%) from the 29 genotype 1a LDV/SOF virologic failure subjects from Phase 3 showed that 55% (16/29) of subjects had virus with emergent NS5A resistance-associated substitutions (RAS) K24R, M28T/V, Q30R/H/K/L, L31M, or Y93H/N at failure. Five of these 16 subjects' viruses also had baseline NS5A polymorphisms at resistance-associated amino acid positions. The most common substitutions detected at failure were Q30R, Y93H or N, and L31M. Of the 8 genotype 1b virologic failure subjects, 88% (7/8) had virus with emergent NS5A resistance-associated substitutions L31V/M/I or Y93H at failure. Virus from three of these 7

subjects also had baseline NS5A polymorphisms at resistance-associated positions. The most common substitution detected at failure was Y93H.[14]

In the HCV-TARGET observational cohort, treatment failure occurred in 3-5% of 2,099 patients treated with LDV/SOF[17]. Treatment failure was more likely in those with cirrhosis, more advanced disease (low albumin and higher bilirubin), and those on concurrent proton pump inhibitors. It can be expected that as more patients are treated with DAA therapies, particularly with the widespread use of LDV/SOF, the need for retreatment options for patients who fail will increase.

3.3 PRIORITIZE Study and HCV-TARGET

The PRIORITIZE study and HCV-TARGET represent real-world cohorts to provide well-characterized patients for a DAA failure clinical trial. In the PRIORITIZE Study approximately 1250 GT1 patients without a history of decompensated cirrhosis will be randomized to receive LDV/SOF, and have virologic, clinical, disease progression, and QOL/PRO data collected for a 5 year period under a pragmatic design. Each patient will have baseline NS5A testing performed, along with a stored sample for research purposes. Upon treatment failure, all patients will have a sample collected for resistance testing. Assuming a 5% treatment failure rate, PRIORITIZE will generate approximately 65 LDV/SOF treatment failures. HCV-TARGET is an observational cohort of patients undergoing DAA therapy. To date, approximately 7,000 patients treated with DAA therapy have been enrolled into HCV-TARGET. Among HCV-TARGET centers, there are more than 450 G1 therapy failures, 300 of which failed therapy with an NS5a-I+SOF and represent another cohort of DAA failures. Between these two studies, well-characterized NS5a-I/SOF failures will be identified to form a unique cohort to rapidly enroll into this DAA failure study.

3.4 Study Rationale

The FDA approved label duration for NS5A-experienced, PI-naïve subjects with or without compensated cirrhosis and HCV GT1 chronic infection is G/P 300 mg/120 mg for 16 weeks.[23] However, the G/P regimen may be further refined based on additional efficacy results in subsets of

NS5A inhibitor experienced, PI-naïve HCV GT1 infected subjects. The goals of this study are to increase the confidence in real world DAA failure patients who are receiving the recommended G/P regimen, to explore a shorter 12-week duration of the G/P regimen in non-cirrhotic subjects, and ribavirin-intensification of a shorter 12-week duration of the G/P regimen in subjects with compensated cirrhosis.

High SVR12 rates were achieved with G/P 300 mg/120 mg when given for 12 and 16 weeks in GT1-infected subjects who were NS5A-experienced and PI-naive (SVR12 90.0% 18/20 and 94% 17/18, respectively, MAGELLAN-1, NCT02446717, AbbVie, data on file). The majority of subjects with prior NS5A inhibitor-experience in MAGELLAN-1 Part 1 & 2 combined were subjects who failed prior LDV/SOF (Harvoni) treatment: GLE/PIB 300 mg/ 120 mg for 12 weeks (n=12, 11 achieved SVR12, 91.7%), GLE/PIB 300 mg/ 120 mg for 16 weeks (n=10, 9 achieved SVR12, 90.0%), and G/P 300 mg/ 120 mg plus 800 mg once daily RBV for 12 weeks (n=4, all 4 achieved SVR12). Among the 42 NS5A-experienced and PI-naïve failures enrolled in MAGELLAN-1, 30/31 (96.8%) subjects without cirrhosis and 9/11 (81.8%) of subjects with compensated cirrhosis achieved an SVR12.

In MAGELLAN-1, NS5A inhibitor-experienced, PI-naïve subjects without cirrhosis who received G/P 300 mg/120 mg for 12 and 16 weeks achieved SVR12 rates of 92.3% (12/13) and 100% (14/14), respectively. As the difference in SVR12 between these two durations was based on a single subject that did not achieve SVR, it is hypothesized that 12 weeks treatment duration with G/P may provide an effective retreatment option. Therefore, the present study will evaluate G/P for 12 and 16 weeks in a larger patient population to determine if treatment duration may be decreased from 16 to 12 weeks in NS5A inhibitor-experienced, PI-naïve subjects without cirrhosis.

MAGELLAN-1 enrolled a total of 11 NS5A inhibitor -experienced, PI-naïve subjects with compensated cirrhosis; 85.7% (6/7) and 75.5% (3/4) subjects achieved SVR12 with G/P 300 mg/120 mg for 12 or 16 weeks, respectively. The two subjects that did not achieve SVR12 experienced on-treatment virologic failure and may benefit from the addition of RBV which has

been shown to decrease the risk of both on-treatment failure and relapse.[16] Therefore, the present study will evaluate G/P for 16 weeks and G/P + RBV for 12 weeks in NS5A inhibitor -experienced, PI-naïve subjects with compensated cirrhosis.

The objective of this study is therefore to obtain additional data with G/P in NS5A inhibitor–experienced, PI-naïve GT1-infected subjects that will help to optimize the G/P regimen for this population. The initial study design did not exclude patients with historical PI exposure prior to the NS5A-inbitor exposure as PI resistance has been shown to quickly revert to wild types, but did exclude only those who received a PI in combination with a NS5a. Since the initial study launch, G/P has been approved by the FDA and was given a label for NS5A experienced, PI naïve patients only; with 16 weeks of therapy. Thus, to minimize treatment failure in this population and more accurately reflect FDA label duration, patients with any prior PI exposure will be excluded from further recruitment into the study and any patient already enrolled or randomized to a 12-week arm will have their treatment extended to 16 weeks duration.

In addition to LDV/SOF-treatment experienced subjects, velpatasvir (VEL)/sofosbuvir (VEL/SOF) and daclatasvir (DCV)/sofosbuvir-experienced subjects will be included. While there is clinical evidence that G/P retreatment of LDV/SOF failures can achieve high SVR rates (see above), there is no clinical data for G/P in VEL/SOF- or DCV/SOF-experienced subjects. NS5A substitution Y93H has been observed in GT1 and GT3 treatment failures with SOF/VEL and confers greater than 100-fold reduction in velpatasvir in-vitro susceptibility.[19] In GT1a-infected subjects who failed a DCV/SOF regimen NS5A resistance-associated substitutions (including pre-existing amino acid polymorphisms or treatment-emergent substitutions): M28T, Q30H/K/R, L31M/V, H54R, H58D/P, or Y93C/N were observed. In GT1b failures the P32-deletion was observed. Among HCV genotype 1a-infected virologic failure subjects, the most common NS5A amino acid substitutions occurred at position Q30 (Q30H/K/R; 73% [8/11], all treatment-emergent). Phenotypic analysis of genotype 1a replicons expressing single NS5A M28T, Q30E, Q30H, Q30R, L31V, Y93C, Y93H, and Y93N substitutions exhibited 500- 18500-, 1083-, 900-, 2500-, 1367-, 8500-, and 34833-fold reduced susceptibility to DCV, respectively. For genotype 1b, L31V and Y93H single substitutions and L31M/Y93H and L31V/Y93H combinations exhibited 33-, 30-,

16000-, and 33667-fold reduced susceptibility to DCV, respectively. The P32-deletion in genotype 1b reduced DCV susceptibility by >1,000,000-fold.[20] None of the studied single NS5A substitutions in GT1 at positions 28, 30, 31, and 93 reduced susceptibility to PIB by more than 6-7 fold[22], and there was no single NS5A baseline polymorphism that was associated with a reduced SVR12 rate in GT1-infected subjects in the G/P Phase 3 trials (Section 3.1.2). Furthermore, and given the different mechanism of action of GLE when compared to SOF and no cross-resistance between SOF and GLE, and GLE with any NS5A inhibitor, the G/P regimen ± RBV should provide high SVR rates for VEL/SOF or DCV/SOF-experienced subjects.

In this study, prior GT1-infected NS5A inhibitor + SOF-experienced subjects without cirrhosis will be randomized 2:1 to receive G/P for 12 or 16 weeks. Prior GT1-infected NS5A inhibitor + SOF-experienced subjects with compensated cirrhosis will be randomized 1:1 to receive 12 weeks of G/P with RBV or 16 weeks of G/P.

In the first several years of HCV DAA therapy, more than 50% of patients undergoing treatment had evidence of cirrhosis. With rapid uptake of HCV treatment in this cirrhotic patient population, the prevalence of cirrhosis among untreated persons with HCV has decreased substantially to only 15 to 20%. This shift in the characteristics of patients presenting for HCV treatment in the US is reflected in several other studies including the PRIORITIZE Study mentioned previously (16% cirrhosis in over 1200 patients enrolled) and the HCV-TARGET observational registry (15% cirrhosis currently with 40% cirrhosis historically). Similar trends in the types of patients treated using pharmacy databases (such as TRIO) are evident. Among the first 130 patients screened for this study, 65% have been non-cirrhotic, reflecting the current real-world treatment population in DAA failure patients. Thus, the patient randomization targets have been adjusted and nearly 70% non-cirrhotic patients are expected to enroll in this study, thereby matching current observed trends in HCV therapy.

In the main study, patients without cirrhosis will be treated with G/P for either 16 or 12 weeks. Patients with compensated cirrhosis will be treated for 16 weeks with G/P or 12 weeks with G/P + ribavirin. Ribavirin is an FDA approved drug that is used in combination with other HCV

treatments. The approved G/P treatment duration for prior GT1-infected NS5A inhibitor failures that are NS3/4A inhibitor naïve and are non-cirrhotic or have compensated cirrhosis is 16 weeks. In addition to the approved G/P treatment duration of 16 weeks, a 12-week duration of G/P without and with ribavirin is tested for non-cirrhotic and compensated cirrhotic patients, respectively. These later treatment arms are considered experimental.

3.4.1 Rationale for Retreatment of G/P Failures in this Study

Combining drugs with different mechanisms of action can increase the probability of achieving a sustained virologic response in HCV-infected patients who have failed one or more prior DAA therapy. Data from GT1-infected patients in the MAGELLAN-3 study who failed prior G/P therapy support the use of the combination of G/P+SOF±RBV as a viable, well-tolerated retreatment option.

3.5 Rationale for Pragmatic Design in Phase 3b Study using HCV-TARGET Network and Methods

The Medicare National Coverage Decision for Clinical Trials provides for a national coverage policy covering the routine costs for items and services given to a patient as part of a clinical trial (see Appendix B) setting the stage to implement clinical research studies under standard of care practice. Typically, trials designed for regulatory approval are highly controlled and restrictive in the patients studied. By the time of the phase 3b drug development, drug safety and efficacy are established from earlier trials yet drugs arrive in the post-marketing environment lacking information needed by post-regulatory decision-makers (providers, patients, payers) to guide treatment and coverage decisions (no established "real-world" effectiveness). In 2009, the Center for Medical Technology Policy (CMTP) convened a large meeting of experts and stakeholders, including the US FDA, to seek input to develop a guidance document to develop and implement informative, pragmatic phase 3/3b pharmaceutical trials that satisfy the regulatory requirements of the FDA (Effectiveness Guidance Document- *Pragmatic Phase 3 Pharmaceutical Trials: Recommendations for the design of clinical trials that are more*

informative for patients, clinicians and payers). The FDA has issued guidance related to Real World Evidence (RWE) use in regulatory decision-making and have stated that "It is important that FDA consider the possibilities of using so-called "real world" data as an important tool in evaluating not only the safety of medications but also their effectiveness." The advantage of RWE is to produce information needed by the post-regulatory decision makers, which avoids delays in coverage decisions and speeds access to beneficial new therapies to a broad range of patients. Domains that are most necessary for making post-regulatory decisions that are often missing from traditional regulatory trials include generalizability of patient population and consistently measured, relevant outcomes.

The HCV-TARGET cohort study has grown into extensive partnership between its academic & community centers, the pharmaceutical industry, an HCV community advocate and the FDA. The registry has enrolled over 10,000 patients prescribed HCV therapy in the real-world since being established in late 2011 and the infrastructure -methods will be leveraged to conduct this study. With the Clinical Coordinating Center (CCC) residing at the University of Florida (PI: Nelson) and Data Coordinating Center (DCC) at the University of North Carolina at Chapel Hill (PI: Fried), HCV-TARGET developed standardized, centralized chart data abstraction methods along with data monitoring to increase the efficiency and quality of an observational registry while also minimizing costs typically associated with performing post-marketing clinical research. The network hosts databases that are CFR 21 Part 11 compliant and includes MEDRA adverse event and WHO drug dictionary coding standardization. It also has a CDISC compliant database allowing the data to be shared directly with the FDA for analyses around safety and efficacy as part of a formal MOU (#**225-13-0012**) executed in 2013 and renewed in 2017. Thus, HCV-TARGET is well positioned to utilize the established observational cohort data collection and monitoring methods to act as an Investigator Coordinating Organization (ICO) to implement this unique approach to non-IND clinical trials using unlabelled combinations of approved drugs and post marketing commitment studies as well as Treatment IND Protocols for Large Population Expanded Access Programs (EAP) and late 3b pragmatic clinical trials related to HCV therapy.

3.6 Benefits and Risks

Main Study

Potential benefits of treatment with G/P in a NS5A-inhibitor+SOF treatment failure population include:

1. Potential for high SVR in a population with limited treatment options (high unmet need) based on results from MAGELLAN-1 which demonstrated a high SVR rate in HCV GT1-infected subjects with and without compensated cirrhosis who failed prior treatment with a NS5A-inhibitor containing regimen.
2. Potent and pangenotypic antiviral activity in vitro, higher genetic barrier to development of drug resistance across genotypes compared to first generation protease and NS5A inhibitors, and the convenience of a once daily regimen.
3. The benefit of shortened therapy for some subjects
4. The benefit of evaluating a RBV-intensified DAA regimen

The safety of G/P has been established in a diverse population of patients with and without compensated cirrhosis in Phase II and III clinical trials (Section 3.1.4) and the overall AE profile supports a safe regimen. The most common AEs in greater than 10% of subjects include headache and fatigue. Additional Safety data for G/P and G/P plus RBV are detailed in the Investigator's Brochure (applicable to Main Study Only) and Prescribing Information. The safety profile of Ribavirin is well established. RBV is a teratogen (pregnancy category X) and the primary toxicity in subjects is reversible hemolytic anemia[21]. In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures.

Risks associated with the combination of G/P±RBV, including the risks of toxicity, virologic failure and development of resistance-associated substitutions (Section 3.1.3), appear to be limited and manageable based upon the available data. Given the potential for high rates of SVR in this population of HCV GT 1-infected subjects with limited current treatment options, the risk-benefit assessment is favorable.

Re-treatment sub-study

Data from the MAGELLAN-3 study support the addition of SOF to G/P±RBV as a retreatment option for G/P failures that was well tolerated.[24] The risks for treatment with the combination of G/P+SOF±RBV include the potential for toxicity, virologic failure and development of additional RASs. However, these risks appear to be limited based on available data. Given the potential for high rate of SVR in this difficult to treat population of HCV GT 1-infected subjects for whom limited data exist regarding retreatment options, the risk-benefit ratio is favorable.

4.0 Study Objective

4.1 Primary Objective

The primary objectives of this study are to:

1. Compare the efficacy (SVR12) of G/P given for 12 weeks to non-cirrhotic GT1-infected subjects who are treatment-experienced with a NS5A inhibitor+SOF±RBV regimen (Arm A) vs. G/P given for 16 weeks (Arm B)
2. Compare the efficacy (SVR12) of G/P plus RBV given for 12 weeks to GT1-infected subjects with compensated cirrhosis and who are treatment-experienced with a NS5A inhibitor+SOF±RBV regimen (Arm C) vs. G/P given for 16 weeks (Arm D)
3. Assess the safety and tolerability of G/P with or without RBV, in these subjects with chronic HCV GT1 infection and treatment-experienced with a NS5A inhibitor+SOF±RBV regimen.

4.2 Secondary Objectives

The secondary objectives are to assess

1. The difference in efficacy (SVR12) of G/P±RBV given for 12 weeks (Arms A+C) versus G/P±RBV given for 16 weeks (Arms B+D).

2. The differences in the percentages of subjects with on-treatment virologic failure for non-cirrhotic subjects (Arm A vs Arm B) and subjects with compensated cirrhosis (Arm C vs Arm D);

3. The differences in the percentages of subjects with post-treatment relapse for non-cirrhotic subjects (Arm A vs Arm B) and subjects with compensated cirrhosis (Arm C vs Arm D).

4.3 Additional Objectives

1. To assess the impact of baseline host and viral factors on treatment outcomes, the emergence and persistence of viral variants in those with treatment failure in the Main study.
2. To assess safety and efficacy of the retreatment regimen of G/P+SOF±RBV in the Retreatment sub-study.

5.0 Investigational Plan

5.1 Overall Study Design, Rationale and Plan: Description

Main Study

This Phase 3b study has been designed as a multi-center, randomized, open-label, pragmatic study of G/P +/- RBV for 12 weeks or G/P 16 weeks in subjects with chronic HCV GT1 infection who are treatment experienced with NS5A inhibitor + SOF therapy. Up to 225 subjects with chronic GT1 infection and prior treatment history of a NS5A inhibitor +SOF±RBV regimen will be enrolled to receive:

Arm A: G/P (300mg /120mg QD) for 12 weeks

Arm B: G/P (300mg /120mg QD) for 16 weeks

Arm C: G/P (300mg /120mg QD) + wt. based RBV (1000 or 1200mg total daily dose given BID for patients with body weight <75kg or ≥75kg, respectively) for 12 weeks

Arm D: G/P (300mg /120mg QD) for 16 weeks

Randomization scheme:

-GT1 non-cirrhotic (up to 150) subjects: randomized 2:1 to Arms A or B.

-GT1 cirrhotic (up to 75) subjects: randomized 1:1 to Arm C or D.

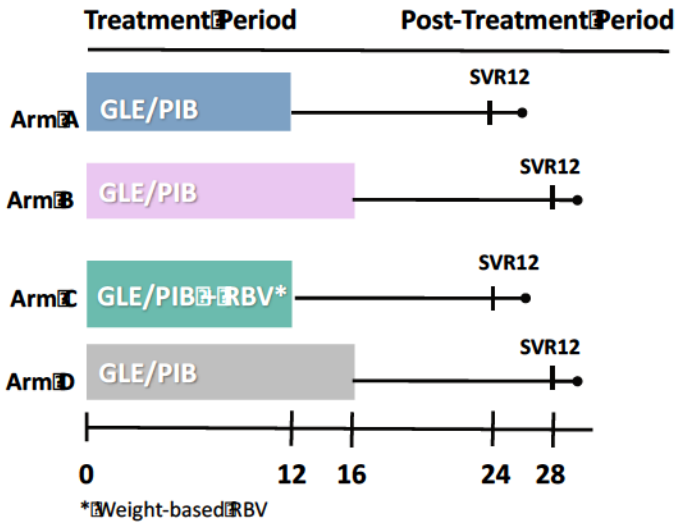
Randomization will be stratified by HCV GT 1b vs non-1b.

The Main study consists of 2 periods:

Treatment Period: Eligible subjects will be enrolled to receive G/P 300 mg/120 mg QD +/- RBV for 12 weeks or G/P for 16 weeks.

Post Treatment Period: Subjects who complete or prematurely discontinue the Treatment Period will be followed for 12 weeks after their last dose of study drug to evaluate efficacy and to monitor HCV RNA and the emergence and persistence of viral substitutions.

Figure 1. Study Schematic



The study is designed to enroll up to 225 subjects with a minimum number of 175 subjects to meet scientific objectives and without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

Retreatment Sub-study

Subjects who experience virologic failure in the Main study will have the option to elect to enter the Retreatment sub-study and receive G/P+SOF±RBV for a total of 16 weeks with the start of retreatment after experiencing G/P failure. The use of RBV in the re-treatment regimen is at the discretion of the investigator, and in consideration of potential RBV benefit and its risks for toxicity as part of the retreatment regimen for the individual subject. Subjects electing to participate in the Retreatment sub-study will be followed for safety and efficacy according to the Main study pragmatic design procedures and Study Activities Tables (5 & 6) with exceptions as noted to screening procedures prior to re-treatment initiation. Retreatment eligibility will be determined prior to administering G/P+SOF±RBV based on Inclusion Criterion 1, 2, 4, 6, 7, 8, 9, and 10, and Exclusion Criterion 1, 3, 4, 6, 8, 10,11 and 12 in Sections 5.2.1 and 5.2.2.

Subjects in both the Main Study and the Retreatment sub-study will be consented and enrolled prospectively at participating sites. Subjects in the Main Study will be treated with open-label G/P +/- RBV according to their randomization while subjects in the Retreatment Sub-Study will receive open-label G/P +/- RBV + SOF. As a pragmatic, phase 3b study both Main and Retreatment Sub-Study subjects will be managed clinically per standard of care guidelines (based on AASLD/ISDA Guidelines for HCV treatment[8]) for disease monitoring and HCV treatment. To standardize some processes across all subjects, there is protocol required lab safety and efficacy monitoring along with required drug dispensing/drug reconciliation intervals outside of standard of care. Source data is the original medical record collected as part of standard of care HCV treatment except for documentation of protocol inclusion/exclusion criteria, blood sample collection, drug dispensing/reconciliation and SAE reporting. All original clinic notes, telephone notes, safety and efficacy labs/evaluations collected during standard of care treatment and in the post treatment observation period are redacted and submitted according to a contract-defined schedule to a central data repository at the University of Florida (UF). Pertinent data from submitted source medical records is abstracted and entered into the database according to uniform guidelines by trained staff at the UF Clinical Coordinating Center. In keeping with the pragmatic study design, efficacy and safety outcomes assessments are recommended as part of the subjects' standard clinical follow up and will be collected and analyzed in the submitted medical records.

5.1.1 Standard of Care Assessments – (patient managed clinically and billed per standard medical practice)

1. Baseline factors (cirrhosis determination- except for Fibrotest to be performed at study central laboratory), prior HCV treatment history, medical history, and co-morbid conditions
2. G/P treatment regimen monitoring, RBV treatment regimen monitoring and RBV dose adjustments, if applicable
3. Clinical factors (physical examinations, vital signs)
4. Adverse events and related management
5. Concomitant medications

5.1.2 Protocol Required Assessments (not billed as standard of care Table 5 and Table 6)

1. All study required safety and efficacy labs outside of standard of care, including Fibrotest and APRI (if assignment of cirrhosis status is unable to be made by site PI).
2. Baseline NS3 and NS5A sequencing
3. NS3, NS5A and *NS5B sequencing at evidence of virologic failure
4. G/P, RBV, *SOF are provided to patients free of charge

* For Retreatment sub-study only

5.1.3. Screening

Screening procedures outlined below are required for both subjects of the Main study and subjects of the Retreatment sub-study. At the Screening Visit, which will be done in conjunction with a standard of care clinical visit, subjects who provide written informed consent (signed and dated) prior to any study-specific procedures will receive a unique subject number assigned sequentially by the study site. Enrolled subjects will keep their screening number as their subject number throughout the Main study and Retreatment sub-study.

The investigator/clinician designee will evaluate whether the subject meets all of the eligibility criteria, applicable to the Main study, specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through Study Day 1 prior to dosing, or meets the subset of the inclusion criteria 1, 2, 4, 6, 7, 8, 9, and 10 and exclusion criteria 1, 3, 4, 6, 8, 10, 11 and 12 specified in Sections 5.2.1 and 5.2.2 for eligibility in the Retreatment sub-study. Results of this assessment and the details of the informed consent process will be recorded in the subject's medical records or associated study source worksheets. Eligible subjects who do not start treatment within 45 days following the Screening Visit will require repeat chemistry, hematology, and coagulation labs prior to randomization into the Main study or Retreatment sub-study. Enrollment into the Main study is competitive; and reasonable effort will be made to start all eligible subjects on therapy, however

there is no guarantee for additional treatment starts once full enrolment of n=225 subjects is achieved. Enrollment into the Retreatment sub-study is only for subjects who failed treatment in the Main study and elect to participate in the Retreatment sub-study.

Medical records to support the medical history will be submitted for centralized data abstraction and include clinic visits, telephone contacts, relevant local laboratory testing and diagnostic/disease screening results (i.e. fibroscan results, liver biopsy pathology report, ultrasound/CT/MRI report for HCC screening, EGD, ECG or other records- if done) collected as part of the standard medical care of the subject in the prior 24 months. The submitted records should also include an updated medical history listing and concomitant medication listing. Older records (greater than 24 months) to document key medical history and liver disease/HCV treatment history will also be submitted for centralized abstraction.

Screening laboratory testing to determine eligibility for the study will be conducted by a central laboratory and will include the testing specified in **Table 5** and **Table 8**. For screening lab results without specific entry criteria that are abnormal and noted as clinically significant by the study investigator, the study investigator or designee will consult with the study medical monitor for approval to enroll the patient in the study.

Prior to randomization, subject eligibility will be verified centrally by the CCC. At a minimum of 5 business days prior to the scheduled Study Day 1 visit, the site will submit the subject's redacted screening/historical medical records according to HCV-TARGET centralized randomization/abstract processes to be verified for meeting enrollment eligibility criteria. After being centrally verified as meeting the eligibility criteria, subjects will be randomized centrally via the study randomization system. Sites will receive the respective randomization and subjects will be administered study drugs at the site on Study Day 1, with dosing instructions.

5.1.3.1 Rescreening

Subjects who at Screening have any of the following are not eligible to rescreen or retest:

- HCV genotype does not meet Inclusion Criterion No. 3, Section 5.2.1, or meets Exclusion Criterion No. 2, Section 5.2.2.

Otherwise subjects may be retested or rescreened only once.

Subjects who have exclusionary laboratory parameter(s) are allowed to retest on chemistry, hematology or coagulation panel(s) (e.g., exclusionary total bilirubin requires a repeat chemistry panel) within the same screening period and must meet all eligibility laboratory criteria on any panel that is repeated. If the retest result(s) are also exclusionary, the subject may not be rescreened or retested again.

Subjects who fail to enroll within 45 days of Screening, may be allowed to rescreen once. These subjects must be rescreened for safety laboratory and eligibility criteria.

For subjects who rescreen or subjects that do not meet the study eligibility criteria upon retest/rescreen, the site personnel must contact the sponsor and identify the subject as a screen failure.

5.1.4 Treatment Period

Efficacy and safety outcomes assessments recorded in the medical record as part of the subject's standard clinical management and follow up will be submitted and abstracted centrally where available in the medical record, except for protocol defined central laboratory assessment collection, drug dispensation and accountability, and required monthly medical record source record verification/submission. The schedule of procedures for the study **Table 5** - Study Activities) is based on the AASLD guidelines[8] for the treatment of HCV, which recommends 1) baseline: hepatic fibrosis assessment, drug-drug interaction assessment, HCV RNA and genotype/subtype, hepatitis B serologies (HBsAg, anti-HBc, anti-HBs, reflex HBVDNA if anti-HBc+) CBC/plts, hepatic function panel, and a calculated glomerular filtration rate; 2) on treatment monitoring: HCV RNA and routine CBC/plts, hepatic panel and

GFR are recommended at week 4 and as clinically indicated; clinic f/u for assessment is typically done at monthly intervals for treatment experienced patients 3) post-treatment monitoring: HCV RNA and routine labs are recommended at 12 weeks post-treatment. G/P ± RBV dosing in the Main study, and G/P +SOF ±RBV dosing in the Retreatment sub-study, treatment/side effect management, and duration will be recorded in the medical record by the site PI and or clinical provider designee and managed according to the AASLD guidelines standard of care with additional assessments required by the protocol according to the Study Activities Table (**Table 5**).

Medical records submitted for centralized data abstraction include clinic visits and telephone contact as clinically indicated to ensure medication adherence and to monitor for adverse events. All original clinic notes, telephone notes, locally available safety labs/evaluations and/or diagnostic tests or health screenings collected during HCV treatment period will be submitted for chart data abstraction to identify and abstract adverse events, vital signs, physical examinations, concomitant medications, HCV RNA, HCV resistance, and clinical laboratory tests that were collected as part of standard of care practice. Sites will also perform a monthly verification for new clinical interactions that may have occurred in the prior 4 weeks at the time the subject visits the site for the monthly central laboratory assessment collection and drug dispensing/accountability.

Methods to abstract the assessments are described in a separate Data Abstraction Conventions Manual.

Study visits and procedures during the Treatment Period are detailed in **Table 5** Section 5.3.1. Safety and tolerability will be assessed throughout the study per AASLD guidelines with additional assessments required by the protocol according to the Study Activities table (**Table 5**). Central laboratory testing will include chemistry, hematology, PT/INR, and samples for HCV RNA analysis as specified in **Table 8**.

All subjects will continue to return to the site on an outpatient basis as outlined in **Table 5**. Sites

should ensure that subjects adhere to all the study visits for central laboratory sample collection and drug dispensing/reconciliation. Subjects who cannot complete their study visit per the visit schedule should ensure that they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

Virologic stopping criteria will be evaluated and applied by the investigator as detailed in Section 5.4.1.1.

Subjects who prematurely discontinue from the Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined **Table 5** and as described in Section 5.3.1.

5.1.5 Post-Treatment Period

All subjects who received at least one dose of study drug will be monitored in the Post-Treatment Period for safety, HCV RNA, and the emergence and persistence of resistance-associated viral substitutions for an additional 12 weeks following the last dose of study drug.
All original clinic notes, telephone notes, locally available safety labs/evaluations and/or diagnostic tests or health screenings collected during the post HCV treatment period will be submitted for chart data abstraction to identify and abstract adverse events, vital signs, physical examinations, concomitant medications, HCV RNA, HCV resistance, and clinical laboratory tests that were collected as part of standard of care practice. Sites will also perform a verification of the medical records to review for new clinical interactions that may have occurred from end of treatment through 12 weeks post treatment which may coincide with applicable central laboratory collection visits. All applicable clinical records for adverse event and serious adverse event monitoring in the post treatment period will be submitted for chart data abstraction.

The Post-Treatment Period will begin the day following the last dose of study drug treatment. Study visits during the Post-Treatment Period are detailed in **Table 6** of Section 5.3.1.

Subjects who prematurely discontinue the Post-Treatment Period should return to the site for a Post-Treatment Discontinuation Visit as outlined in **Table 6** and will be followed for all post-treatment safety, HCV RNA, and resistance-associated substitutions according to the post treatment period schedule.

5.1.6 Retreatment Sub-study

Retreatment Sub-study Dosing and Post-Treatment Period

The Retreatment sub-study Dosing Period will begin the day the subjects receive the first dose of the retreatment regimen of G/P+SOF±RBV through the last dose of retreatment. The Post-Treatment Period will begin the day following the last dose of study drug treatment. Study visits during the Post-Treatment Period are detailed in **Table 6** of Section 5.3.1.

The visit schedules for safety and efficacy evaluations will be based on the Main Study pragmatic design procedures and Study Activities Tables (5 & 6) with exceptions as noted to screening procedures prior to re-treatment dosing.

Subjects who prematurely discontinue the Retreatment sub-study should return to the site for a Retreatment Discontinuation Visit as outlined in Table 6 and will be followed for all post-retreatment safety, HCV RNA, and resistance-associated substitutions according to the post treatment period schedule detailed in the Study Activities Tables (5 & 6).

5.2 Selection of Study Population

The study population consists of HCV GT1-infected adult male and female subjects including those with and without compensated cirrhosis who are prior treatment experienced with an NS5A inhibitor+SOF ± RBV.

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

1. Voluntary signed and dated written informed consent form in accordance with regulatory and institutional guidelines obtained before the performance of any protocol-related procedures not part of normal patient care.

2. Male or female, at least 18 years of age at time of screening.

3. Screening laboratory result indicating HCV GT 1 infection (applicable during Screening for Main Study only).

4. If cirrhotic, has compensated cirrhosis defined as Child-Pugh score of ≤ 6 at screening and no current or past clinical evidence of Child-Pugh B or C classification or clinical history of liver decompensation including ascites, bleeding varices or hepatic encephalopathy. In patients with history of liver transplantation, hepatic decompensation history for the determination of study eligibility will be limited to the period since the liver transplant.

5. Treatment experienced with NS5A inhibitor+SOF±RBV regimen and followed in PRIORITIZE or HCV-TARGET. NS5A inhibitor+SOF±RBV treatment -experienced subjects not observed in HCV-TARGET or PRIORITIZE can be included if the NS5A inhibitor+SOF±RBV regimen and treatment failure is well-characterized in the medical records supplied as source from the participating site. Subjects who are treatment experienced to LDV/SOF±RBV (Harvoni ®), VEL/SOF±RBV (Epclusa ®), or DCV/SOF±RBV will be included (applicable during screening for Main Study only).
   - The subject must not have discontinued the NS5A inhibitor+SOF±RBV treatment for known non-compliance
   - The NS5A inhibitor+SOF±RBV regimen must have been taken for at least 4 weeks
   - The subject's medical records must include sufficient detail of the NS5A inhibitor+SOF±RBV therapy treatment experience to confirm eligibility

6. If cirrhotic, absence of HCC as indicated by a negative ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) for HCC within 6 months prior to Screening or at Screening. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver for HCC will be eligible for the study.

7. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.

8. If female, the subject must be either postmenopausal, permanently surgically sterile, or for women of childbearing potential must be willing to use protocol specified method(s) of contraception (Appendix C) and have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 1 prior to dosing.
   If male, the subject must be surgically sterile, have a female partner who is postmenopausal or permanently sterile, or if sexually active with female partner(s) of childbearing potential, must be willing to use protocol specified method(s) of contraception (Appendix C).

9. HIV+ subjects must be on a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to Screening.
   The HIV-1 ART regimen must include at least one of the following ARV agents:
   - Raltegravir (RAL) PO BID
   - Dolutegravir (DTG) PO QD or PO BID
   - Rilpivirine (RPV) PO QD
   - Elvitegravir/cobicistat (EVG/COBI) PO QD

   In addition to the above medications, subjects may take a nucleoside/nucleotide reverse transcriptase inhibitor (N(t)RTI) backbone containing any of the following:
   - Tenofovir disoproxil fumarate (TDF) PO QD
   - Tenofovir alafenamide (TAF) PO Q

- Abacavir (ABC) PO QD or BID
- Emtricitabine (FTC) PO QD
- Lamivudine (3TC) PO QD or BID

Subjects receiving any other HIV-1 ART in addition to those noted above would not be eligible for enrollment in the study.

Subjects on a stable ART regimen must have the following:

- Two consecutive locally obtained CD4+ count ≥ 200 cells/mm3 (or CD4+ % ≥ 14%) closest to the date of the Screening visit; and
- Two consecutive locally obtained Plasma HIV-1 RNA < 50 copies/mL closest to the date of the Screening visit

10. For subjects participating in the Retreatment sub-study, must have failed treatment with G/P ±RBV in the Main study.

5.2.2 Exclusion Criteria

1. Female subject who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for 30 days after the last dose if randomized to G/P or 6 months after the last dose if randomized to RBV (or as directed per the local RBV label).

   Male subject whose partner is pregnant or planning to become pregnant during the study or for 30 days after the last dose if randomized to G/P or 7 months after the last dose of if randomized to RBV (or as directed per the local RBV label).

2. HCV genotype performed during screening indicating infection with any non-GT1 HCV genotype (applicable during screening for Main Study only).

3. Requirement for and inability to safely discontinue the medications or supplements listed in **Table 4** at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of any study drug.

4. Clinically significant abnormalities or co-morbidities, or recent (within 6 months prior to study drug administration) alcohol or drug abuse that make the subject an unsuitable candidate for this study in the opinion of the investigator.

5. Positive test result at Screening for hepatitis B co-infection (HBsAg positive or Hep B Core Ab -Total positive with detectable HBV DNA) or anti-human immunodeficiency virus antibody (HIV Ab) in a patient without known history of HIV+ and stable HART therapy (applicable during screening for Main Study only).

6. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - Total bilirubin ≥ 3.0 mg/dL.
   - Albumin < 2.8 g/dL.
   - Hemoglobin < 11 g/dL for women; < 12 g/dL for men, applicable only to subjects receiving RBV

7. Prior therapy with a HCV Protease Inhibitor at any time (applicable during screening for Main Study only).

8. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks (whichever is longer) to study drug administration.

9. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive G/P or, if cirrhotic, RBV (applicable to Main Study only, see exclusion #12 for considerations for Retreatment sub-study).

10. History of severe, life-threatening or other significant sensitivity to any excipients of the study drugs.

11. Subjects who cannot participate in study per local law.

12. For subjects participating in the Retreatment sub-study, consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive G/P plus SOF with or without RBV.

5.2.3 Guidance for Determination of Cirrhosis

All patients will be evaluated for the presence of cirrhosis and the final assessment will be made by the site PI or clinician designee. The presence of cirrhosis is defined at screening by biopsy and/or a combination of clinical, laboratory, elastography, and imaging criteria established *a priori*. For post-transplant recipients, cirrhosis determination will be made based on medical records post allograft.
Patients will be determined to have cirrhosis if they have:

1) evidence of stage 4 (Metavir) fibrosis by liver biopsy at any time prior to screening;

2) evidence of stage 3 (Metavir) fibrosis by liver biopsy at any time prior to screening with any ONE of the following criteria (for post-transplant recipients, biopsy staging must be from the allograft);
   - platelet count <140x 10^9/L,
   - presence of esophageal varices on esophagogastroduodenoscopy at any time prior to screening,
   - evidence of cirrhosis and/or portal hypertension by imaging studies at any time prior to screening,
   - FibroTest® >0.75,
   - Vibration-Controlled Transient Elastography (VCTE) >12.5 kPa, or equivalent magnetic resonance elastography (MRE) compatible with stage 4 fibrosis

3) in the absence of liver biopsy, any TWO of the following criteria:

- platelet count <140x 10^9/L during screening,
- presence of esophageal varices on esophagogastroduodenoscopy at any time prior to screening,
- evidence of cirrhosis and/or portal hypertension by imaging studies at any time prior to screening,
- FibroTest® >0.75,
- AST:platelet ratio index (APRI) >2 during screening
- Vibration-Controlled Transient Elastography (VCTE) >12.5 kPa, or equivalent MRE compatible with stage 4 fibrosis

If subjects do not meet any of the above definitions of cirrhosis, they will be considered non-cirrhotic.

5.2.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving from the time of signing the consent, through the Treatment Period, and 30 days after study drugs are stopped, must be recorded in the medical record along with the reason for use according to standard medical care. Where the reason for use of a concomitant medication or the start/stop date is missing from the submitted medical records, the site will be queried. For the Main study, the investigator/designee should review all concomitant medications for any potential interactions with G/P via the DDI tool and the MAVYRET™ Prescribing Information[23]. For the Retreatment sub-study, the investigator/designee should review all concomitant medications for any potential interactions with G/P via the DDI tool and the MAVYRET™ Prescribing Information[23], and also should review all concomitant medications for any potential interactions with sofosbuvir utilizing the Sovaldi™ Prescribing Information.[27]

During the Post-Treatment Period, all concomitant medications taken will be recorded in the

medical record until 30 days following the last dose of study drugs. Only medications taken for SAEs and for treatment of HCV will be recorded thereafter.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapies.

Subjects with HIV-1/HCV co-infection must be on a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to Screening. If on an HIV-1 ART regimen, it must include at least one of the ARV agents as per Inclusion Criterion 9 (Section 5.2.1).
Subjects will maintain the same dose and dosing interval of their HIV-1 ART regimen upon initiating the study drugs regimen. Subjects should remain on the same HIV-1 ART regimen for the entire Treatment Period. Any change in the HIV-1 ART regimen during the Treatment Period must be discussed with the medical monitor prior to the change, unless the change is being made to address an immediate safety concern.

Subjects receiving any other HIV-1 ART in addition to those listed in Inclusion Criterion 9 (Section 5.2.1) would not be eligible for enrollment in the study.

5.2.4.1 Prior HCV Therapy

Subjects must be HCV treatment-experienced with an NS5A-inhibitor+SOF with or without RBV. The subject may also have had an additional past treatment with any HCV regimen that did not include administration of a protease inhibitor.

For subjects who had multiple HCV treatment courses, the categorization of previous response category will be based on the NS5A inhibitor+SOF treatment.

5.2.4.2 Concomitant Therapy

Subjects should be on stable doses of concomitant medications for at least 2 weeks prior to the initiation of study drugs. The investigator should confirm that a concomitant medication/supplement can be safely administered with study drugs. Some concomitant medications may require dose adjustments due to the potential for drug-drug interactions.

During the Post-Treatment Period, investigators should reassess concomitant medications/supplements, and subjects may resume previously prohibited medications/supplements or revert to pre-study doses 2 weeks following discontinuation of study drugs as applicable.

5.2.4.3 Prohibited Therapy

Subjects must be able to safely discontinue any prohibited medications or supplements listed in **Table 4** at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of any study drug and not use these during the entire Treatment Period and for 2 weeks following discontinuation of study drugs.

Table 4. ***Prohibited Medications and Supplements***

Medication or Supplement Name
red yeast rice (monacolin K), St. John's Wort
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin*
Astemizole, cisapride, terfenadine
Ethinyl estradiol
Atazanavir, darunavir co-administered with ritonavir, darunavir/r, lopinavir/r, efavirenz, etravirine, tipranavir/r, nevirapine
Azathioprine-if subject is taking RBV
Amiodarone- Applicable to Retreatment sub-study subjects receiving sofosbuvir

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drugs. Subjects receiving these statins should either switch to pravastatin or rosuvastatin prior to the first dose of study drugs or may interrupt statin therapy throughout the treatment period and until 14 days after the last dose of study drug, based on investigator's judgment. If switching to or continuing pravastatin or rosuvastatin, it is recommended to reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drugs.

Use of high dose (0.035mg) ethinyl estradiol containing oral contraceptives with G/P combination was associated with asymptomatic ALT increases (one Grade 3, and one Grade 2) without concurrent bilirubin increases in 2 healthy female subjects. Therefore, hormonal contraceptives (including oral, topical [including vaginal rings], injectable or implantable varieties) containing any ethinyl estradiol may not be used from 2 weeks prior to the first dose of study drug until 2 weeks after the end of study drug dosing. Progestin-only contraceptives, such as those containing norethindrone, desogestrel, or levonorgestrel, without ethinyl estradiol, may be used with G/P.

Post-menopausal hormone replacement therapy, such as with esterified or conjugated estrogens, i.e., not containing ethinyl estradiol, may be used with G/P at the discretion of the Investigator.

For HCV/HIV-1 coinfected subjects, the investigator must refer to the current package insert(s) or product label(s) of a subject's ART regimen for a complete list of medications prohibited to be used with those drugs, which should not be used at least 2 weeks prior to the first dose of any study drug and not use these during the entire Treatment Period and for 30 days following discontinuation of study drugs. G/P is not recommended for use in patients requiring stable cyclosporine doses > 100 mg per day. G/P may be initiated in subjects receiving cyclosporine ≤ 100 mg per day and cyclosporine doses may be adjusted up to 400 mg per day following standard therapeutic monitoring practices.

5.3 Efficacy, Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described in this protocol are summarized in **Table 5** and **Table 6**

Table 5. Study Activities – Treatment Period for Main study and Retreatment sub-study

Subjects assigned to a 12-week treatment duration will not complete the Wk16 EOT visit. Any patient eligible to receive treatment in the Retreatment sub-study will be assessed as noted for screening and according to ALL on-treatment evaluations outlined in the activities table.

Activity	Screening	Day 1[a]	Wk 4	Wk 8	Wk 12 or EOT	Wk 16 EOT	Premature D/C[b]
STANDARD OF CARE and documented in Medical Record							
Demographics & Medical History (including history of hepatic decompensation and Prior HCV Therapy)	X						
Physical Exam & Child-Pugh Score	X	As available for abstraction per SOC in the submitted redacted medical records					
Vital Signs, Weight, Height[d]	X	As available for abstraction per SOC in the submitted redacted medical records					
Cirrhosis Determination (per Section 5.2.3)	X						
Concomitant Medication Assessment	X[n]	As available for abstraction per SOC in the submitted redacted medical records					
Adverse Event/Serious Adverse Event Assessment[e]	X[m]	As available for abstraction per SOC in the submitted redacted medical records					
HCC Screening documentation as applicable to subjects with cirrhosis (within 6 months of screening)[f]	X	Submit every 6 months imaging per AASLD standard of care guidelines for HCC screening					
For HIV co-infected subjects, CD4+ & HIV RNA results obtained locally (per Inclusion 9)	X[p]	As available for abstraction per SOC in the submitted redacted medical records					

Activity	Screening	Day 1[a]	Wk 4	Wk 8	Wk 12 or EOT	Wk 16[i] EOT	Premature D/C[b]
REQUIRED ASSESSMENT outside of Standard of Care							
Informed Consent[c]	X						
Verification of Eligibility/Randomization	X[j]						
Hematology/Chemistry/PT/INR[g]	X	X	X	X	X	X	X
Pregnancy Test (serum [s][g] urine [u][k]) for WOCBP only	X (s)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)
HCV Genotype and Subgenotype; HBV serologies[g]	X[o]						
HIV Ab[g,l]	X[o]						
FibroTest and APRI[g,h]	X[o]						
HCV RNA Samples[g]	X	X	X	X	X	X	X
HCV Resistance Sample[g]		X	X	X	X	X	X
Archive Plasma Sample[g]	X	X	X	X	X	X	X
Study Drugs Dispensed		X	X	X	X[i]		
Randomization Request submitted centrally at least 5 business days prior to planned Day 1	X[j]						
Perform Study Drug Accountability and Review of Study Drug Adherence			X	X	X	X	X
Authorization Request for Retreatment	X[j]						
Upload signed central lab reports evaluating clinical significance of abnormal results	X	X	X	X	X	X	X
Medical Records & Blood sample collection Verification Worksheet and Records Submission	X	X	X	X	X	X	X

Wk = Week; EOT = End of treatment; D/C = Discontinuation

a. All procedures to be performed prior to first dose

b. Subjects who prematurely discontinue the Treatment Period should return to the site to complete the Premature D/C Visit Procedures (preferably prior to the initiation of any

other anti-HCV therapy).

c. Subjects need to sign an IRB/IEC approved informed consent for the study prior to performing any screening or study-specific procedures. All re-treatment substudy subjects will be required to sign additional informed consent inclusive of re-treatment substudy information.

d. Height only collected at Main Study Screening

e. During the treatment period, all SAEs must be collected that occur during the screening period through discontinuation of study treatment and all non-serious AEs must be collected that occur from the time of study drug administration through 30 days after discontinuation of dosing. (see Section 6.1.4).

f. Subjects with a historical negative Liver Ultrasound, CT or MRI within 6 months prior to screening for main study and within 6 month prior to screening for the Retreatment sub-study are not required to have a screening Liver Ultrasound performed.

g. Collected for central laboratory processing.

h. Fibrotest/APRI will only be collected at the screening visit if the subject does not have a qualifying liver biopsy, Fibroscan, or MRE

i. Only applies if subject assigned to 16-week treatment arm (B or D), and subjects of the Retreatment sub-study

j. Main study: Site must submit documentation that the subject meets all eligibility criteria to the CCC at least business 5 days prior to their Day 1 visit. Randomization will be performed by the CCC. Retreatment sub-study: Prior to starting treatment, the site will upload subject redacted records to REDCap for verification of eligibility by the CCC. Prescription for Sofosbuvir +/- RBV must be included in upload.

k. If the urine pregnancy result is positive, site must confirm immediately with a serum test collected through the central laboratory

l. HIV Ab collected only in subjects without historical positive HIV antibody.

m. Non-serious Adverse Events will not be collected between Post-Treatment Week 12 of Main Study and first dose of Retreatment sub-study Dosing Period. Serious Adverse Events will not be collected between Post-Treatment Week 12 of the Main Study and date of informed consent for the Retreatment sub-study

n. Concomitant medications will not be collected between Post-Treatment Week 4 of Main Study through 14 days prior to Screening for Retreatment sub-study

o. Not required for Retreatment sub-study

p. As available for abstraction per SOC in the submitted redacted medical records.

Table 6. Study Activities – Post-Treatment (PT) Period for Main study and Retreatment sub-study

Activity	PT Wk 4	PT Wk 12
Physical Exam & Child-Pugh Score	As available for abstraction per SOC in the submitted redacted medical records	
Vital Signs, Weight	As available for abstraction per SOC in the submitted redacted medical records	
Concomitant Medication Assessment[a]	As available for abstraction per SOC in the submitted redacted medical records	
Adverse Event/Serious Adverse Event Assessment[b]	As available for abstraction per SOC in the submitted redacted medical records	
Hematology/Chemistry/PT/INR[c]	X	
HCV RNA Samples[c]	X	X
Pregnancy Test (urine [u]) for WOCBP only[e]	X (u)	X(u)[d]
HCV Resistance Sample[c]	X	X
Archive Plasma Sample[c]	X	X
Upload signed central lab reports evaluating clinical significance of abnormal results	X	X
Medical Records & Blood sample collection Verification Worksheet and Records Submission	X	X
For HIV co-infected subjects, CD4+ & HIV RNA results obtained locally	As available for abstraction per SOC in the submitted redacted medical records	

Wk = Week; PT D/C = Post-Treatment Discontinuation

a Only medications taken for SAEs and for treatment of HCV will be collected after 30 days post-dosing.

b Non-serious AEs will be collected until 30 days post dosing. All SAEs will be collected through PT WK 12. (see Section 6.1.4).

c Collected for central laboratory processing

d Required for WOCBP randomized to RBV arm only, or subjects of Re-treatment study who receive RBV as part of the retreatment regimen

e If the urine pregnancy result is positive, site must confirm immediately with a serum test collected through the central laboratory

Note: Day 1 of the Post-Treatment Period will be defined as the day after the last dose of study drug.

5.3.1.1 Study Procedures

Informed Consent

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. Subjects who failed treatment in the Main study and elect participation in the Retreatment sub-study require additional informed consent before any procedure of the Retreatment sub-study is performed.

Medical History, Physical Examinations, Vital Signs and Weight, Clinical Assessment of Hepatic Decompensation

All original clinic notes, telephone notes, locally available safety labs/evaluations and/or diagnostic tests or health screenings collected prior to, during and post HCV treatment period will be submitted for chart data abstraction to identify and abstract medical history, vital signs, weight (and height historically) and physical examinations that were collected as part of standard of care practice. The medical history listing, assessment for historical/current hepatic decompensation and Child Pugh score examination procedures will be updated at the standard of care visit where study informed consent is obtained. The site will submit medical records created as part of screening/informed consent, as well as medical records available in the site medical records system, for up to 24 months prior to the study screening. Older records to document key medical history and liver disease/HCV treatment history will also be submitted for centralized abstraction.

Child-Pugh Score and Category

The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments). Child-Pugh score will be determined at the visits indicated in **Table 5** and **Table 6**.

Table 7. Child-Pugh Score for Classification of Severity of Cirrhosis

	Points Assigned for Observed Findings		
Parameter	**1**	**2**	**3**
Total bilirubin, µmol/L (mg/dL)	< 34.2 (< 2)	34.2 – 51.3 (2 – 3)	> 51.3 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28 – 35 (2.8 – 3.5)	< 28 (< 2.8)
INR	< 1.7	1.7 – 2.3	> 2.3
Ascites*	None	Slight	Moderate to severe
Hepatic encephalopathy**	None	Grade 1 or 2 (or suppressed with medication)	Grade 3 or 4 or refractory

* None; Slight ascites = Ascites detectable only by ultrasound examination; Moderate ascites = Ascites manifested by moderate symmetrical distension of the abdomen; Severe ascites = Large or gross ascites with marked abdominal distension.

** Grade 0: normal consciousness, personality, neurological examination, electroencephalogram; Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves; Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves; Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves; Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

Clinical Laboratory Tests

A central laboratory will be utilized to process and provide results for the clinical laboratory tests. Samples will be obtained at a minimum for the central laboratory tests outlined in **Table 8** at the visits indicated in **Table 5** and **Table 6**.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study.

Table 8. Clinical Laboratory Tests

Hematology	Clinical Chemistry
White Blood Cell (WBC) count Red Blood Cell (RBC) count Hemoglobin Hematocrit Platelets Neutrophils Lymphocytes Monocytes Eosinophils Basophils Bands, if detected Prothrombin Time (PT) INR	Albumin Alkaline phosphatase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bilirubin, Direct Bilirubin, Indirect Bilirubin, Total Blood Urea Nitrogen (BUN) Calcium Carbon Dioxide Chloride Cholesterol Creatinine Glucose Phosphorus Potassium Sodium Total protein Uric Acid eGFR by MDRD
Other Tests	
Urine and Serum Human Chorionic Gonadotropin (hCG) for females (pregnancy) HCV RNA HCV genotype and subtype HBsAg, Hep B Core Ab-Total, Hep B Surface Ab reflex HBV DNA[a] HIV 1-2[b] APRI and Fibrotest	

[a] If HBsAg neg, Hep B Core AB-Total positive at Screening
[b] Only required for subjects without historical positive test result for HIV Ab

For any laboratory test value outside the reference range that the investigator considers to be clinically significant:

- The investigator will repeat the test through the central laboratory to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.
- A laboratory test value that requires a subject to be discontinued from the study, a dose modification of RBV, or requires a subject to receive treatment will be recorded as an adverse event.

The management of laboratory abnormalities that may occur during the study is described in Section 6.1.6

Contraception Recommendations and Pregnancy Testing

A serum pregnancy test will be performed for all female subjects of childbearing potential at Screening. Additional urine pregnancy tests will be performed at all the visits indicated in **Table 5** and **Table 6**. Pregnancy testing is not required for females of non-childbearing potential. Determination of postmenopausal status will be made during the Screening period, based on the subject's history.

Concomitant Medication Assessment

Excluding the medications and substances listed in Table 4, use of medications (prescription or over-the-counter, including vitamins, herbal supplements, and vaccines) from the time of signing the consent, through the Treatment Period, and 30 days after study drugs are stopped must be recorded in the medical record according to the local standard of care. Only medications taken for SAEs and for treatment of HCV will be abstracted from the submitted medical records 30 days after study drugs are stopped as indicated in **Table 6** (Post-Treatment Period). The concomitant medication listing will be updated in the standard of care medical record at the time of informed consent. All original clinic notes

and telephone notes collected prior to, during, and post HCV treatment period will be submitted for chart data abstraction to identify and abstract concomitant medication(s) that were prescribed as part of standard of care practice.

Hepatocellular Carcinoma Screening: Liver Ultrasound

In order to monitor for the presence of hepatocellular carcinoma (HCC), per standard of care AASLD guidelines, cirrhotic patients must have had an ultrasound, CT, or MRI to screen for hepatocellular carcinoma 6 months or less from screening and continued at 6 month intervals. A redacted copy of the imaging findings will be submitted for verification of study entry criteria and centralized abstraction.

Enrollment and Assignment of Subject Numbers

Screening numbers will be unique numbers and will be assigned sequentially at the site beginning with the first digits representing the investigative site, and the last digits representing the subjects at that site. Enrolled subjects will keep their screening number as their subject number throughout the Main study and the Retreatment sub-study (if applicable).

All screening activities must be completed and reviewed prior to enrollment. Prior to randomization, subject eligibility will be verified centrally. **Main Study:** At a minimum of 5 business days prior to the scheduled Study Day 1 visit, the site will submit subject redacted screening/historical medical records to be verified for meeting enrollment eligibility criteria. After being centrally verified as meeting the eligibility criteria, subjects will be randomized centrally via the study randomization system. Sites will receive the respective randomization and subjects will be administered study drugs at the site on Study Day 1, with dosing instructions. **Retreatment sub-study**: There is no randomization for subjects who enter the Retreatment sub-study. Prior to starting treatment, the site will upload subject redacted records to REDCap for verification of eligibility by the CCC.

Prescription for Sofosbuvir with or without RBV must be included in upload.

Study Drug Compliance for Kits

G/P and RBV will be provided for subject dosing to the site. Each subject will have compliance documented by the site in the subject's source records for G/P and/or RBV. In addition, compliance will be documented for SOF in the Retreatment sub-study. At each study drug accountability visit in **Table 5**, the overall number of tablets*** of G/P, RBV (as applicable), and SOF (as applicable) remaining will be recorded in the source along with the date of reconciliation and submitted centrally for abstraction.

HCV Genotype and Subtype

Plasma samples for HCV genotype and subtype determination will be collected at Screening. Genotype and subtype will be assessed using the Versant® HCV Genotype Inno LiPA Assay, Version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY). If the LiPA assay is unable to genotype a sample, its genotype will be determined by a Sanger sequencing assay of NS5B region.

HCV RNA Levels

Plasma samples for HCV RNA levels will be collected as indicated in **Table 5** and **Table 6**. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. The lower limit of detection (LLOD) and lower limit of quantification (LLOQ) for this assay (regardless of genotype) are both 15 IU/mL.

HCV Resistance Testing Sample

A plasma sample for HCV resistance testing will be collected prior to dosing on Day 1 and at the required lab collection visits indicated in **Table 5** and **Table 6** for each the Main study as well as the Retreatment sub-study. Specific instructions for preparation and storage of HCV RNA and HCV resistance samples will be provided by the central laboratory.

Archive Plasma Sample

Archive plasma samples will be collected at the study visits, indicated in **Table 5** and **Table 6** for the Main study as well as the Retreatment sub-study. Archive plasma samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, HCV RNA levels, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by AbbVie and the sponsor. Specific instructions for preparation and storage of archive samples will be provided by the central laboratory.

5.3.1.2 Meals and Dietary Requirements

Tablets*** of G/P and RBV should be taken with food. In the Retreatment sub-study, SOF should be taken daily at the same time as G/P.

5.3.1.3 Handling/Processing of Samples

Specific instructions for collection of blood samples and subsequent preparation will be provided by the central laboratory.

5.3.2 Efficacy Variables

Virologic response will be assessed by plasma HCV RNA levels in IU/mL at various time points from Day 1 through 12 weeks after completion of treatment in both the Main study and the Retreatment sub-study.

5.3.2.1 Primary Variable

The primary efficacy variable is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

5.3.2.2 Secondary Variable

The secondary efficacy variables are on-treatment virologic failure and post-treatment relapse.

5.3.3 Resistance Variables

For all subjects receiving G/P, the substitutions at resistance-associated amino acid positions in NS3 and NS5A at baseline identified by population sequencing or NGS and comparison to the appropriate prototypic reference sequence will be analysed, along with the impact of baseline substitutions on SVR12.

For subjects enrolled in the Retreatment sub-study, the substitutions at resistance-associated amino acid positions in NS3 and NS5A (and NS5B for those subjects enrolled in the Retreatment sub-study who experience virologic failure) at baseline will be identified by population sequencing or NGS, compared to the appropriate prototypic reference sequence, along with an analysis of impact of baseline substitutions on SVR12.

The following resistance information will be analyzed for subjects receiving G/P who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA ≥ 1000 IU/mL: 1) the amino acid substitutions in NS3 and NS5A in available post-baseline samples identified by population sequencing or NGS and comparison to the baseline sequence, 2) the amino acid

substitutions in NS3 and NS5A in available post-baseline samples at resistance-associated positions identified by population sequencing or NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral resistance by population sequencing or NGS.

For subjects enrolled in the Retreatment sub-study receiving G/P+SOF±RBV who experience virologic failure and who have a post-baseline sample with HCV RNA ≥ 1000 IU/mL the following resistance information will be analyzed: 1) the amino acid substitutions in NS3, NS5A, and NS5B in available post-baseline samples identified by population sequencing or NGS and comparison to the baseline sequence, 2) the amino acid substitutions in NS3, NS5A, and NS5B in available post-baseline samples at resistance-associated positions identified by population sequencing or NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral resistance by population sequencing or NGS.

5.3.4 Safety Variables

The following safety evaluations will be performed during the Main study and the Retreatment sub-study: adverse events, vital signs & physical examination (abstracted from submitted clinical records) and laboratory tests assessments from the central laboratory.

5.4 Removal of Subjects from Therapy or Treatment Duration Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the Main study or Re-treatment substudy at any time. In addition, the investigator may discontinue a subject from the Main study or Re-treatment substudy at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.

If, during the course of study drug administration, the subject prematurely discontinues, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in **Table 5** and **Table 6**. Ideally this should occur on the day of study drug discontinuation, but no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV 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. 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 will be recorded in the medical record and submitted for centralized abstraction. The subject should then begin the Post-Treatment Period where the subject will be monitored for 12 weeks for HCV RNA and the emergence and persistence of resistant viral variants.

If a subject is discontinued from study drugs or the Post-Treatment Period with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

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 G/P in Main study as well as G/P and/or Sofosbuvir in the Retreatment sub-study to that subject may be continued at the Principal Investigator's discretion after discussion with the subject, if the benefit of continuing prescribed regimen is felt to outweigh the potential risk. The administration of RBV (if applicable) to that subject must be discontinued immediately. Specific instructions regarding subject pregnancy can be found in Section 6.1.6. If a subject is discontinued, the Subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

5.4.1.1 Virologic Stopping Criteria

Individual Patient

Virologic stopping criteria are defined as one of the following:

1. Confirmed HCV RNA ≥ 100 IU/mL (defined as 2 consecutive HCV RNA measurements ≥ 100 IU/mL) after HCV RNA < LLOQ during treatment.

2. Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment,

When confirmatory testing is required it should be completed as soon as possible and the subject should remain on study treatment until the virologic stopping criteria has been confirmed. Subjects meeting virologic stopping criteria will be discontinued from study drug and will continue to be followed in the Post-Treatment Period for the emergence and persistence of resistant viral variants until 12 weeks post-treatment.

Treatment Arm Efficacy Adjustment Criteria

Based on interim virologic data, the following adjustments will be made to individual treatment arms within the Main Study. Treatment Arm Efficacy Adjustment Criteria do not apply to the Retreatment sub-study:

1. If more than 2 subjects have confirmed on-treatment virologic failure among the first 20 non-cirrhotic subjects with available HCV viral load data across Arms A and B, the virologic failures will be examined to determine if all new enrollment into the arms should stop and if weight-based twice daily RBV (1000 mg <75 kg or 1200 mg ≥75 kg body weight total daily dose) should be added to the regimen for all future and current subjects in Arm A and Arm B, or a subset of subjects in Arms A and B. Similar analyses will continue every two weeks until all subjects in Arms A and B reach the end of treatment.
2. If more than 2 subjects have confirmed post-treatment relapse in the Post-Treatment

period among the first 20 subjects in Arm A with available post treatment HCV viral load data, the virologic failures will be examined to determine if treatment should be extended to 16 weeks for all future and current subjects in Arm A or for a subset of subjects in Arm A. Similar analyses will continue every two weeks until all subjects in Arm A reach the end of treatment.

3. If more than 2 subjects have confirmed post-treatment relapse among the first 20 subjects in Arm C with available post treatment HCV viral load data, the virologic failures will be examined to determine if treatment should be extended to 16 weeks for all future and current subjects ongoing in Arm C or for a subset of subjects in Arm C. Similar analyses will continue every two weeks until all subjects in Arm C reach the end of treatment.
4. If more than 2 subjects have confirmed on-treatment virologic failure among the first 20 subjects across Arms A, B and D, the virologic failures will be examined to determine if weight-based twice daily RBV (1000 mg <75 kg or 1200 mg ≥75 kg body weight total daily dose) should be added for all current and future patients in Arm D or a subset of subjects in Arm D. Similar analyses will continue every two weeks until all subjects in Arms A, B and D reach the end of treatment.

Treatment failures due to non-compliance with study drugs, stopping or holding of study drugs due to adverse events, or other reasons for study drug interruptions will not count towards virologic failures.

5.4.2 Discontinuation of Entire Study

The sponsor, in agreement with AbbVie, may terminate this study prematurely, either in its entirety or the sponsor may terminate this study at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to the sponsor in advance of the intended termination.

Advance notice is not required by either party if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Each dose of G/P study drug will be dispensed in the form of co-formulated G/P tablets at the visits listed in **Table 9**. Subjects will be instructed to take study drugs at approximately the same time every day with food.

G/P will be provided to the investigator as G/P 100 mg/40 mg tablets. G/P will be taken orally as three tablets once daily with food, which corresponds to G/P 300 mg/120 mg QD. The maximal dose of G/P is 300mg/120mg for 16 weeks. There is no dose adjustment of G/P for any reason in this study.

RBV will be provided to the investigator as 200 mg tablets***. RBV is dosed based on weight as 1000 or 1200 mg divided twice daily per local label. For subjects <75 kg, RBV may be taken orally as 2 tablets*** in the morning and 3 tablets*** in the evening or 3 tablets*** in the morning and 2 tablets*** in the evening which corresponds to a 1000 mg total daily dose. For subjects weighing ≥75 kg, RBV will be taken orally as 3 tablets*** in the morning and 3 tablets in the evening which corresponds to a 1200 mg total daily dose. RBV should be taken with food. The maximal daily dose of RBV in this study is not to exceed 1200 mg for 16 weeks. Based on tolerability, renal function, and hemoglobin level, RBV daily dose may be reduced, held, or permanently discontinued at the investigator's discretion and in accordance with local RBV prescribing information/product label.

All subjects who receive at least one dose of study drug and meet the virologic stopping

criteria defined in Section 5.4.1.1 will be discontinued from treatment.

*** In the Retreatment sub-study, RBV dosage form will be determined by dispensing pharmacy.

5.5.1.1 Retreatments Administered

The re-treatment study drug regimen of G/P plus SOF ±RBV will be dispensed to Retreatment sub-study subjects at the subject's study site and following study drug dispensation schedule of Table 5. Retreatment regimen is given for 16 weeks. There is no dose adjustment of SOF or G/P for any reason in the Retreatment sub-study.

5.5.2 Identity of Investigational Products

Information about the study drugs to be used in this study is presented in **Table 9**.

Table 9. Identity of Investigational Products

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Tablets/ Capsule***/ bottle
Glecaprevir/ Pibrentasvir*	AbbVie	Oral	Tablet	100 mg/40 mg	30
Ribasphere®* Ribavirin**	As available in dispensing pharmacy	Oral	Tablet/ Capsule***	200 mg	168***
Sovaldi® Sofosbuvir**	Gilead Sciences, Inc.	Oral	Tablet	400 mg	28

Main Study
***G/P and Ribasphere® dispensed by AbbVie Inc., North Chicago, IL**
Retreatment sub-study
***G/P dispensed by AbbVie Inc., North Chicago, IL**
****Ribavirin and Sofosbuvir to be dispensed by BioPlus Specialty Pharmacy, Altamonte Springs, FL**
***** RBV dosage form as available in dispensing pharmacy**

5.5.3 Packaging and Labelling

All study drug will be supplied in bottles.

Each bottle will be labelled as required per country requirements.

The labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to subject.

5.5.3.1 Storage and Disposition of Study Drugs

Study Drug	Storage Conditions
Glecaprevir/Pibrentasvir 100 mg/40 mg	15° to 25°C (59° to 77°F)
Ribasphere® Ribavirin 200 mg (Main Study)	15° to 25°C (59° to 77°F)
Ribavirin 200 mg (Retreatment sub-study)	****
Sovaldi® Sofosbuvir 400 mg	Room Temperature to below 30°C (86°F)

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use, destroyed on-site, or returned to AbbVie (or designee).

**** RBV Storage conditions during the Retreatment sub-study to be provided via FDA-approved Prescribing Information.

5.5.4 Method of Assigning Subjects to Treatment Groups-

At the Screening Visit, all subjects will be assigned a unique subject number assigned sequentially by the study site. Enrolled subjects will keep their screening number as their subject number throughout the Main study and the Retreatment sub-study (if applicable).

For subjects who do not meet the study selection criteria, the site personnel will identify

the subject as a screen failure by submitting applicable medical records to the central abstraction team documenting the screen failure. Submitted data and reason for screen failure will be abstracted centrally.

For enrollment of eligible subjects into the study, subject eligibility will be verified centrally by the CCC. At a minimum of 5 business days prior to the scheduled Study Day 1 visit, the site will submit the subject's redacted screening/historical medical records to be verified for meeting enrollment eligibility criteria. After being centrally verified as meeting the eligibility criteria, subjects will be randomized centrally via the study randomization system (applicable to Main study only). After verification of subject meeting eligibility criteria, study drug will be shipped as a bulk supply from AbbVie and BioPlus Specialty Pharmacy Services, Inc. (Re-treatment sub-study only) to study site to dispense to eligible study subjects.

Sites will receive the respective randomization and subjects will be administered study drugs at the site on Study Day 1, with dosing instructions.

5.5.5 Selection and Timing of Dose for Each Subject

G/P is a fixed-dose combination tablet of 100 mg glecaprevir and 40 mg Pibrentasvir. The dose used for all subjects in this study is 300 mg/120 mg G/P, given together once daily with food. The maximum dose of G/P will not exceed 300 mg/120 mg per day for 16 weeks in the Main study and also in the Retreatment sub-study, if applicable.
For the Retreatment sub-study, SOF is provided as 400 mg tables and should be taken simultaneously with G/P.

Ribavirin (RBV) (if applicable) is provided as 200 mg tablets*** and should be dosed BID, e.g., with 2 to 3 tablets*** taken in the morning, and 2 to 3 tablets*** taken in the evening based on body weight and must also be taken with food. For subjects with body

weight less than 75kg RBV is dosed at 1000 mg per day (e.g., 400 mg in AM and 600 mg in PM, or 600 mg in AM and 400 mg in PM). For subjects with body weight equal or greater than 75kg, RBV is dosed at 1200 mg per day (e.g., 600 mg in AM and 600 mg in PM). The maximal dose of RBV will not exceed 1200 mg per day for 16 weeks.

***** RBV dosage form to be determined by dispensing pharmacy**.

Study drug dosing will be initiated at the Day 1 Visit in the Main study and the Retreatment sub-study if applicable. Study drug initiation does not need to be witnessed at the Day 1 visit. Based on Treatment Arm Efficacy Adjustment criteria in Section 5.4.1.1, if virologic futility criteria are met, RBV dosing may be added to already ongoing or new initiation of G/P dosing in Arms A, B, or D.

5.5.6 Blinding

Both the Main study and Retreatment sub-study will be open-label.

5.5.7 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/ dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

At the start of the study, each subject should receive counselling regarding the importance of dosing compliance with the treatment regimen with regard to virologic response and potential development of resistance due to poor compliance.

At each study drug dispensing visit during the Treatment Period denoted in **Table 5**, subjects will be instructed to bring all study drug (full, partial or empty) for assessment of treatment compliance. Subjects will be instructed to dose from each bottle of study medication until the bottle is empty. At post-baseline dispensing visits denoted in **Table**

6, study site personnel will assess subject compliance by inspecting the contents of the bottles and record the status of each one, as well as the exact number of remaining tablets*** of G/P and/or RBV in the source. Treatment compliance will be based on the number of tablets*** dispensed, as recorded in source and the number of remaining tablets***.
***RBV Dosage form to be determined by dispensing pharmacy.

Dosing compliance will also be assessed for patients receiving treatment in the Retreatment sub-study. In addition to G/P and RBV, accounting of SOF dosing will be completed and recorded in the study source.

5.5.8 Drug Accountability & Destruction

The investigator/designee will verify that study drug supplies are received intact and in the correct amounts. A current (running) and accurate inventory of study drug will be kept by the investigator/designee and will include lot number, kit number, number of tablets*** dispensed, subject number, initials of person who dispensed study drug and date dispensed for each subject. An overall accountability of the study drug will be performed and verified by the study monitor. Final accountability will be verified by the monitor at the site or via an alternate approved method.

Study drug start dates for each drug and the last dose of the regimen will be documented in the subject's source documents.

Upon completion of or discontinuation from the Treatment Period, all original study drug bottles (containing unused study drugs) will be destroyed at the study site or returned to AbbVie (or its designee). All unused study drugs can only be destroyed after being inspected and reconciled by the Study Monitor. The number of tablets*** of each type of study drug returned will be noted in a drug accountability log.

On-site destruction is preferred, provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to HCV-TARGET.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met, the responsible monitor will make arrangements for return of all unused and/or partially used study drug to AbbVie (or its designee).

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. Empty containers can only be destroyed on-site or returned to AbbVie (or its designee) after being inspected and reconciled by the monitor at the site or via an alternate approved method.
***RBV Dosage Forms to be determined by dispensing pharmacy.

5.5.8.1 Risk of Development of Resistance-Associated Substitutions During Combination DAA Trials

In subjects treated with a DAA, variants with amino acid substitution(s) in the targeted protein conferring resistance to the DAA can be selected. For example, in AbbVie HCV Phase 3 studies in which patients with GT1 infection were treated with the NS3/4A protease inhibitor paritaprevir and NS5A inhibitor ombitasvir, variants that conferred resistance to paritaprevir or ombitasvir were detected in patients experiencing virologic failure. While data from patients treated with the combination of G/P are limited, it is expected that PIB, will be able to suppress the appearance of virus containing resistance-associated variants in NS3 that confer resistance to GLE, because there should not be any cross-resistance in variants resistant to DAAs targeting different proteins. The converse is expected to be true as well – GLE should be able to suppress the appearance of virus containing NS5A substitutions conferring resistance to PIB. In addition, in vitro resistant colony selection studies in HCV replicon cells containing GT1 – 6 NS5A demonstrated that PIB had a high genetic barrier to resistance – very few colonies were selected, and those that were selected contained NS5A substitutions that conferred only modest levels of resistance to PIB. Based on accumulated clinical and in vitro data to date, the risk of development of resistant variants to G/P is reduced when compared to treatment with first generation protease and NS5A inhibitors. Among the 2258 TN and TE-PRS subjects infected with GT1-6 treated with GLE/PIB 300/120 mg included in the integrated resistance analysis from the Phase 2 and Phase 3 studies, only 22 (0.97%) experienced virologic failure. Among these 22 subjects, treatment-emergent substitutions were detected in NS3 in 54.5% (12/22) and in NS5A in 81.8% (18/22). Subjects frequently had multiple substitutions in NS5A at the time of failure indicating that, in contrast to first generation NS5A inhibitors, single substitutions in NS5A do not confer sufficient resistance to allow the virus to overcome PIB drug pressure. These results support the prediction that the risk of development of resistance-associated variants with GLE and PIB combination treatment is low.

For subjects enrolled in the Retreatment sub-study, exposure to SOF is not expected to result in development of resistant viral variants, due to the high resistance barrier for SOF. In clinical studies with LDV/SOF and SOF/VEL, only a small proportion of patients who experienced virologic failure had RASs that conferred resistance to SOF at

the time of virologic failure. In analyses of post-treatment resistance from patients in phase II/III clinical trials with LDV/SOF[25] or SOF/VEL[26], among 51/2144 (2.4%) and 20/1778 (1.1%) patients who experienced virologic failure, respectively, only 1 patient harboured virus that contained a RAS that conferred resistance to SOF at the time of virologic failure.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Section 6.1. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study in accordance with standard medical practice and the AASLD HCV treatment guidelines. The adverse events and actions taken (concomitant therapy, etc.) identified centrally in the submitted medical records generated as part of clinical care will be abstracted into the study database. The HCV-TARGET Abstraction Conventions manual will be used to assign adverse event start dates for any event abstracted from the medical record without a specific start date noted.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore

be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the treatment regimen.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to the sponsor as a SAE within 24 hours of the site being made aware of the serious adverse event:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive

treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Sites will use the SAE reporting template provided by the sponsor to report all SAEs. If an SAE is observed in the submitted clinical records during data abstraction that was not previously reported by the site, the site will be queried for the report and supporting records. The query must be responded to within 24 hrs of receipt of the query.

Minimum supporting records required for all SAE reports:

1. Admit and Discharge note
2. Daily consult with VS/PE
3. All labs
4. Imaging/procedure reports
5. Medication Administration Record (MAR)

For serious adverse events with the outcome of death, the date and cause of death (if known) will be recorded on the appropriate case report form. The site will make all reasonable efforts to obtain a death or autopsy certificate, if available.

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

6.1.2 Adverse Event Severity

For the purposes of this study, adverse events will be defined and coded centrally based on the following definitions:

1. **MILD:** Adverse events and/or symptoms recorded in the medical record where no therapy was given to treat the event or where an over-the-counter medication/intervention ONLY was given to treat the event.

2. **MODERATE**: Adverse events and/or symptoms recorded in the medical record requiring prescription medication treatment or any dose reduction in study drug ribavirin.

3. **SEVERE:** Adverse events and/or symptoms requiring any study drug discontinuation will be defined and coded as severe. ANEMIA events requiring blood transfusion will be coded as severe.

6.1.3 Relationship to Study Drug

Assessment of relatedness will be made with respect to both G/P and/or RBV in the Main study and both G/P + SOF and/or RBV in the Retreatment sub-study. The investigator/clinician designee will use the following definitions to assess the relationship of the adverse event to the use of study drug(s):

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In

addition, when the investigator has not reported a causality or deemed it not assessable, the sponsor will consider the event associated.

For serious adverse events, if an investigator's opinion of relatedness is "no reasonable possibility of being related to study drug" an "Other" cause of event must be provided by the investigator/clinician designee.

After adverse event data is abstracted from the submitted records, the site investigator/ clinician designee will be provided an adverse event listing to assess relationship of the adverse event to study drug(s). Site will be queried to provide adverse event stop dates/continuation for any adverse events for which no end date is evident in the submitted medical records during the Treatment Period and up to 30 days post treatment.

6.1.4 Adverse Event Collection Period

From the time of study drug administration until 30 days following discontinuation of study treatment has elapsed, all non-serious adverse events will be collected as part of standard clinical care in accordance with the AASLD HCV treatment guidelines and abstracted from the submitted clinical records. After 30 days following completion of study treatment and throughout the Post-Treatment Period, only spontaneously reported SAEs will be collected (non-serious AEs will not be collected).

Following the subject's written consent to participate in the Main study and the Retreatment sub-study (as applicable), all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and through the final study visit.

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be submitted within 24 hours using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.1.5 Serious Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator/designee will notify the Medical Monitor within 24 hours of the site being made aware of the serious adverse event by submitting the available serious adverse event data to:

HCV-TARGET REPORTING CONTACT INFORMATION

Email to (preferred method): [redacted]

FAX to: [redacted]

For safety concerns, contact the physician listed below:

Primary HCV-TARGET Designated Physician: [redacted] MD

Office: [redacted]

Email: [redacted]

The HCV-TARGET designated Physician must also report any serious adverse event to AbbVie within 24 hours after receipt of the serious adverse event information from the study site.

6.1.6 Pregnancy

Female subjects randomized or assigned to non-RBV containing regimen in Main study or Retreatment sub-study should avoid pregnancy starting with screening and through 30 days after completion of study drug. Female subjects randomized or assigned to RBV containing regimen in Main study or Retreatment sub-study should avoid pregnancy starting with Screening and through 6 months after completion of study drug (or as per

local RBV label). Male subjects randomized to G/P in Main study or receiving G/P plus SOF in Retreatment sub-study and their partners should avoid pregnancy starting with screening and through 30 days after completion of study drug. Male subjects randomized or assigned to RBV containing regimen in Main study or Retreatment sub-study and their partners should avoid pregnancy starting with Screening and through 7 months after completion of study drug (or as per local RBV label).

Pregnancy in a study subject must be reported to the sponsor within 1 working day of the site becoming aware of the pregnancy and should be reported to the Ribavirin Pregnancy Registry, as applicable. Administration of G/P in Main study or G/P plus SOF in Retreatment sub-study may be continued at the investigator's discretion after discussion with the subject, if the benefit of continuing therapy is felt to outweigh the risk (Section 5.4.1). If a subject is discontinued, the subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected for pregnancies occurring up to 30 days after the end of treatment for subjects receiving a non-RBV containing regimen or up to 6 months (female subjects) or 7 months (male subjects) after the end of treatment for subjects receiving a RBV containing regimen.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to the sponsor within 24 hours of the site becoming aware of the event.

6.1.7 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the Main study or Retreatment sub-study must be evaluated by the

investigator/clinician designee. All adverse events and laboratory abnormalities will be managed and followed to a satisfactory clinical resolution.

To facilitate this process in a pragmatic study, after adverse event data is abstracted from the submitted records, the site investigator/clinician designee will be provided an adverse event listing to assess relationship of the adverse event to study drug(s). The site will also upload signed central lab reports where the investigator/clinician designee completed the evaluation of clinical significance of abnormal results. Actions taken for clinically significant abnormal laboratory results and/or adverse events will be recorded in the site medical record or source and uploaded for centralized abstraction.

6.2. Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the study drug product(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labelling, labelling discrepancies/inadequacies in the labelling/instructions (example: printing illegible), missing components/product, or packaging issues. Any product complaints identified centrally in the submitted medical records will be abstracted into the study database.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the sponsor within 24 hours of the time it is observed or the data is abstracted centrally from the submitted medical records via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion via specific

query to the site for any available clinical information. All follow-up information is to be reported to the sponsor and documented in the source medical record. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator/site to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the Independent Ethics Committee (IEC)/Independent Review Board (IRB) and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following personnel:

If by e-mail: [redacted]
If by phone: [redacted] [redacted] (alternate contact)
Office: [redacted] Office: [redacted]

Such contact must be made as soon as possible to permit a review by the sponsor to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The primary analysis will occur after all subjects in the Main Study have completed the PT Week 12 Visit or prematurely discontinued study. The data for subjects treated in the Main study will be locked after data cleaning. Data from the Retreatment sub-study will be analyzed separately as described below and be included in the end-of study analysis.

The data analysis will be generated using SAS/STAT software, version 9.4 or higher of the SAS system for Windows. Copyright © [2001-2012] SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. All statistical tests (if applicable) and confidence intervals will be two-sided with an alpha level of 0.05. Descriptive statistics will be provided, such as the number of observations (N), mean, and standard deviation (SD) for continuous variables and counts and percentages for discrete variables.

The primary efficacy analyses in the Main study will be performed on the intention to treat population summarized according to the treatment arm in which the subject actually received treatment. This primary efficacy analysis dataset will be referred to as the modified ITT (mITT) population and defined as all enrolled subjects who receive at least one dose of study drug according to each subject's final treatment arm assignment (Arm A, Arm B, Arm C or Arm D). Analyses in the Retreatment sub-study will be performed overall on the Evaluable Patient population for that sub-study (EP-RS) defined as all subjects who receive at least one dose of study drug in the Retreatment sub-study.

The traditional ITT population, which includes all subjects who received at least one dose of study drug categorized by the patients' randomized treatment arm, along with other modified ITT populations will be employed in the sensitivity analyses. Specifically, sensitivity analyses of the primary endpoint of the Main Study will be performed on the following modified ITT populations:

1) Modified ITT-Genotype (mITT-GT) Population
-includes the mITT population (or "as treated") but excludes subjects with genotype other than GT1 infection.

2) Modified ITT- Genotype and Virologic Failure (mITT- GT-VF) Population

- includes the mITT-GT population but excludes subjects who did not achieve SVR12 for reasons other than virologic failure (mITT-GT-VF), when applicable.

Similarly, for the Retreatment sub-study, sensitivity analyses of the SVR_{12} endpoint will be performed on the EP-RS population modified to exclude subjects other than GT1 (EP-RS-GT) and further modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (EP-RS-GT-VF).
No data will be imputed for any efficacy or safety analysis except for analyses of SVR endpoints (HCV RNA data). HCV RNA values will be selected for the analyses of all SVR endpoints (e.g., SVR_4 and SVR_{12}) based on defined visit windows. A backward imputation method will be used to impute missing responses for SVR analyses.
Additional details of analyses to be performed are specified in the Statistical Analysis Plan.

8.1.1 Demographics

Demographics and baseline characteristics will be summarized for all treated subjects by treatment arm for the Main Study and separately on the overall EP-RS population. Demographics include age, weight, height, BMI, gender, race, and ethnicity. Baseline characteristics will be summarized as continuous variables (where appropriate) and as categorical variables, including HCV genotype subtype, most recent HCV treatment history, baseline HCV RNA level, and fibrosis stage.

Summary statistics (N, mean, median, SD, and range) will be generated by treatment arm for continuous variables (e.g., age and BMI), and the number and percentage of subjects will be presented for categorical variables (e.g., sex and race).

Study drug exposure and compliance will be summarized by treatment arm and separately on the overall EP-RS population. Treatment compliance to study drug will be calculated based on the percentage of tablets*** taken relative to the total tablets*** expected to be taken for each tablet*** type G/P, RBV, SOF tablets as applicable. A subject is considered to be compliant if the percentage is between 80% and 120% for each tablet type. Compliance will be calculated for each subject and summarized with the mean, median, standard deviation, minimum, and maximum. The percentage of compliant subjects will be summarized.

***RBV Dosage Form to be determined by dispensing pharmacy.

8.1.2 Efficacy

All efficacy analyses will be performed on the mITT and EP-RS populations, unless otherwise specified. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. The notation "HCV RNA < LLOQ" is used to represent all HCV RNA values < 15 IU/mL that are HCV RNA detected or HCV RNA not detected. HCV RNA ≥ LLOQ are all quantifiable values.

8.1.2.1 Primary Efficacy Endpoints

The primary efficacy endpoints for the mITT population are the difference in SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) rates between Arm A and Arm B in non-cirrhotic subjects, and difference in SVR_{12} rates between Arm C and Arm D in cirrhotic subjects.

The difference in SVR_{12} rates will be summarized with a two-sided 95% confidence interval for the comparison between Arm A and Arm B in non-cirrhotic subjects, and for the comparison between Arm C and Arm D in cirrhotic subjects. The number and percentage of subject achieving SVR_{12} by treatment arm will also be summarized with a two-sided 95% confidence interval. The confidence interval for the difference in SVR_{12}

rates will be calculated using Wilson's score method. The confidence interval for the SVR_{12} rates by treatment arm will be calculated using the normal approximation to the binomial distribution if the number of subjects who failed to achieve SVR_{12} is at least 5. If the number of subjects who failed to achieve SVR_{12} is less than 5, Wilson's score method will be used instead.

A summary of reasons for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse, other) will be provided.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for the mITT population in the Main Study are:

- the difference in SVR12 rates between G/P given for 12 weeks (Arm A and C combined) and G/P given for 16 weeks (Arm B and D combined);
- the difference in the percentage of subjects with on-treatment virologic failure (confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment) between Arm A and Arm B in non-cirrhotic subjects, and between Arm C and Arm D in cirrhotic subjects;
- the difference in the percentage of subjects with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment, excluding subjects with reinfection) between Arm A and Arm B in non-cirrhotic subjects, and between Arm C and Arm D in cirrhotic subjects.

For the analysis of relapse, completion of treatment is defined as any subject with study drug duration of 77 days or greater for 12-week arms (Arms A and C), or 105 days or greater for 16-week arm (Arm B and D).

The difference in SVR12 rates between 12 week (Arms A+ C) and 16 week (Arms B+D)

treatment durations will be summarized calculated along with a two-sided 95% confidence interval using Wilson's score method. The difference in the percentage of subjects with on-treatment virologic failure and post-treatment relapse will be summarized with two-sided 95% Wilson score intervals, as will the percentage of subjects with on-treatment virologic failure and post-treatment relapse in each treatment arm.

8.1.2.3 Sensitivity Analysis

As sensitivity analyses, the difference in the percentage of subjects in the mITT-GT and mITT-GT-VF populations achieving SVR_{12} between Arm A and Arm B in non-cirrhotic subjects, and between Arm C and Arm D in cirrhotic subjects, as applicable, will be summarized. The SVR_{12} rates in the EP-RS-GT and EP-RS-GT-VF populations overall will be calculated.

8.1.2.4 Subgroup Analysis

In the mITT population for the Main study, association of the proportions of subjects with SVR12 with each of the following subgroups will be compared across treatment arms (Arms A and B, and Arm C and D separately) using Zelen's exact tests. In addition, two-sided 95% Wilson score intervals will be calculated for the difference between Arms A and B and Arms C and D, for the following subgroups:

- HCV GT1 subtype;
- Most recent HCV treatment history;
- All prior HCV treatment history;
- Type of non-response to NS5A-inhibitor+SOF± RBV treatment;
- Sex;
- Age;
- Race;
- Ethnicity;
- BMI;
- Baseline HCV RNA level;

- Baseline platelet count;
- Baseline albumin;
- Baseline APRI;
- Baseline FIB-4;
- Baseline AST/ALT ratio;
- Baseline Child-Pugh Score (for cirrhotic subjects only);
- History of concomitant diseases: (a) diabetes, (b) HIV coinfection (c) post-organ transplant;
- Concomitant use of Proton Pump inhibitors
- DAA compliance.
- Baseline resistance polymorphisms (any NS3/4A variant [yes/no]; any NS5A variant [yes/no]; any NS3/4A and any NS5A [yes/no], any NS3/4A or any NS5A [yes/no]) and [NS3/4A only, NS5A only, both NS3/4A and NS5A, or none]).

The difference in SVR12 rates between G/P given for 12 weeks (Arm A and C combined) and G/P given for 16 weeks (Arm B and D combined) will also be examined within the combined arms by HCV sub-genotype (1b vs. non-1b).

Further details about subgroup analyses will be described in the Statistical Analysis Plan.

8.1.2.5 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized for each treatment arm in the mITT population and overall in the EP-RS population, as specified below:

- The percentage of mITT subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of mITT subjects with SVR_4;
- The percentage of EP-RS subjects achieving SVR_{12}.
- The percentage of EP-RS subjects with on-treatment virologic failure and with post-treatment relapse.

In the above analyses for SVR, the percentage of subjects and a two-sided 95% Wilson score interval will be summarized. A summary of reasons for SVR non-response will also be provided for subjects in the EP-RS populations who do not achieve SVR12.

8.1.3 Resistance Analyses

The following analyses will be performed for all subjects in the mITT population and the EP-RS populations separately. In the EP-RS population, baseline polymorphisms in NS3 and NS5A will be reassessed prior to treatment with G/P + SOF ± RBV.

The HCV NS3 and NS5A amino acid sequences from baseline samples as determined by population sequencing or NGS will be compared to the appropriate prototypic reference sequence. A listing by subject of all baseline polymorphisms relative to prototypic reference sequence at signature amino acid positions will be provided for each DAA target (NS3 and NS5A).

The following analyses will be performed for subjects who do not achieve SVR_{12} and who have post-baseline resistance data available:

(1) The HCV NS3 and NS5A amino acid sequences from the sample closest in time after virologic failure or treatment discontinuation with an HCV RNA level of ≥ 1000 IU/mL as determined by population sequencing or NGS will be compared to the baseline sequence. A listing by subject of all post-baseline substitutions at signature amino acid positions relative to the baseline amino acid sequence will be provided for each DAA target (NS3 and NS5A).

(2) The HCV NS3 and NS5A amino acid sequences from the sample closest in time after virologic failure or treatment discontinuation with an HCV RNA level of ≥ 1000 IU/mL will be compared to the appropriate prototypic reference sequence. A listing by subject of

all post-baseline substitutions at signature amino acid positions relative to the appropriate prototypic reference amino acid sequence will be provided for each DAA target (NS3 and NS5A).
(3) The persistence of post-baseline substitutions at signature amino acid positions for each target (NS3 and NS5A) will be assessed by population sequencing or NGS at Post-Treatment Week 12. A listing by subject and time point of all substitutions relative to the baseline amino acid sequence will be provided for each DAA target (NS3 and NS5A).

For subjects who experience virologic failure in the Retreatment sub-study, the NS3, NS5A, and NS5B sequences from the baseline sample and from the sample closest in time after virologic failure with an HCV RNA level of ≥ 1000 IU/mL will be evaluated as described in analyses (1) and (2) above.

8.1.4 Adverse Events

All subjects who receive at least one dose of study drug will be included in the safety analyses. Safety analyses will be conducted separately for the Main study and the Retreatment sub-study.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) for each treatment arm. The tabulation of the number of subjects with treatment-emergent adverse events by severity grade and relationship to study drug also will be provided. Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe grade for the severity grade table and the most related for the relationship to study drug table. Subjects reporting more than one type of event within a SOC will be

counted only once for that SOC. Selected adverse events will be summarized separately for the Re-treatment Substudy.

8.1.5 Clinical Laboratory Data

Clinical laboratory tests will be summarized at each visit by treatment arm. The baseline value will be the last non-missing measurement prior to the initial dose of study drug. Mean changes from baseline to each post-baseline visit, including the Final Treatment Visit, will be summarized descriptively for each treatment arm.

In addition, the number and percentage of subjects with post-baseline laboratory values showing increase in CTCAE toxicity grade during treatment will be summarized by treatment arm for the Main study and overall for the Retreatment sub-study.

8.2 Determination of Sample Size

Based on actual real-world pragmatic enrollment observed in the ongoing study, more non-cirrhotics and less compensated cirrhotic subjects are enrolling than was previously projected. This will improve precision for the point estimated SVR12 rates of the non-cirrhotic patient and decrease precision for the point estimated SVR12 rates in compensated cirrhotic subjects. For the comparison between Arm A and Arm B in non-cirrhotic subjects, if the observed SVR12 rate in Arm B is 92%-96%, with 100 subjects in Arm A and 50 subjects in Arm B, the half widths of 95% confidence interval of the difference between SVR12 rates are displayed in the table below:

SVR12 in Arm B	92%	93%	94%	95%	96%
Half width (SVR12 in Arm A = SVR12 in Arm B)	0.092	0.087	0.081	0.074	0.067
Half width (SVR12 in Arm A = SVR12 in Arm B – 1%)	0.094	0.088	0.083	0.076	0.069
Half width (SVR12 in Arm A = SVR12 in Arm B – 2%)	0.095	0.090	0.085	0.078	0.072

For the comparison between Arm C and Arm D in cirrhotic subjects, if the observed SVR12 rate in Arm D is 94%-98%, with 40 subjects in Arm C and 40 subjects in Arm D, the half widths of the 95% confidence interval of the difference between SVR12 rates are displayed in the table below:

SVR12 in Arm D	94%	95%	96%	97%	98%
Half width (SVR12 in Arm C = SVR12 in Arm D)	0.104	0.096	0.086	0.075	0.061
Half width (SVR12 in Arm C= SVR12 in Arm D – 1%)	0.108	0.100	0.091	0.081	0.068
Half width (SVR12 in Arm C = SVR12 in Arm D – 2%)	0.112	0.104	0.095	0.086	0.075

In Study M15-410, subjects with prior NS5A inhibitor experience only (ie. PI naïve) had an SVR12 rate of 94.4% for 16 weeks treatment duration. This SVR12 rate would give half widths of 95% confidence intervals of ≤ 11% in most cases where Arm A or Arm C are no more that 1% worse than Arm B or Arm D, respectively.

8.3 Randomization Methods

The Main study is randomized. In it, eligible subjects without cirrhosis will be randomized 2:1 into Arms A and B. Subjects with compensated cirrhosis will be randomized 1:1 into Arms C and D. Randomization will be stratified by HCV genotype 1 subtype (1b or non-1b) and cirrhosis status.

The Retreatment sub-study is not randomized; all subjects who experience virologic failure in the Main study and consent to the Retreatment sub-study will receive G/P + SOF ± RBV for 16 weeks.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure (applicable to Main Study only), the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study

before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to the sponsor.

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A signed

copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

All original clinic notes, telephone notes, locally available safety labs/evaluations and/or diagnostic tests or health screenings collected prior to, during and post HCV treatment period will be submitted for chart data abstraction to identify and abstract medical history, vital signs, weight (and height historically) HCV treatment, dosing, adverse events, clinical management and physical examinations that were collected as part of standard of care practice. Additionally, sites will be provided standardized source worksheets to manage drug supply, drug accountability and various other study related activities that are not routinely covered under clinical care or recorded in the patient medical record along with the records associated with central laboratory test collection and results. These documents comprise the study source and will be submitted for centralized data abstraction (Section 10.3).

The source documentation for this pragmatic study is largely the medical record generated in the clinical management of the subjects. The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic

devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

10.2 Case Report Forms

Case report forms (CRF) are completed for each subject by the centralized data abstraction team at the University of Florida. Site staff is responsible to upload redacted records into the applicable case book for each respective patient according to the Study Activities Schedule (**Table 5**). These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called REDCap. REDCap has been used in over 15,360 projects with over 23,000 end users across 6 continents. REDCap is designed for interactive web-based data entry with real-time field validation. A dedicated instance of the web-based Research Electronic Data Capture (REDCap) data management software package, which is utilized extensively throughout the national CTSA program and beyond, is implemented and supported by the University of North Carolina –Chapel Hill for the HCV-TARGET registry program. This secure server environment housing the database hardware is located within a hardened data center on the UNC campus and is governed by standardized University and School of Medicine information security guidelines.

The "FDA regulation 21 CFR Part 11" details recommendations for electronic records and electronic signatures. According to this regulation, systems generating electronic records which are to be considered equivalent to paper records, should be validated, produce a time-stamped audit trail of data modifications, require electronic signatures and restrict access to authorized users. The REDCap based data management system implemented for the HCV-TARGET registry has been adapted to the specified FDA recommendations, and annual internal audits are performed to ensure compliance with Title 21 CFR Part 11 is achieved.

10.3 Centralized Data Abstraction

In order to reduce chart data abstraction errors and inconsistencies and improve data quality, the HCV-TARGET Network operations utilizes a specially trained Centralized Chart Data Abstraction Service (CDAS) team at the CCC/respective country Abstraction Core (CDAS) as the method for chart abstraction. Participating sites upload redacted copies of clinically available medical record source data on enrolled subjects into the study database. This data includes ALL clinic notes, nursing/staff telephone notes, evaluations and lab results generated in standard care to monitor the HCV baseline condition, on-treatment safety and efficacy, concomitant therapy, actions taken in treatment management as well as outcomes. The CDAS will abstract and enter the data from those provided participant medical records into the database and query as needed to fill data gaps not addressed by the study Data Abstraction Conventions.

10.4 Submitting Records for Abstraction

Before submitting records for abstraction, site staff redacts all elements of PHI (see Section 10.6) defined by HIPAA *except dates of services* on all records. Sites will add a study-coded identifier to the submitted records to help maintain subject

confidentiality. Patient identifiers such as patient name, full date of birth, address, etc. can be viewed by the DCC or CCC to facilitate onsite and remote monitoring of the data and compliance with the protocol, however, with the exception of dates, PHI identifiers will not be included on any datasets used for the overall safety and efficacy database and analyses, making the database a *limited data set*. In instances where a PHI identifier other than a date of service is present on a redacted record received for CDAS, delegated CDAS personnel will redact that information.

To ensure security with transmitting the records, sites will upload the redacted medical records onto the secure study REDCap database. Chart Data Abstractors will access the redacted records from this location to abstract the protocol-defined data into the study database. Those records will be maintained by CDAS staff to facilitate data monitoring as needed.

The abstracted data is transmitted to the Data Coordinating Center (DCC) via a distributed web-based data entry system, REDCap, which is 21 CFR Part 11 validated and compliant.

10.5 Subject Confidentiality Associated with Uploaded Records for Abstraction

All patient and study documents are kept confidential. Study sites and the CDAS team will be responsible for the confidentiality of the data associated with subjects enrolled into this study in the same manner they are responsible for the confidentiality of any patient information within their spheres of responsibility. All forms and submitted records used for abstraction of the study data will be identified by coded identifiers to maintain subject confidentiality. All study staff will identify patients by the patient identifier number generated at the study site. The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review and regulatory inspection(s), providing direct access to source data documents. AbbVie (or their representative) will

also be allowed access to all source documents pertinent to the study in order to verify EDC entries. Participants grant permission to share research data with these entities in the consent document. Federal regulations govern the protection of patient's rights relative to data confidentiality and use of research data.

Consent procedures and forms, and the communication, transmission and storage of patient data will comply with individual site IRB and federal requirements for compliance with HIPPA.

10.6 HIPAA Privacy Rule for Elements of PHI and Uploaded Records for Abstraction

Established in 1996, the U.S. Department of Health and Human services issued the Privacy Rule as part of the Health Insurance Portability and Accountability Act to establish a national set of standards for the protection of certain health information. This rule protects all "individually identifiable health information" held or transmitted by a covered entity or its business associate in any form or media whether electronic, paper, or oral. A list of 18 Identifiers was established:

1. Names
2. All geographical subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

4. Phone numbers
5. Fax numbers
6. Electronic mail addresses
7. Social Security numbers
8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, or code (note this does not mean the unique code assigned by the investigator to code the data)

Records submitted for Centralized Abstraction and through RED-I are redacted for these PHI identifiers *except for dates of service/activities*. In instances where a PHI identifier other than a date of service is present on a redacted record delegated CCC personnel will redact that information.

11.0 Monitoring

The study monitor will review data centrally (remote monitoring) to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

The study monitor must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On-site they will review study records, the Investigator Site File, and study medication; discuss the conduct of the study with the

investigator; and verify that the facilities remain acceptable. To supplement routine medical monitoring, a data monitoring committee comprised of Dr. Nelson, Dr. Fried and at least 3 participating site investigators will review any safety or treatment efficacy findings that may affect study-wide dosing decisions and application of futility criteria in section 5.4.1.1.

The investigator must notify the sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the sponsor.

12.0 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact the sponsor prior to destroying any records associated with the study. The sponsor will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to the sponsor.

13.0 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include study drug(s). Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number

- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to AbbVie (or designee), if applicable
- dates and initials of person responsible for Investigational Product dispensing/ accountability, as per the Delegation of Authority Form.

The sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

14.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the electronic CRF.

15.0 Completion of the Study

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

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify the sponsor to arrange alternative archiving options.

The end-of-study is defined as the date of the last subject's last visit.

16.0 Investigator's Agreement

1. I have received and reviewed the Mavyret™ Prescribing Information, Sovaldi®(Sofosbuvir) Prescribing Information, and Ribavirin Prescribing Information.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Phase 3b, Multi-Center, Randomized, Open-Label, Pragmatic Study of Glecaprevir/Pibrentasvir (G/P) +/- Ribavirin for GT1 Subjects with Chronic Hepatitis C Previously Treated with an NS5A Inhibitor + Sofosbuvir Therapy

Protocol Date: November 20, 2018

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies managed by HCV-TARGET are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 16.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying the sponsor, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to the sponsor and the site director.
5. Reading the information in the Investigator's Brochure (applicable to Main Study)/Prescribing Information(s) provided, including the instructions for use and the potential risks and side effects of the investigational product(s)/study drugs.
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of the sponsor and/or the appropriate regulatory agency, and retaining all study-related documents until notification from the sponsor.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated

problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and the sponsor.

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. Medicare National Coverage Decision for Clinical Trials

This national coverage policy is based upon the authority found in §1862(a)(1)(E) of the Social Security Act (Act). It is binding on all Medicare carriers, fiscal intermediaries, Peer Review Organizations, Health Maintenance Organizations, Competitive Medical Plans, Health Care Prepayment Plans, and Medicare+Choice organizations (§1852(a)(1)(A) of the Act). In addition, an administrative law judge may not disregard, set aside, or otherwise review a national coverage decision issued under §1862(a)(1) of the Act. 42 C.F.R. §405.860.
Clinical Trials

Effective for items and services furnished on or after September 19, 2000, Medicare covers the routine costs of qualifying clinical trials, as such costs are defined below, as well as reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials. All other Medicare rules apply.

Routine costs of a clinical trial include all items and services that are otherwise generally available to Medicare beneficiaries (i.e., there exists a benefit category, it is not statutorily excluded, and there is not a national noncoverage decision) that are provided in either the experimental or the control arms of a clinical trial except:

- the investigational item or service, itself,
- items and services provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient (e.g., monthly CT scans for a condition usually requiring only a single scan); and
- items and services customarily provided by the research sponsors free of charge for any enrollee in the trial.

Routine costs in clinical trials include:

- Items or services that are typically provided absent a clinical trial (e.g., conventional care);
- Items or services required solely for the provision of the investigational item or service (e.g., administration of a noncovered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; and
- Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service--in particular, for the diagnosis or treatment of complications.

This policy does not withdraw Medicare coverage for items and services that may be covered according to local medical review policies or the regulations on category B investigational device exemptions (IDE) found in 42 C.F.R. §405.201-405.215 and §411.15 and §411.406. For information about LMRPs, refer to www.lmrp.net, a searchable database of Medicare contractors' local policies.

For noncovered items and services, including items and services for which Medicare payment is statutorily prohibited, Medicare only covers the treatment of complications arising from the delivery of the noncovered item or service and unrelated reasonable and necessary care. (Refer to MCM 2300.1 and MIM 3101.) However, if the item or service is not covered by virtue of a national noncoverage policy in the Coverage Issues Manual and is the focus of a qualifying clinical trial, the routine costs of the clinical trial (as defined above) will be covered by Medicare but the noncovered item or service, itself, will not.

Requirements for Medicare Coverage of Routine Costs

Any clinical trial receiving Medicare coverage of routine costs must meet the following three requirements:

1. The subject or purpose of the trial must be the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids).
2. The trial must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent.
3. Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers. Trials of diagnostic interventions may enroll healthy patients in order to have a proper control group.

The three requirements above are insufficient by themselves to qualify a clinical trial for Medicare coverage of routine costs. Clinical trials also should have the following desirable characteristics; however, some trials, as described below, are presumed to meet these characteristics and are automatically qualified to receive Medicare coverage:

1. The principal purpose of the trial is to test whether the intervention potentially improves the participants' health outcomes;
2. The trial is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use;
3. The trial does not unjustifiably duplicate existing studies;
4. The trial design is appropriate to answer the research question being asked in the trial;
5. The trial is sponsored by a credible organization or individual capable of executing

the proposed trial successfully;

6. The trial is in compliance with Federal regulations relating to the protection of human subjects; and
7. All aspects of the trial are conducted according to the appropriate standards of scientific integrity.

Qualification Process for Clinical Trials

Using the authority found in §1142 of the Act (cross-referenced in §1862(a)(1)(E) of the Act), the Agency for Healthcare Research and Quality (AHRQ) will convene a multi- agency Federal panel (the "panel") composed of representatives of the Department of Health and Human Services research agencies (National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), AHRQ, and the Office of Human Research Protection), and the research arms of the Department of Defense (DOD) and the Department of Veterans Affairs (VA) to develop qualifying criteria that will indicate a strong probability that a trial exhibits the desirable characteristics listed above. These criteria will be easily verifiable, and where possible, dichotomous. Trials that meet these qualifying criteria will receive Medicare coverage of their associated routine costs. This panel is not reviewing or approving individual trials. The multi-agency panel will meet periodically to review and evaluate the program and recommend any necessary refinements to CMS.

Clinical trials that meet the qualifying criteria will receive Medicare coverage of routine costs after the trial's lead principal investigator certifies that the trial meets the criteria. This process will require the principal investigator to enroll the trial in a Medicare clinical trials registry, currently under development.

Some clinical trials are automatically qualified to receive Medicare coverage of their routine costs because they have been deemed by AHRQ, in consultation with the other agencies

represented on the multi-agency panel to be highly likely to have the above- listed seven desirable characteristics of clinical trials. The principal investigators of these automatically qualified trials do not need to certify that the trials meet the qualifying criteria, but must enroll the trials in the Medicare clinical trials registry for administrative purposes, once the registry is established.

Effective September 19, 2000, clinical trials that are deemed to be automatically qualified are:

1. Trials funded by NIH, CDC, AHRQ, CMS, DOD, and VA;
2. Trials supported by centers or cooperative groups that are funded by the NIH, CDC, AHRQ, CMS, DOD and VA;
3. Trials conducted under an investigational new drug application (IND) reviewed by the FDA; and
4. Drug trials that are exempt from having an IND under 21 CFR 312.2(b)(1) will be deemed automatically qualified until the qualifying criteria are developed and the certification process is in place. At that time the principal investigators of these trials must certify that the trials meet the qualifying criteria in order to maintain Medicare coverage of routine costs. This certification process will only affect the future status of the trial and will not be used to retroactively change the earlier deemed status.

Medicare will cover the routine costs of qualifying trials that either have been deemed to be automatically qualified or have certified that they meet the qualifying criteria unless CMS's Chief Clinical Officer subsequently finds that a clinical trial does not meet the qualifying criteria or jeopardizes the safety or welfare of Medicare beneficiaries.

Should CMS find that a trial's principal investigator misrepresented that the trial met the necessary qualifying criteria in order to gain Medicare coverage of routine costs, Medicare

coverage of the routine costs would be denied under §1862(a)(1)(E) of the Act. In the case of such a denial, the Medicare beneficiaries enrolled in the trial would not be held liable (i.e., would be held harmless from collection) for the costs consistent with the provisions of §1879, §1842(l), or §1834(j)(4) of the Act, as applicable. Where appropriate, the billing providers would be held liable for the costs and fraud investigations of the billing providers and the trial's principal investigator may be pursued.

Medicare regulations require Medicare+Choice (M+C) organizations to follow CMS's national coverage decisions. This NCD raises special issues that require some modification of most M+C organizations' rules governing provision of items and services in and out of network. The items and services covered under this NCD are inextricably linked to the clinical trials with which they are associated and cannot be covered outside of the context of those clinical trials. M+C organizations therefore must cover these services regardless of whether they are available through in-network providers. M+C organizations may have reporting requirements when enrollees participate in clinical trials, in order to track and coordinate their members' care, but cannot require prior authorization or approval. For the initial implementation, Medicare contractors will pay providers directly on a fee for service basis for covered clinical trial services for beneficiaries enrolled in M+C plans.

Appendix C. Methods of Contraceptives

The below listed methods meet the requirements for contraception as per the CTFG guidance.[18]

If female, subject must be either postmenopausal defined as:

- Age ≥ 55 years with no menses for 12 or more months without an alternative medical cause.
- Age < 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

OR

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

OR for Women of Childbearing Potential

- Agreeing to practice ONE effective method of birth control while receiving G/P or G/P + SOF; TWO effective methods of birth control while receiving G/P + RBV, or G/P + SOF + RBV (as outlined in the subject information and consent form or other subject information documents), starting with Day 1 and for 30 days after stopping G/P (if randomized to non-RBV Arm), or G/P + SOF, or 6 months after stopping RBV (or per local RBV label).
  - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
  - Bilateral tubal occlusion/ligation.
  - Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.
  - Non-ethinyl estradiol hormone-releasing Intrauterine device (IUD)
  - Non-ethinyl estradiol hormone-releasing Intrauterine hormone-releasing system (IUS)
  - Male or female condom with spermicide (male and female condom must not be used together)
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Contraceptive sponge with spermicide
  - True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence] e.g., calendar, ovulation, symptothermal, post-ovulation

methods] and withdrawal are not acceptable).
○sexually active with female partners only

Male Subjects
Subject must be surgically sterile (vasectomy with medical assessment confirming surgical success)

OR

Have a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy)

OR

if sexually active with female partner(s) of CBP must agree to practice ONE effective method of birth control while receiving G/P, or G/P + SOF; or TWO effective methods of birth control while receiving G/P + RBV, or G/P + SOF +RBV (as outlined in the subject information and consent form or other subject information documents), starting with Day 1 and for 30 days after stopping G/P (if randomized to non-RBV Arm), or G/P + SOF; or 7 months after stopping RBV (or per local RBV label).

- Any approved and commercially available hormonal contraception for female partners
- Any approved and commercially available, including any hormone-eluting, devices for female partners of male subjects
- Male or female condom with spermicide (male and female condom must not be used together)
- Female partner using a diaphragm with spermicide
- Female partner using a cervical cap with spermicide
- Female partner using a contraceptive sponge with spermicide
- True abstinence: Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).
  sexually active with male partners only

Additionally, male subject agrees not to donate sperm from Study Day 1 through 7 months after the last dose of study drug (or as directed by the RBV prescribing information).