1.0 Title Page

Statistical Analysis Plan

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

Clinical Study Protocol B16-439

March 8, 2019

2.0 Table of Contents

List of Tables

List of Figures

Glossary of Population Definitions

ITT	All subjects enrolled in the Main Study receiving at least one dose of study drug and according to the treatment arm to which they were randomized
mITT	All subjects enrolled in the Main Study receiving at least one dose of study drug and according to the treatment arm in which they were actually treated.
mITT-GT	mITT population, excluding subjects with HCV genotypes other than genotype 1.
mITT-GT-VF	mITT-GT population, further excluding subjects with non-virological failures (e.g., lost to post-treatment follow-up, without virological outcome)
Evaluable population	Equivalent to the mITT population
EP-RS	All subjects enrolled in the Re-Treatment Sub-Study receiving at least one dose of study drug (G/P+SOF±RBV of a prescribed 16 week regimen, with ribavirin used at the discretion of the investigator)
EP-RS-GT	EP-RS population, excluding subjects with HCV genotypes other than genotype 1.
EP-RS-GT-VF	EP-RS-GT population, further excluding subjects with non-virological failures (e.g., lost to post-treatment follow-up without virological outcome, death, etc.)
Primary efficacy analysis population	Equivalent to the mITT population
Safety population	Equivalent to the mITT population

3.0 Introduction

This document presents the detailed statistical analyses to be executed by the HCV-TARGET Data Coordinating Center (DCC) for AbbVie Study B16-439. This study is designed to support comparison of the efficacy, safety, and viral resistance of glecaprevir and pibrentasvir (G/P) for 12 weeks to that of G/P for 16 weeks, with and without addition of RBV to the treatment regimen. Study subjects will be restricted to NS5A-inhibitor plus sofosbuvir ± RBV treatment-experienced adults with HCV genotype 1 (GT1) infection and with either no cirrhosis or compensated cirrhosis. An overarching description of the study is presented in the Study Protocol (1).

This Statistical Analysis Plan (SAP) presents formal guidance for the statistical programming to produce the results which will address the analyses conventions of the study. Analyses will be performed using SAS® Version 9.4 (SAS Institute, Inc., Cary, NC) under the Microsoft Windows operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objectives of this study are to:

1. Compare the efficacy (SVR12) of G/P administered for 12 weeks to non-cirrhotic HCV 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 HCV 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.

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)

The additional objectives are

1) to assess the impact of baseline host and viral factors on treatment outcomes,

2) the emergence and persistence of viral variants in those with treatment failure in this treatment regimen, and

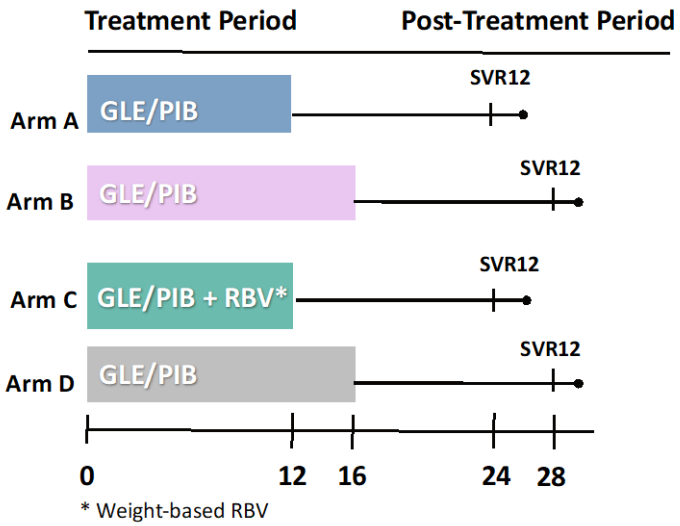
3) the safety and efficacy of the re-treatment regimen of G/P+SOF±RBV.

4.2 Design Diagram

This Phase 3b study will embrace a multi-center, randomized, open-label, pragmatic evaluation of G/P +/- RBV for 12 weeks or G/P 16 weeks in subjects with chronic HCV GT1 infection who are treatment experienced with a prior NS5A inhibitor+SOF±RBV therapy.

The main part of this study consists of a Treatment Period of 12 weeks or 16 weeks and a Post-Treatment Period of 12 weeks after the last dose of study drug (Figure 1).

Figure 1. Study Schematic for the Main Study



Randomization will be stratified by HCV genotype 1 subtype (1b or non-1b).

- HCV GT1 non-cirrhotic subjects (up to 150): randomized 2:1 to Arms A or B..
- HCV GT1 cirrhotic subjects (up to 75): randomized 1:1 to Arm C or D.

The initial study design did not exclude patients with historical PI exposure prior to the NS5A-inhibitor 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 with 16 weeks of therapy for NS5A experienced, PI naïve patients only.. 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.

Subjects who experience virologic failure in the Main Study will have the option to to enter the Re-Treatment Sub-Study and receive G/P+SOF±RBV with the start of retreatment within 1 year after experiencing G/P failure. Patients who are confirmed by phylogenetic analyses to having been re-infected rather than experiencing virological failure are excluded. The Treatment Period for the Re-Treatment Sub-Study will be for a total of 16 weeks. The Post-Treatment Period for the Re-Treatment Sub-Study will be 12 weeks following the last dose of the re-treatment regimen.

4.3 Sample Size

The objective of this study is to enroll up to 225 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 a previous study (ref. study M15-410), subjects with prior NS5A inhibitor experience only (i.e., 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.

4.4 Primary Analysis

Primary data analysis will commence when all subjects in the Main Study have completed the Post Treatment Week 12 Visit or have prematurely discontinued the study. The data for subjects treated in the Main Study will be preserved after data cleaning is completed for the Main study and will be analyzed for the Primary analysis clinical study report. Data from the Re-Treatment Sub-Study will be analyzed separately.

An analysis-level dataset will be created, subjected to thorough inter- and intra-variable evaluation, and independent code assessment to ensure optimal data integrity prior to certification for subsequent statistical summaries and analyses. All descriptive and inferential statistical evaluations (as applicable) and confidence intervals will be two-sided with a significance level (α) of 0.05. Descriptive statistics, including but not restricted to number of observations (N), mean, and standard deviation (SD) for

continuous variables and counts and percentages for discrete variables, will be generated to support summary data tabulations and/or graphics.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

5.1.1 Intention-to-Treat (ITT) Population and Primary Efficacy Analysis Population

All randomized subjects who receive at least one dose of study drug in the Main Study will comprise the ITT population. However, in accordance with Protocol Amendment 10/13/17 the Primary safety and efficacy analyses will be performed on the study population "as treated" and summarized according to the treatment arm in which they had actually received treatment. The primary efficacy analysis dataset in this pragmatic trial, comprised of subjects as treated, will be referred to elsewhere in this document as the modified ITT (mITT) population. The traditional ITT population, reflecting the patients' randomized treatment arm, will be employed, along with other modified ITT populations, in sensitivity analyses to be discussed later in this document.

5.1.2 Modified Intent-to-Treat (mITT) Populations

Sensitivity analyses of the primary endpoint of the Main study will be performed on the modified ITT populations as defined below:

Modified ITT- Genotype (mITT -GT) Population

As stated in the previous section, the mITT population (or "as treated") includes all subjects representing their actual study regimen and who received at least one dose of study drug. The mITT-GT population includes subjects from the mITT population but excludes subjects with genotype other than GT1 infection.

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

mITT-GT-VF includes all subjects in the mITT-GT population defined above, but excludes subjects who did not achieve SVR12 for reasons other than virologic failure.

Demographic analyses will also be performed on the mITT population(s).

5.1.3 Patient Populations for the Re-Treatment Sub-Study (EP-RS)

Analyses in the Re-Treatment Sub-Study will be performed overall on the EP-RS population, which is defined as all subjects who receive at least one dose of the re-treatment drug with or without ribavirin as specific by the investigator.

Sensitivity analyses of the SVR12 endpoint will be performed for the Re-Treatment Sub-Study 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).

5.1.4 Safety Population

For the Main Study, all subjects who receive at least one dose of study drug will be included in the safety analyses according to their actual treatment arm (mITT≡Safety population).

Safety analyses for the Re-Treatment Sub-Study will be performed on the overall EP-RS population as defined above.

6.0 Analysis Conventions

6.1 Definition of Baseline and End of Treatment Assessment

6.1.1 Baseline

The baseline result is defined for the Main study as the last non-missing measurement collected prior to administering the first dose of study drug. For subjects who enrolled in the Re-Treatment Sub-Study, baseline result is defined as the last non-missing measurement collected prior to administering the first dose of re-treatment drug. The protocol specifies that all Day 1 assessments shall be performed prior to administering the first dose of study drug. Therefore, all Day 1 assessments for which time is not recorded will be assumed to be pre-dose. In this case, the baseline value will be the last non-missing result, for a given measurement, collected on or before the first day of study drug administration.

All Day 1 assessments, for which time is recorded, must be before the time of first dose to be considered baseline. The last non-missing measurement collected before the date and time of the first dose of study drug will be considered the baseline result. In instances where multiple measurements, made prior to dosing, are recorded on the same date and with the same time, or without time, the average of these measurements will be considered the baseline result. This same baseline result will be assigned for analyses of the Treatment and Post-Treatment Periods.

Safety assessments related to a serious adverse event occurring on the day of first dose of study drug are excluded when applying this algorithm.

For subjects who enroll in the Re-Treatment Sub-Study and who experience virologic failure during the Re-Treatment or Post-Re-Treatment periods, HCV NS3 and NS5A resistance analyses will be conducted on the plasma sample collected at the last visit prior to the start of the re-treatment and on the first available sample with an HCV viral load ≥1000 IU/mL after the time of virologic failure.

6.1.2 Study Days

Study days are determined for each time point (recorded in days) relative to administration of the first dose of study drug. Study days are negative when the time point of interest is prior to the first study drug dose day. Similarly, study days are positive when the time point of interest is after the first study drug dose day. There is no Study Day 0. Study Day 1 is the day of the first dose of study drug.

Study Drug End Days (Days Relative to the Last Dose of Study Drug)

Study drug end days are calculated for each time point relative to the last dose of study drug. The last day of study drug dosing is defined as Study Drug End Day 0. Days before it are recorded as negative study drug end days and days after it have positive study drug end days.

Final Treatment Value

The final treatment value is defined as the last non-missing measurement collected after Study Day 1 and on or before Study Drug End Day 2.

Final Post-Treatment Value

The final post-treatment value for each subject shall be the last non-missing measurement recorded after Study Drug End Day 2 and on or before final study visit.

6.2 Definition of Analysis Windows

For efficacy and resistance analyses for both the Main Study and the Re-Treatment Sub-Study, the time windows specified in Table 1 and Table 2 represent guidelines for assignment of efficacy data to protocol-specified time points during the treatment and post-treatment periods, respectively. All time points and corresponding time windows are based on the date/time of blood specimen collection.

For laboratory data, the time window specified in Table 1 and Table 3 describes how data are assigned to protocol specified time points.

If more than one assessment is included in a time window, the assessment closest (except in analyses of SVR outcomes) to the nominal day will be used. If there are two observations equally distant to the nominal time, the latest one will be used in analyses. For analyses of SVR (e.g., SVR12), the last value in the window will be used.

If multiple laboratory measurements are made on the same day for a particular safety or vital sign parameter, the average of the values will be used to calculate descriptive statistics for that parameter and to support analyses of the mean change from baseline.

Table 1. Treatment Period Time Windows for Analyses Relating to HCV RNA, Resistance Endpoints, and Laboratory Measurements

Scheduled Visit	Nominal Day (Study Day)	Time Window (Study Day Range)
Day 1/Baseline[a]	1	≤ 1[a]
Week 4	28	14 to 42
Week 8	56	43 to 70
Week 12	84	71 to 98
Week 16 [b]	112	99 to 126
Final Treatment Visit[c]	2 to ≤ 2 days after last dose of study drug	

a. Day of first dose of study drug.

b. For 16-week treatment arms, and subjects of the Re-Treatment Sub-Study.

c. The last value within the window will be used to define the Final Treatment Visit value. The upper bound of this Final window is Study Drug End Day ≤ 2.

Note: Data must also have Study Drug End Day ≤ 2 for all windows. The result closest to the scheduled time point will be used.

Table 2. Post-Treatment Period Time Windows for Analyses Relating to HCV RNA and Resistance Endpoints

Scheduled Visit[a]	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Day Range)
Post-Treatment Week 4	28	14 to 56
Post-Treatment Week 12	84	57 to 126
SVR4	28	3 to 56
SVR12[b]	84	57 to 126

a. Post-Treatment Visits are applicable for subjects who received at least one dose of study drug.

b. For SVR windows, the last value in the window will be used.

Note: The result closest to the scheduled time point will be used, except for SVR_4, and SVR12. Data must also have Study Drug End Day > 2 for all windows. Study Drug End Day 0 is defined as the day of the last dose of study drug.

Table 3. Post-Treatment Visit Windows for Safety Laboratory Data

Scheduled Time	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Days Range)
Post-Treatment Week 4	28	14 to 56
Post-Treatment Week 12	84	57 to 126
Final Post-Treatment Visit[a]	> 2 days after last dose of study drug	

a. The last value within the Post-Treatment Period window will be used to define the final post-treatment value. The lower bound of this Final window is Study Drug End Day 3.

Note: The result closest to the scheduled time point will be used. Data must also have Study Drug End Day > 2. Vital signs are recorded at every PT visit if available in the record; hematology, chemistry, urinalysis, and coagulation panels are collected at PTW4 and PTDC (if subject discontinued prior to PTW4).

6.3 Missing Data Imputation

Missing SVR Result Imputation

In this study, it is expected that HCV RNA results will be provided for all subjects by a central laboratory. In that regard and where feasible, missing HCV RNA results for specific subject visits will be imputed using a backward imputation method according to the following backward imputation rules:

- If the most proximate HCV RNA value beyond the SVR window is "Not quantified" or "Target not detected", then that result will be used to replace a missing HCV RNA value within the preceding SVR window.
- If an HCV RNA value within the SVR window is still missing after performing backward imputation, then an HCV RNA value within the SVR window from a local laboratory, if present, will be imputed; otherwise, the HCV RNA value in the window will remain missing and the SVR status of that patient shall be interpreted as a failure.

- HCV RNA values collected during the Re-Treatment Sub-Study will not be imputed backward for the SVR analyses during the Main Study. That is, subjects who experience virologic failure in the Main Study will remain as non-SVR for the Main Study even if cured in the Re-Treatment Sub-Study.

Regardless of the imputation method employed, all HCV RNA values for a subject who starts a different treatment for HCV measured on or after the start date of the new HCV treatment, will be excluded from subsequent analyses (other than the protocol-specified re-treatment which will be analyzed separately). The subject will be considered a failure in summaries of viral response at all time points on the current study once new HCV treatment has commenced.

Missing Data Imputation for Virologic Failure

If HCV RNA results from the central laboratory are missing but a local laboratory result is present in the appropriate time period, then the local laboratory value will be used to assess post-treatment relapse and on-treatment virologic failure.

7.0 Demographics, Baseline Characteristics, Medical History, and Other Medications

Data from the safety population will be used to create demographic and baseline characteristic summaries as described below based on the final assigned treatment arm for the Main Study. The safety population will be used to summarize medical history and previous, concomitant, and post-treatment medications for each treatment arm for the Main Study. Similar summaries will be created for the subjects who enroll in the Re-Treatment Sub-Study

7.1 Demographic and Baseline Characteristics

Demographic and baseline characteristic data will be summarized for all treated subjects by treatment arm. Summary statistics (N, mean, median, SD, and range) will be generated, by treatment arm, for continuous variables (e.g., age and BMI); number and percentage of subjects will be presented for categorical variables (e.g., sex and race).

Continuous demographic variables include age, weight, height, and body mass index (BMI). Categorical demographic variables include sex, race, black race (black or non-black), ethnicity, age category (< 65 or ≥ 65 years; < 75 or ≥ 75 years), BMI category (< 30 or ≥ 30 kg/m^2). Continuous baseline characteristics include $\log_{10}$ HCV RNA, eGFR, platelet count, albumin, APRI, FIB-4, AST, ALT, ALT/AST and total bilirubin for all subjects. Categorical baseline characteristics include:

- HCV genotype 1 subtype (as determined by the central laboratory);
- Type of previous regimen (SOF/DCV, SOF/LDV, SOF/VEL, Other);
- HCV mono-infected vs. HCV/HIV-1 co-infected;
- HCV RNA level ($< 1{,}000{,}000$ or $\geq 1{,}000{,}000$ IU/mL);
- Cirrhosis status (yes/no);
- History of HCC (yes/no);
- Child Pugh score for cirrhotic patients only (A, B)
- Platelet count (< 100 or $\geq 100 \times 10^3$/L);
- Albumin (< 3.5 or ≥ 3.5 g/dL);
- ALT/AST (< 1 or ≥ 1)
- eGFR (< 60, ≥ 60 to < 90, ≥ 90 mL/min/1.73 m^2);
- History of diabetes (yes/no);
- Post organ transplant by transplanted organ (yes/no);
- Concomitant use of Proton Pump Inhibitors (PPIs) (yes/no);

- Baseline resistance (as described below).

For the baseline resistance analysis and efficacy subgroup analyses, baseline NS3 and NS5A variants are defined based on ≥ 15% NGS detection threshold. Amino acid positions of NS3 and NS5A in genotype 1 subjects for subgroup analysis are listed in Table 4.

Table 4. Amino Acid Positions by DAA Target for Patients with HCV Genotype 1 Infection for Subgroup Analysis

Target	Genotype	Subgroup Amino Acid Positions (All Variants at These Positions Are to Be Included)	Other Specific Variants
NS3	1	155, 156, 168	
NS5A	1a	28, 30, 31, 93	H58D, E62A
	1b	31, 93	

The number and percentage of subjects by treatment arm in the mITT and mITT-GT-VF populations will be summarized for the presence of baseline resistance-associated variants of:

- Any NS3 variant at baseline (yes/no);
- Any NS5A variant at baseline (yes/no);
- Any NS3 variant at baseline **or** any NS5A variant at baseline (yes/no);
- Any NS3 variant at baseline **and** any NS5A variant at baseline (yes/no).
- Any NS3 variant at baseline (yes/no) only (without baseline NS5A variants);
- Any NS5A variant at baseline (yes/no) only (without baseline NS3 variants).

Differences in proportions of discrete variables will be compared across treatment arms and their statistical significance determined with a Mantel-Haenszel chi-square test. Comparisons of continuous variables across treatment arms will be conducted with general linear modeling or one-way analysis of variance (ANOVA).

Any concomitant medication coded to the WHO Drug Dictionary ATC code of A02BC will be counted as a PPI. All patients will be evaluated for the presence of cirrhosis and the final assessment will be made by site PI. The presence of cirrhosis is defined at screening by biopsy (liver biopsy results up to 3 years prior to screening are acceptable if the results showed no cirrhosis) and/or a combination of clinical, laboratory, elastography, and imaging criteria established *a priori*. 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 therapy (for post-transplant recipients, biopsy staging should be from the allograft);

2) Evidence of stage 3 (Metavir) fibrosis by liver biopsy prior to therapy with any one of the following criteria (for post-transplant recipients, biopsy staging should be from the allograft);

- Platelet count <140x 10^9/L during screening,
- Presence of esophageal varices on esophagogastroduodenoscopy at any time
- Evidence of cirrhosis and/or portal hypertension by imaging at any time
- 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:

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

Baseline APRI and FIB-4 are defined as the equations below. Subjects who do not have concurrent AST and platelet values at baseline will be excluded from the summary of baseline APRI. Age is defined in years at baseline. Subjects who do not have concurrent values of AST, ALT, and platelet count at baseline, or subjects who are missing age will be excluded from the summary of FIB-4.

$$\text{APRI} = \frac{\frac{\text{AST Level (U/L)}}{\text{AST (Upper Limit of Normal)(U/L)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

$$\text{FIB} - 4 = \frac{\text{Age (years)} \times \text{ AST Level (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

History of diabetes will be based on the Medical History (MH) eCRF, as defined in Table 5.

Table 5. Medical History eCRF

		Medical History eCRF
Subgroup	**Body System**	**Condition/Diagnosis**
Diabetes	Metabolic	Diabetes mellitus

7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized for each treatment arm. Subjects reporting

more than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Prior, Concomitant and Post-Treatment Medications

A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as:

- Any medication that was started prior to the date of the first dose of study drug and continued to be taken on or after the first dose of study drug or
- Any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug.

A post-treatment medication for the treatment of HCV is defined as any medication taken on or after the last dose of study drug as entered on the "Concomitant Medications" eCRF.

The number and percentage of subjects taking prior medications, concomitant medications, and post-treatment HCV medications will be summarized for each treatment arm by generic drug name based on the WHO Drug Dictionary. Prior medications will be divided by the following categories:

- The prior HCV medications for all subjects;
- All other prior medications for all treated subjects.

8.0 Patient Disposition

The number and percentage of subjects who screen failed for any reason, and for each screen fail reason, will be summarized for all subjects who screen failed.

The number of subjects in each of the following categories will be summarized by investigator for each treatment arm and overall.

- Randomized subjects;
- Subjects who took at least one dose of the Main study drug;
- Subjects who completed the Main study drug;
- Subjects who prematurely discontinued the Main study drug;

A summary of the disposition of subjects in ITT population (by arm as randomized) will be created for the subjects who enroll in the main study.

A summary of the disposition of subjects will be created for the subjects who enroll in the Re-Treatment Sub-Study:

- Subjects who took at least one dose of retreatment regimen in the retreatment-sub-study
- Subjects who completed the re-treatment sub-study
- Subjects who prematurely discontinued the re-treatment sub-study

The number and percentage of subjects who discontinued study drug prematurely will be summarized by reason (per eCRF) for each treatment arm and overall for the Main Study. Similar summaries will be provided for discontinuations from the study. A similar summary of the reasons for discontinuation of retreatment drug will be created for the subjects who enroll in the Re-Treatment Sub-Study.

The number and percentage of subjects with reported study drug interruptions will be summarized by treatment arm for the Main Study.

Reasons for study drug interruptions will be presented in the CSR listings.

9.0 Study Drug Exposure and Compliance

9.1 Exposure

The duration of exposure to study drug is defined for each subject as the last study drug dose date minus the first study drug dose date plus 1 day. If any study drug interruptions occurred, the days on which subject did not take study drug will be subtracted from the duration of exposure. The duration of exposure to study drug will be summarized by actual treatment arm and overall for the Main Study on the safety population. A similar summary will be created for the subjects who enroll in the Re-Treatment Sub-Study.

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented for exposure during the treatment period.

Study drug duration will be summarized with frequencies and percentages using the following categories:

- 1 to 15 days
- 16 to 30 days
- 31 to 45 days
- 46 to 60 days
- 61 to 76 days
- 77 to 90 days
- 91-104 days
- >= 105 days

9.2 Compliance

At each visit (starting with the Week 4 visit) during the Treatment Period, the total number of tablets dispensed and returned is recorded. The compliance for study drug will be calculated as the percentage of tablets taken by the subject relative to the total tablets expected to be taken. The total number of tablets expected to be taken will be the protocol-specified total number of tablets specified in the Treatment Period (date of last dose of study drug – date of first dose of study drug + 1). The Treatment Period will not be adjusted for Study drug interruptions recorded on the eCRF.

A subject is considered 'compliant' if this percentage is between 80% and 120%. Compliance will be listed for each subject, and will be summarized by treatment arm as mean, median, standard deviation, minimum, and maximum. The percentage of compliant subjects will also be summarized for each treatment arm, based on data as recorded (i.e., patients missing any compliance data should not be included).

10.0 Efficacy Analysis

10.1 General Considerations

Plasma HCV RNA levels will be determined by certified, central, clinical laboratories for each sample collected 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 RNA results that are classified as detectable but are not quantifiable are reported as "< 15 IU/ML "; those that are not detected are reported as "TARGET NOT DETECTED" in the database. The notation "HCV RNA < LLOQ" is used to represent all HCV RNA values < 15 IU/mL, including values reported as "HCV RNA NOT DETECTED" or "< 15 IU/ML." HCV RNA ≥ LLOQ are all quantifiable values of 15 IU/mL or greater.

Missing HCV RNA endpoints of SVR, where encountered in the dataset, will be resolved by imputation as described in Section 6.3.

Definitions for Efficacy Endpoints

A confirmed quantifiable result during treatment is defined as any two, time-sequential and consecutive HCV RNA measurements at or above LLOQ (or 100 IU/mL for **Breakthrough**), either both during treatment, or at the end of treatment measurement and at the next consecutive post-treatment measurement. A confirmed quantifiable post-treatment value is defined as any two consecutive post-treatment HCV RNA measurements at or above LLOQ. Specific virologic end points, as applied in this analysis plan, are defined in detail below.

Breakthrough: Either 1) Confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ at some point during the Treatment Period or confirmed increase from *nadir* in HCV RNA (two consecutive measurements > 1 $\log_{10}$ IU/mL above nadir) at any time point during the Treatment Period, or 2) a single value indicating viral breakthrough (≥ 100 IU/mL or > 1 $\log_{10}$ above nadir), followed by patient status of 'Lost to Follow-up', the latter not requiring confirmation by a proximate measurement).

EOT failure: HCV RNA ≥ LLOQ at end of treatment and following at least 6 weeks of treatment. The HCV RNA value must reflect a plasma specimen collected on or after Study Drug Day 36.

On-treatment virologic failure: Either **Breakthrough** or **EOT** (end of treatment) **failure.**

SVR_4 = HCV RNA < LLOQ in the SVR_4 window (4 weeks after the last actual dose of study drug) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

SVR12: HCV RNA < LLOQ in the SVR12 window (12 weeks after the last actual dose of study drug) without any confirmed quantifiable (≥ LLOQ) post-treatment result prior to or within the SVR12 window.

Relapse: confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last dose of study drug (up to and including the SVR12 assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit and who completed treatment, excluding re-infection as described below.

Analyses of relapse will include only subjects who have at least one post-treatment HCV RNA result. Completion of treatment is defined as study drug duration of 77 days or greater for subjects receiving 12 weeks of treatment, and 105 days or greater for subjects receiving 16 weeks of treatment. If the last available post-treatment value is ≥ LLOQ, then the subject will be categorized as a relapse (i.e., confirmation not required).

HCV re-infection in a subject is defined as: 1) confirmed HCV RNA ≥ LLOQ after the end of treatment but for whom HCV RNA < LLOQ at Final Treatment Visit, and 2) post-treatment detection of a *different* HCV genotype, subtype, or clade compared with baseline, as determined by phylogenetic analysis of the NS3 or NS5A, and/or NS5B gene sequences. Re-infection in the case of the same HCV subtype is defined as a clade switch, as indicated by the lack of clustering between the baseline and post-treatment sequences by phylogenetic analysis. If phylogenetic analysis results are unavailable,

HCV re-infection may be determined with a confirmed HCV genotype or subtype switch by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Post-treatment relapse is defined as described earlier and with no genotype, subtype, or clade switch compared with baseline as determined by phylogenetic analysis of the NS3 or NS5A gene sequences. If phylogenetic analysis results are unavailable, the subject will be categorized as having a post-treatment relapse unless an HCV genotype or subtype switch is confirmed by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Treatment failure

Subjects who do not achieve SVR12 will be assigned type of SVR12 'Non-Response' according to the following assignment criteria:

1. On-treatment virologic failure, per definition above;
2. HCV re-infection, per definition
3. Relapse for subjects who complete treatment;
4. Premature discontinuation of study drug without on-treatment virologic failure defined as:
    a. SVR12 non-responder who prematurely discontinued study drug (study drug duration < 77 days for subjects receiving 12 weeks of treatment , and < 105 days for subjects receiving 16 weeks of treatment) and
    b. **On-treatment virologic failure** definition not met;
5. Missing follow-up data in the SVR12 window according to:

a. Any subject who completed study drug without a virologic result in the SVR12 window after applying the imputation rules and

b. Not meeting the definitions of 1, 2, 3, or 4

6. Other (i.e., SVR12 non-response not meeting the definitions of 1 – 5)

10.2 Handling of Multiplicity

The primary efficacy endpoints (Section 10.3) of the difference in SVR12 rates will be assessed for GT1 non-cirrhotic and cirrhotic populations separately. Each of the primary endpoints will use 95% confidence intervals without multiplicity adjustment as they are on two independent populations.

10.3 Primary Efficacy Analysis

The primary endpoints of this study are:

1. The difference in SVR12 rates between G/P given for 12 weeks (Arm A) and G/P given for 16 weeks (Arm B) to non-cirrhotic GT1infected subjects who are treatment-experienced with a NS5A inhibitor+SOF±RBV regimen
2. The difference in SVR12 rates between G/P plus RBV given for 12 weeks (Arm C) and G/P given for 16 weeks (Arm D) to GT1infected subjects with compensated cirrhosis and who are treatment-experienced with a NS5A inhibitor+SOF±RBV regimen

The difference in SVR12 rates will be summarized with a two-sided 95% confidence interval for: 1) the comparison between Arm A and Arm B in non-cirrhotic subjects and 2) the comparison between Arm C and Arm D in cirrhotic subjects. The number and

percentage of subject achieving SVR12 by treatment arm will also be summarized with a two-sided 95% confidence interval. The confidence intervals for the differences in SVR12 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. A summary of reasons for SVR12 non-response (e.g., on-treatment virologic failure, re-infection, relapse, other) will be provided.

10.4 Secondary Efficacy Analyses

The secondary endpoints 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), further differentiated within the combined arms by genetic subtype (1b vs. non-1b).
2. The difference in the percentage of subjects with on-treatment virologic failure (defined as **On-treatment virologic failure** in Section 10.1) between Arm A and Arm B in non-cirrhotic subjects, and between Arm C and Arm D in cirrhotic subjects;
3. The difference in the percentage of subjects with post-treatment relapse (defined as **relapse** in Section 10.1) between Arm A and Arm B in non-cirrhotic subjects, and between Arm C and Arm D in cirrhotic subjects.

The difference in SVR12 rates will be summarized with a two-sided 95% confidence interval using Wilson's score method the comparison between 12 week (Arms A+C) and 16 week (Arms B+D) treatment durations. The difference in the percentage of subjects with on-treatment virologic failure and post-treatment relapse between Arms A and B and between Arms C and D 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 arm.

Treatment effects will be evaluated based on a 2-sided significance level (α= 0.050, rounded to three decimal places), and all efficacy analyses will be performed on the mITT population, unless otherwise specified.

Sensitivity analyses will be performed that summarize the difference, and provide 95% Wilson's score confidence intervals of the percentage of subjects in the ITT, mITT-GT and mITT-GT-VF populations achieving SVR12 between Arm A and Arm B in non-cirrhotic subjects, and between Arm C and Arm D in cirrhotic subjects, as applicable.

The following sensitivity analyses will assess difference in SVR12 rates between treatment arms or treatment durations.

- Differences in proportions of subjects achieving SVR12 will be computed between Arms A and B and Arms C and D using contrasts within a logistic regression model. Treatment arm and HCV genotype 1 subtype as contrast factor; baseline $\log_{10}$ HCV RNA level will be included in the model as a continuous covariate. Contrast and parameter estimates will also be reported for each arm pair (A/B or C/D)
- The difference in SVR12 rates between Arms A and B and Arms C and D will be determined using a stratum-adjusted Mantel-Haenszel (MH) proportion

with a continuity correction for variance, adjusting for each of the randomization stratum.

- The difference in proportions of SVR12 rates will be determined for 12-week vs. 16-week treatment durations using contrasts within a logistic regression model with cirrhosis status and HCV genotype 1 subtype (e.g., 1b, non-1b) as factors. Contrast and parameter estimates will also be reported.

The SVR12 rates and accompanying 95% Wilsons' score method confidence intervals) in the EP-RS-GT and EP-RS-GT-VF populations overall will also be calculated,

10.5 Efficacy 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 (1b or non-1b);
- Treatment duration (12-week or 16-week)
- Most recent HCV treatment history (i.e., specific NS5A inhibitor with SOF combination);
- Time from end of prior NS5A inhibitor +SOF combination treatment to start of main study treatment with G/P (e.g., <365 days and >365 days).
- Sex (male or female);
- Age (< 65 or ≥ 65 years; < 75 or ≥ 75 years);
- Race (White, Black/African-American, Asian, or other) and (black or non-black);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);

- BMI (< 30 or ≥ 30 kg/m^2);
- Baseline HCV RNA level (< 1,000,000 or ≥ 1,000,000 IU/mL);
- Baseline platelet count (< 100 or ≥ 100 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline APRI (< 1.0 or ≥ 1.0);
- Baseline FIB-4 (< 1.45, ≥ 1.45 to ≤ 3.25, or > 3.25);
- Baseline AST/ALT ratio (< 1.0 or ≥ 1.0);
- Baseline Child-Pugh Score (A/B; for cirrhotic subjects only);
- History of concomitant diseases: (a) diabetes (yes/no), (b) HIV co-infection (yes/no) (c) post-organ transplant by transplanted organ (yes/no) HCC(yes/no);
- Concomitant use of Proton Pump inhibitors (yes/no);
- DAA compliance (yes/no);
- 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]).

Within each subgroup, the percentage of subjects meeting SVR12 within each arm and the difference between treatment arms will be calculated, as will the corresponding two-sided 95% Wilson score intervals. Also within each subgroup, the percentage of subjects meeting SVR12 within combined Arm A+ArmC and ArmB+ArmD will be calculated, as will the corresponding two-sided 95% Wilson score intervals. A test of homogeneity will be conducted (Zelen's exact test) to evaluate whether differences between treatment arms (Arm A vs. Arm B, and Arm C vs. Arm D, separately) are consistent across subgroups. Tests will be conducted at the nominal 0.05 level. The 2-sided 95% Wilson

score confidence intervals will be produced if there are at least 10 subjects in each subgroup.

For the subgroup analyses, the presence of baseline resistance-associated polymorphisms is defined in Section 7.1; this subgroup analysis will be conducted on the mITT and mITT-GT-VF populations. All other subgroup analysis will be conducted on the mITT population.

Subgroup analysis will also be performed on relevant combinations of subgroup variables if deemed clinically meaningful.

Extending the results of the univariate subgroup analyses, a stepwise logistic regression model will be used to explore the associations between each of the subgroup variables, actual treatment arm and SVR12 by fitting a logistic regression model on all subjects in the mITT-GT-VF population. Among all candidate predictors, continuous measurements will be used where possible (e.g., continuous baseline $\log_{10}$ HCV RNA level, continuous age, continuous BMI) in the logistic regression model. For the variables on presence of baseline resistance-associated variants, only the unique variables (NS3 only vs. NS5A only vs. both NS3 and NS5A vs. none) will be used in the logistic regression model. A stepwise logistic regression approach will be used to assess the strength of each subgroup variable in predicting SVR12, with a significance level of 0.10 to enter and remain in the model.

A similar analysis will be conducted among the subjects in the mITT-GT-VF population with GT1a.

Finally, logistic regression models will be used to explore the associations of baseline RAPs in NS5A using the Key Subset of amino acid positions (Appendix 1) among the subjects in the mITT-GT-VF population with GT1a. First, a univariate logistic regression will explore whether the number of linked baseline NS5A RAPs (0, 1, 2, 3, or more than 3) is associated with SVR12. Secondly the association of any RAP in NS5A at each of the amino acids positions in the Key Subset (Appendix 1) with SVR12 will be explored using a stepwise logistic regression approach with a significance level of 0.10 to enter and remain in the model.

10.6 Additional Efficacy Analyses

The following additional efficacy endpoints will be summarized by treatment arm for the mITT population or for the EP-RS population overall, 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 SVR4;
- The percentage of EP-RS subjects achieving SVR12.
- The percentage of EP-RS subjects with on-treatment virologic failure or with post-treatment relapse.

In the above analyses for SVR, the percentages of subjects and two-sided 95% Wilson score intervals will be summarized. A summary of reasons for SVR non-response will also be provided.

10.7 Resistance Analyses

Except for the summary of baseline resistance associated polymorphisms and subgroup analysis of SVR12, the resistance analyses will be performed for all subjects in the mITT population and the EP-RS populations separately per attached Resistance Analysis Plan (Appendix 1). In the EP-RS population, presence of polymorphisms in NS3 and NS5A will be reassessed prior to treatment with G/P + SOF ± RBV in the Re-Treatment Sub-Study.

11.0 Safety Analysis

11.1 General Considerations

Safety data will be summarized for each treatment arm using safety population (as defined in section 5.1.4); all AE related analyses are for the safety population of the Main Study unless otherwise specified; all laboratory data related analyses are for the safety population of the Main Study unless otherwise specified. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Organ Class (SOC) and preferred term. The actual version of the MedDRA coding dictionary will be noted in the clinical study report.

11.2 Analysis of Adverse Events

11.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events are defined as any adverse event (AE) with an onset date that is on or after the first dose of study drug and no more than 30 days after the last dose of study drug. If an incomplete onset date was recorded for an adverse event, the event will be assumed to be treatment-emergent, unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

11.2.2 Tabulations of Treatment-Emergent Adverse Events

The number and percentage of subjects with treatment-emergent adverse events will be tabulated by treatment arm and overall for the Main Study and overall for the Retreatment Substudy by primary MedDRA System Organ Class (SOC) and preferred term (PT). The system organ classes will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each system organ class. 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 (most severe/highest grade incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one AE will be counted only once in the overall total.

Adverse Event Overview

A tabulation of adverse events (AE) will be presented by treatment arm and overall for the Main Study and for the single Re-Treatment Sub-Study arm, and will consist of the

number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE;
- Treatment-emergent AEs with a "reasonable possibility" of being related to DAA (G/P);
- Severe Treatment-emergent AEs;
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAA (G/P);
- Treatment-emergent AEs leading to discontinuation of study drug;
- DAA-related treatment-emergent AEs leading to discontinuation of study drug;
- Treatment-emergent Severe AEs with a "reasonable possibility" of being related to DAA (G/P);
- Serious treatment-emergent AEs leading to discontinuation of study drug;
- Treatment-emergent AEs leading to interruption of study drug;
- Treatment-emergent AEs leading to death;
- Deaths.

Adverse Events by SOC and Preferred Term (MedDRA)

The following summaries of AEs by SOC and Preferred Term will be generated by treatment arm and overall:

- Treatment-emergent adverse events (for the Main Study and the Retreatment substudy);
- Treatment-emergent adverse events occurring in 5% or more of Safety population in any of the Arms (for the Main Study and the Retreatment substudy);

- Treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs (G/P) (for the Main study, and broken down by relationship to G/P or, SOF, or Ribavirin in the Re-treatment Sub-study as applicable);
- Serious treatment-emergent adverse events;
- Serious treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs (G/P);
- Severe treatment-emergent adverse events;
- Treatment-emergent adverse events leading to discontinuation of study drug;
- DAA-related treatment-emergent adverse events leading to discontinuation of study drug;
- Treatment-emergent severe adverse events with a "reasonable possibility" of being related to DAAs (G/P);
- Serious treatment-emergent adverse events leading to discontinuation of study drug;
- Treatment-emergent adverse events leading to interruption of study drug;
- Treatment-emergent adverse events leading to death.

A listing of treatment-emergent adverse events grouped by body system and preferred term with subject numbers will be created by treatment arm for the Main Study and for the single Retreatment Substudy arm.

Adverse Events by Preferred Term

The number and percentage of subjects experiencing treatment-emergent adverse events by treatment arm and overall in the Main study will be tabulated according to Preferred Term and sorted by overall frequency for the total number of subjects overall. Similar summaries will be provided for Severe treatment-emergent adverse events, DAA related treatment-emergent adverse events, DAA related treatment-emergent serious adverse event, and DAA-related Severe treatment-emergent adverse events.

Adverse Events by Maximum Severity Grade Level

Treatment-emergent adverse events and DAA-related treatment-emergent adverse events will be summarized by maximum severity level of each preferred term by treatment arm and overall in the Main study. Each adverse event will be assigned a Severity level (grade 1, 2, 3, 4, or 5) by the investigator. If a subject has an AE with unknown severity, then the subject will be counted in the severity level category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same AE with the highest grade level (Severe). In this case, the subject will be counted under the "Severe" category.

Adverse Event by Maximum Relationship

Treatment-emergent adverse events also will be summarized by maximum relationship of each preferred term to study drug (DAA), as assessed by the investigator, by treatment arm and overall in the Main study. If a subject has an adverse event with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same adverse event with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.

11.2.3 Listing of Adverse Events

The following listings of adverse events will be prepared:

- All serious adverse events (from the time the subject signed the study-specific informed consent through the end of the study),
- Treatment-emergent serious adverse events,

- Treatment-emergent adverse events leading to death,
- Treatment-emergent adverse events leading to discontinuation of study drug,
- Treatment-emergent adverse events leading to study drug interruption.

11.3 Analysis of Laboratory Data

Data collected from the central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses. Clinical laboratory tests will be summarized at each visit by treatment arm and overall in the Main study. 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 and Final Post 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 and overall for the Main Study as well as for the single Re-Treatment Sub-Study arm.

Baseline results falling on Day 1 must also be attributable to specimens collected prior to the first dose, if determinable. In all cases, this same baseline value will be used for Change to Treatment Period and Change to Post-Treatment Period visits.

Mean changes from baseline to each post-baseline visit, including applicable post treatment visits, will be summarized for each treatment arm. Each protocol-specified laboratory parameter will be summarized with the sample size, baseline mean, visit mean, change from baseline mean, standard deviation, minimum, median, and maximum.

11.3.1 Variables and Criteria Defining Abnormality

Hematology variables include: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, basophils, eosinophils, platelet count, prothrombin time (PT), and international normalized ratio (INR).

Chemistry variables include: blood urea nitrogen (BUN), creatinine, total bilirubin, direct and indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, sodium, potassium, calcium, phosphorus, uric acid, cholesterol, total protein, glucose, albumin, chloride, bicarbonate, and estimated glomerular filtration rate (eGFR) calculated using the modification of diet in renal disease (MDRD) equation defined below.

Some of the above laboratory variables are calculated by the laboratory vendor including indirect bilirubin, and eGFR by MDRD. The central lab calculates eGFR by MDRD using the following equation, where serum creatinine is measured in mg/dL and age is measured in years:

GFR (mL/min/1.73 m^2) = 175 × (Serum Creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × 1.212 (if Black) × 0.742 (if Female).

11.3.2 Statistical Methods

The laboratory parameters defined in Table 6 will be assigned a toxicity grade of 1, 2, 3, or 4. The number and percentage of subjects with a maximum toxicity grade of 1, 2, 3 or 4 will be summarized for each treatment arm. The post-baseline value must be in a toxicity grade that is more extreme than the toxicity grade corresponding to the baseline value to be counted. The summary will also include the number and percentage of subjects with a maximum of at least Grade 3 for all laboratory parameters in Table 6. A

listing of all relevant laboratory parameters will be provided for each subject who had an increase to Grade 2 or higher for all laboratory variables in Table 6.

Table 6. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values

Test	Grade 1	Grade 2	Grade 3	Grade 4
ALT/SGPT	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
AST/SGOT	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Alkaline Phosphatase	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Total Bilirubin	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 10 × ULN	> 10 × ULN
Hemoglobin	< LLN – 100 g/L	< 100 – 80 g/L	< 80 g/L	--
White blood cells	< LLN – 3.0 × 10^9/L	< 3.0 – 2.0 × 10^9/L	< 2.0 – 1.0 × 10^9/L	< 1.0 × 10^9/L
Absolute Neutrophil Count	< LLN – 1.5 × 10^9/L	< 1.5 – 1.0 × 10^9/L	< 1.0 – 0.5 × 10^9/L	< 0.5 × 10^9/L
Platelet count	< LLN – 75.0 × 10^9/L	< 75.0 – 50.0 × 10^9/L	< 50.0 – 25.0 × 10^9/L	< 25.0 × 10^9/L
INR	> 1 – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN	--
Glucose (increased)	> ULN – 8.9 mmol/L	> 8.9 – 13.9 mmol/L	> 13.9 – 27.8 mmol/L	> 27.8 mmol/L
Glucose (decreased)	< LLN – 3.0 mmol/L	< 3.0 – 2.2 mmol/L	< 2.2 – 1.7 mmol/L	< 1.7 mmol/L
Creatinine	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 6 × ULN	> 6 × ULN
eGFR	< LLN – 60 mL/min	< 60 – 30 mL/min	< 30 – 15 mL/min	< 15 mL/min
Cholesterol	> ULN – 7.75 mmol/L	> 7.75 – 10.34 mmol/L	> 10.34 – 12.92 mmol/L	> 12.92 mmol/L
Albumin	< LLN – 30 g/L	< 30 – 20 g/L	< 20 g/L	--

Assessment of Hepatotoxicity

The number and percentage of subjects in each treatment arm and overall in the Main Study and overall in the Retreatment Sub-Study with maximum on-treatment lab values meeting the following criteria will be summarized:

- ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN;
- ALT ≥ 3 × ULN and total bilirubin < 2 × ULN;

- ALT > 5 × ULN and total bilirubin < 2 × ULN;
- ALT < 3 × ULN and total bilirubin ≥ 2 × ULN.

The maximum ratio relative to the ULN will be used to determine if subjects meet the criteria listed above. The ALT and total bilirubin values do not need to be concurrent in order to meet the defined criteria. For ALT, the post-baseline value must represent an increase from the first nadir (including baseline) to be counted. First nadir is defined as the last value prior to the first increase. For total bilirubin, a subject will be counted if the post-baseline laboratory value meets the above criteria regardless of the baseline laboratory value (i.e., the post-baseline laboratory value does not need to be worse than the baseline laboratory value).

A listing of all ALT, AST, total, indirect and direct bilirubin, ratio of direct to total bilirubin, and alkaline phosphatase values will be provided for each subject who met any of the criteria defined above. The listings will be reviewed to assess bilirubin (e.g., mixed or direct predominance) and temporal relationships for subjects with ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN.

The number and percentage of subjects with post-baseline values during the Treatment Period meeting the following criteria will be summarized:

- ALT > 5 × ULN and ≥ 2 × baseline;
- AST > 5 × ULN and ≥ 2 × baseline;
- Total bilirubin ≥ 2.0 × ULN and > baseline.

As noted above, a post-baseline value must be more extreme than the baseline value to be considered. A separate listing will be provided that presents all lab values for the subjects meeting any of these criteria during treatment.

12.0 References

1. (Study protocol)

Appendix 1. Resistance analysis plan (Version Date: July 10, 2017)

1. Main Study Patient Cohort (NS5A + SOF experienced): 4 arms, GT1a and GT1b
    a. G/P x 12 wks, non-cirrhotic
    b. G/P x 16 wks, non-cirrhotic
    c. G/P + RBV x 12 wks, compensated cirrhosis
    d. G/P x 16 wks, compensated cirrhosis
2. Samples for resistance analysis
    a. Baseline samples for all patients
    b. Earliest time point at treatment failure (and sequential samples, if available) from patients who failed G/P treatment
    c. In the ITT-RS population, presence of polymorphisms in NS3 and NS5A will be reassessed prior to treatment with G/P + SOF ± RBV in the Re-Treatment Sub-Study.
3. Signature Amino Acid Positions and the Key Subset of Amino Acid Positions (provided by AbbVie)

Genotype, Target	Signature Amino Acid Positions	Key Subset of Amino Acid Positions
GT1, NS3	36, 43 (GT1a only), 54, 55, 56, 80, 155, 156, 168	155, 156, 168
GT1, NS5A	24, 28, 29, 30, 31, 32, 58, 62, 92, 93	24, 28, 30, 31, 58, 92, 93

4. Methods: Quantitative resistance analysis and mutation linkage – methods of Liu et al. 2016 (PMID 26645605)
    a. Primer-ID approach
        i. Advantages
            1. More accurate quantification of proportion of RASs
            2. Improved sensitivity and specificity
    b. Illumina paired-end sequencing, consensus clustering, bioinformatics analysis
    c. Reference sequence: H77 or CON-1
    d. Query each AA position (list provided by AbbVie)
        i. Signature AA positions
        ii. Key subset of AA positions
    e. Raw data output
        i. For each AA position, polymorphism relative to the reference sequence (and for treatment failures, baseline sequence) and read abundance (after consensus clustering) will be reported

5. Analysis plan for baseline RAPs (separately for mITT population or EP-RS population)

    a. Primary analysis

        i. Initial filtering

            1. 2% threshold -> generate a table of all RAPs present at >=2%

            2. 15% threshold -> generate a table of all RAPs present at >=15%

        ii. Analysis output (will be done for both 2% and 15% cutoff)

            1. List of patients with RAPs, including specific substitutions and % reads

            2. Prevalence of specific RAPs in all patients at baseline, stratified by treatment arms and GT1a vs GT1b

            3. Proportion of patients with no NS3 or NS5A RAP, NS3 RAP only, NS5A RAP only, and both NS3 and NS5A RAPs

                a. Will generate separate reports for “any signature AA position” and for “key subset of AA position”

    b. Exploratory analysis

        i. Initial filtering

1. 1% filter to remove potential/equivocal erroneous resistance calls due to technical artifacts from amplification/sequencing

ii. Analysis output (reads >=1% will be reported as % abundance)

1. Linkage of RASs within each target

a. Example A

i. Data

1. Q30H (4.7%)/Q30N (83%)/Q30S(12%)

2. Y93H (100%)

ii. Linkage analysis will be reported as

1. Q30H/Y93H (4.7)

2. Q30N/Y93H (83%)

3. Q30S/Y93H (12%)

b. Example B

i. Data

1. R30Q (72%)

2. Y93H (68%)

ii. Linkage analysis based on sequence analysis

1. Y93H (2.7%)
2. R30Q (6%)
3. R30Q/Y93H (65%)

2. Linkage of RASs between targets (NS3 and NS5A)
    a. Our current methods cannot definitively demonstrate linkage by analysis of sequence reads (NS3 and NS5A are in two different amplicons), and thus, if possible, will infer linkage based on % reads
    b. Example
        i. Data
            1. NS3 R155K (8%)
            2. NS5A Y93H (99%)
        ii. Linkage analysis
            1. NS3 R155K/NS5A Y93H (~8%)

6. Analysis plan for impact of baseline RASs on G/P efficacy (SVR12; mITT-GT-VF population or EP-RS-GT-VF population)
    a. Filtering of dataset
        i. Apply 2% and 15% threshold to define presence/absence of each RAP

ii. Four separate "baseline RAP datasets" will be generated, using the following filters:

1. 2% threshold, including signature RAPs
2. 2% threshold, including key RAPs only
3. 15% threshold, including signature RAPs
4. 15% threshold, including key RAPs only

b. Primary analysis

i. mITT-GT-VF analysis: 1) population, stratified by treatment arms (x4) and GT1 subtype (x2); 2) population, stratified by treatment duration (x2) and GT1 subtype (x2)

ii. For each of the four "baseline RAP datasets" (above), will perform the following comparisons with respective to SVR12, using Fisher's Exact Test

1. Patients with and without NS3 only baseline RAPs
2. Patients with and without NS5A only baseline RAPs
3. Patients with and without both NS3 and NS5A baseline RAPs

iii. For each NS3 and NS5A "Signature RAP", defined by 2% and 15% threshold, will perform the following comparisons with respective to SVR12

1. Patients with and without specific "Signature RAP"

2. Patients with only 1 and with >1 NS5A "Signature RAP"

c. Exploratory analysis

i. Depending on the number of treatment failures, will use their baseline and treatment failure RAP dataset to guide the selection of RAP linkage and abundance for further analysis

7. Analysis plan for patients with treatment failure (separately for mITT population or EP-RS population)

a. Data

i. For each signature position

1. Presence/absence of RAP (according to 2% and 15% threshold)

2. Changes in the read abundance of RAP (based on % reads)

3. Characterize RAP linkage, if any

ii. "Treatment emerging RAP" will be defined as

1. Absent at baseline, present at treatment failure (2%, 15% threshold)

2. Present at both baseline and treatment failure (2%, 15% threshold), but % read increase by >=20%

b. Primary analysis

i. List of patients with RAPs including specific substitutions and % reads

ii. Comparison of baseline vs treatment failure samples (as well as all subsequent samples, if available) will be performed for each Signature position

iii. Phylogenetic analysis of NS3 and NS5A sequences to exclude re-infection

c. Exploratory analysis

i. Examine and compare AA changes in all positions between baseline vs treatment failure with respective to changes in AA and read abundance