Statistical Analysis Plan for Study M20-350

A Multicenter, Single-Arm Prospective Study to Evaluate Safety and Efficacy of GLE/PIB 8-Week Treatment in Adults and Adolescents with Acute Hepatitis C Virus (HCV) Infection

Date: 12 August 2024

Version 4.0

Table of Contents

List of Tables

List of Figures

List of Appendices

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for glecaprevir (GLE)/pibrentasvir (PIB) Study M20-350, "A Multicenter, Single-Arm Prospective Study to Evaluate Safety and Efficacy of GLE/PIB 8-Week Treatment in Adults and Adolescents with Acute Hepatitis C Virus (HCV) Infection."

Study M20-350 examines the efficacy and safety of GLE/PIB in adults and adolescents with confirmed acute HCV infection.

This SAP provides details to further elaborate the statistical methods outlined in Clinical Study Protocol M20-350. The SAP will not be updated in case of future administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

This SAP includes changes to analyses described in the protocol. Details are outlined in Section 13.0.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses, and Estimands

The primary objective is to demonstrate the efficacy of 8-week treatment with GLE/PIB in adults and adolescents with confirmed acute HCV infection by comparing the sustained virologic response 12 weeks post-treatment (SVR_{12}) rate from this study to the historical SVR_{12} rate in subjects with chronic HCV infection who were treated with GLE/PIB. The primary efficacy objective will be assessed based on the intention-to-treat (ITT) population which is defined as all enrolled subjects who received at least 1 dose of study treatment.

The primary hypothesis is that 8-week treatment with GLE/PIB in the ITT population is superior to the efficacy threshold (described in Section 2.4) based on the historical

ITT SVR_{12} rates of treatment with GLE/PIB in subjects with chronic HCV infection.[1] This will be shown if the lower bound of the two-sided 95% confidence interval (CI; using Wilson's score method[2]) for the percentage of subjects in the ITT population achieving SVR_{12} is greater than the efficacy threshold.

The estimand corresponding to the primary efficacy objective is the percentage of acutely infected HCV subjects assigned 8 weeks of GLE/PIB in the ITT population who achieve SVR_{12}. Subjects who discontinue the study with an unknown SVR_{12} status will be counted as a failure for SVR_{12}.

The key secondary objective is the same as the primary objective except that the key secondary objective will be assessed in the modified ITT virologic failure (mITT-VF) population. The mITT-VF population is defined as all enrolled subjects who received at least one dose of study treatment, excluding those who did not achieve SVR_{12} for reasons other than virologic failure (i.e., those with HCV reinfection, those who did not achieve SVR_{12} due to early premature discontinuation of study treatment, and those who were missing HCV RNA data in the SVR_{12} window after backward imputation).

The key secondary hypothesis is that 8-week treatment with GLE/PIB for subjects in the mITT-VF population is superior to an efficacy threshold (described in Section 2.4) based on the historical mITT-VF SVR_{12} rates of treatment with GLE/PIB in the chronically infected HCV population.[1] This will be shown if the lower bound of the two-sided 95% CI (using Wilson's score method[2]) for the percentage of subjects in the mITT-VF population achieving SVR_{12} is greater than the efficacy threshold.

The estimand corresponding to the key secondary efficacy objective is the percentage of acutely infected HCV subjects assigned 8 weeks of GLE/PIB in the mITT-VF population (i.e., excluding those in the ITT population who did not achieve SVR_{12} for reasons other than virologic failure) who achieve SVR_{12}.

The other secondary objectives of this study are to determine the on-treatment virologic failure (OTVF), post-treatment relapse, and post-treatment reinfection rates in the ITT population.

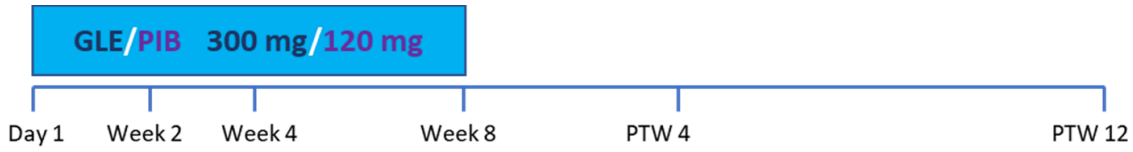
The safety objectives of this study are to examine the safety with respect to alanine aminotransferase (ALT) elevations, adverse events (AEs) leading to study treatment discontinuation, serious AEs (SAEs), and AEs of hepatic decompensation during an 8-week treatment with GLE/PIB in adults and adolescents with confirmed acute HCV infection in the Safety Analysis Set (defined as all subjects who received at least 1 dose of study treatment).

2.2 Study Design Overview

This study will be conducted as a Phase 3b, multicenter, single-arm, prospective study to evaluate the safety and efficacy of GLE/PIB 8-week treatment in adult and adolescent subjects with acute HCV infection.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



GLE glecaprevir; PIB pibrentasvir; PTW post treatment week

2.3 Treatment Assignment and Blinding

All subjects will be assigned to receive 8 weeks of treatment with GLE/PIB.

2.4 Choice of Control Group

An integrated analysis of Phase 2 and Phase 3 studies of GLE/PIB in chronically HCV-infected adults and adolescents who were self-reported as people who inject drugs (PWID) currently or recently (referred to hereafter as PWID) versus those who self-reported as formally or never injecting drugs (referred to hereafter as non-PWID) was performed, and results of the analysis are presented in the Mavyret US Prescribing Information 2020, Section 14.9.[1] This analysis will provide the historical efficacy control for the current trial. The threshold for comparison for the primary efficacy hypothesis will be derived from a weighted average of the ITT SVR_{12} rates in the PWID and non-PWID chronically infected populations of subjects. In the Phase 2 and Phase 3 studies, the overall SVR_{12} rate was 88.7% (55/62) in PWID subjects in the ITT population, with a virologic failure rate of 1.6% (1/62); the overall SVR_{12} rate was 97.8% (4147/4241) in non-PWID subjects in the ITT population, with a virologic failure rate of 1.2% (50/4241). Excluding subjects who failed to achieve SVR_{12} due to reasons other than virologic failure yields SVR_{12} rates of 98.2% (55/56) for PWID subjects and 98.8% (4147/4197) for non-PWID subjects, for the mITT-VF population. The observed SVR_{12} rates from subjects with chronic HCV infection (ITT and mITT-VF populations) will be used as historical controls to provide comparators for assessment of GLE/PIB in subjects with acute HCV. A threshold for each of the primary and key secondary efficacy analyses of the 8-week GLE/PIB regimen in acute HCV to the historical control is determined by subtracting a margin of 6% from the weighted average of the PWID and non-PWID historical SVR_{12} rates. A margin of 6% was selected to ensure a minimal loss of efficacy of the 8-week GLE/PIB regimen in acute HCV relative to the historical SVR_{12} rate in subjects with chronic HCV. Details for calculating the efficacy thresholds are provided in Section 2.5.

2.5 Sample Size Determination

The threshold for comparison for the primary efficacy estimand will be derived from a weighted average of the ITT SVR_{12} rates in the PWID and non-PWID chronically infected populations of subjects who received GLE/PIB in Phase 2 and 3 trials. As presented in the

Mavyret US Prescribing Information 2020, Section 14.9,[1] the ITT SVR_{12} rate among chronically infected HCV PWID (current/recent PWID) is 88.7% and is 97.8% among chronic non-PWID (former/non-PWID). The threshold for comparison will be calculated by (proportion of PWID in the ITT population of this study × 88.7%) + (proportion of non-PWID in the ITT population of this study × 97.8%) minus a margin of 6%. Therefore, the threshold would be 82.7% if all subjects in the ITT population of this study are PWID, and it would be 91.8% if all subjects in the ITT population of this study are non-PWID. Similarly, the threshold for the comparison of the key secondary estimand will be derived from a weighted average of the mITT-VF SVR_{12} rates in the PWID and non-PWID chronically infected populations. The mITT-VF SVR_{12} rate among chronically infected HCV PWID is 98.2% and is 98.8% among chronic non-PWID. The threshold for comparison will be calculated by (proportion of PWID in the mITT-VF population of this study × 98.2%) + (proportion of non-PWID in the mITT-VF population of this study × 98.8%) minus a margin of 6%. It follows that the threshold would be 92.2% if all subjects in the mITT-VF population of this study are PWID, and it would be 92.8% if all subjects in the mITT-VF population of this study are non-PWID.

It is planned to enroll approximately 283 subjects. Assuming all of the subjects in the ITT population of this study are PWID, 283 subjects will provide 80% power to show that an 88.7% SVR_{12} rate among acutely infected HCV subjects in the ITT population is superior to a threshold of 82.7% based on the historical ITT SVR_{12} rate among chronically infected HCV subjects, using a two-sided 95% CI. Assuming all of the subjects in the ITT population of this study are non-PWID, 283 subjects will provide greater than 95% power to show that a 97.8% SVR_{12} rate among acutely infected HCV subjects in the ITT population is superior to a threshold of 91.8% based on the historical ITT SVR_{12} rate among chronically infected HCV subjects, using a two-sided 95% CI.

Assuming that approximately 10% of the ITT subjects will not be included in the mITT-VF population and that all of the subjects in the mITT-VF population of this study are PWID, a total of 255 subjects will provide greater than 95% power to show that a 98.2% SVR_{12} rate among acutely infected HCV subjects in the mITT-VF population is

superior to a threshold of 92.2% based on the historical mITT-VF SVR_{12} rate among chronically infected HCV subjects using a two-sided 95% CI. Assuming all of the subjects in the mITT-VF population of this study are non-PWID, 255 subjects will provide greater than 95% power to show that a 98.8% SVR_{12} rate among acutely infected HCV subjects in the mITT-VF population is superior to a threshold of 92.8% based on the historical mITT-VF SVR_{12} rate among chronically infected HCV subjects, using a two-sided 95% CI.

Note that for calculation of the efficacy thresholds, PWID is defined as current/recent PWID, and non-PWID is defined as former/non-PWID; see SAP Section 7.1 for the PWID definitions.

Additionally, the proposed sample size of 283 will provide greater than 94% probability to detect any toxicity that has a true incidence rate of at least 1% in subjects with acute HCV infection. Table 1 shows the probability that a given AE or laboratory toxicity would be observed with a sample size of 283 subjects in the Safety Analysis Set.

Table 1. Sample Size Justification Based on Probability of Observing Any Toxicity

True Toxicity Rate	Sample Size	Probability of at Least 1 Subject with Toxicity
0.5%	283	75.8%
1%	283	94.2%
2%	283	99.7%
3%	283	100%

3.0 Endpoints

3.1 Primary Endpoint

The primary endpoint is the achievement of SVR_{12} (defined as HCV RNA < the lower limit of quantification [LLOQ] 12 weeks after the last actual dose of study treatment) for each subject in the ITT population.

3.2 Secondary Endpoints

Key Secondary Endpoint

The key secondary endpoint is the achievement of SVR_{12} for each subject in the mITT-VF population.

Supportive Secondary Endpoints

- On-treatment virologic failure (defined as confirmed increase of > 1 log10 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 [EOT] with at least 6 weeks of treatment) for each subject in the ITT population;
- Post-treatment relapse ($Relapse_{12}$: defined as confirmed HCV RNA ≥ LLOQ between EOT and 12 weeks after the last dose of study treatment [up to and including the SVR_{12} assessment time point], excluding cases of reinfection) for each subject in the ITT population who completed treatment as planned (defined as study treatment duration ≥ 52 days) with the HCV RNA < LLOQ at EOT and with at least 1 post-treatment HCV RNA value;
- Post-treatment reinfection with HCV (defined as confirmed HCV RNA ≥ LLOQ in the Post-Treatment Period along with the post-treatment detection of a different HCV genotype, subtype, or clade compared with baseline) for each subject in the ITT population.

3.3 Additional Efficacy Endpoints

Additional efficacy endpoints are described in Section 9.5.

3.4 Safety Endpoints

- ALT elevations of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade 1, 2, 3, or 4 during the Treatment Period with ALT grade increased from baseline for each subject in the Safety Analysis Set;

- Post-nadir ALT elevation > 3 × upper limit of normal (ULN) with total bilirubin > 2 × ULN during the Treatment Period for each subject in the Safety Analysis Set;
- Treatment-emergent hepatic decompensation/hepatic failure events for each subject in the Safety Analysis Set;
- Treatment-emergent AEs leading to discontinuation of study treatment for each subject in the Safety Analysis Set;
- Treatment-emergent SAEs for each subject in the Safety Analysis Set.

These endpoints, along with additional safety endpoints based on AEs, laboratory data, and vital signs are included in Section 10.2, Section 10.3, and Section 10.4, respectively.

4.0 Analysis Populations

The following population sets will be used for the analyses.

The ITT population is defined as all enrolled subjects who received at least 1 dose of study treatment. The ITT population will be used for the primary efficacy analysis and other secondary efficacy analyses.

The mITT-VF population is defined as all enrolled subjects who received at least 1 dose of study treatment, excluding those who did not achieve SVR_{12} for reasons other than virologic failure (i.e., those with HCV reinfection, those who did not achieve SVR_{12} due to early premature discontinuation of study treatment, and those who were missing HCV RNA data in the SVR_{12} window after backward imputation). The mITT-VF population will be used for the key secondary efficacy analysis.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study treatment.

5.0 Subject Disposition

The number and percentage of subjects who failed to enroll in the study (i.e., failed to receive at least 1 dose of study treatment) for any reason and for each reason, will be summarized for the set of all subjects who failed to enroll.

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be tabulated overall and by investigator:

- Subjects enrolled/treated (i.e., received at least 1 dose of study treatment) in the study;
- Subjects who completed study treatment;
- Subjects who prematurely discontinued study treatment;
- Subjects who completed the study;
- Subjects who prematurely discontinued from the study;
- Subjects in each analysis population (ITT, mITT-VF, and Safety Analysis Set).

The number and percentage of subjects in the Safety Analysis Set who discontinued study treatment will be summarized by primary reason (per eCRF). A similar summary will be provided for discontinuations from the study. The number and percentage of subjects in the Safety Analysis Set with reported study treatment interruptions will be summarized.

Protocol deviations as described in Appendix A will be summarized for the Safety Analysis Set by the number and percentage of subjects in each category and in at least one category, including a list of subject numbers for each category.

6.0 Study Treatment Duration and Compliance

The duration of study treatment will be summarized for the Safety Analysis Set. Duration of treatment is defined for each subject as the last study treatment dose date minus the first study treatment dose date plus 1 day.

Descriptive statistics (number of subjects, mean, standard deviation, median, Q1 and Q3 of inter-quartile range, minimum, and maximum) will be presented.

Treatment duration also will be summarized with frequencies and percentages using the following categories:

- 1 to 15 days, 16 to 35 days, 36 to 55 days, ≥ 56 days;
- < 52 days, ≥ 52 days.

Treatment compliance will be summarized for the ITT population. 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 treatment (GLE/PIB) during the Treatment Period will be calculated as the percentage of tablets taken relative to the total tablets expected to be taken. The total number of tablets expected to be taken will be equal to the total number of tablets that should have been taken per the protocol (i.e., 3 tablets per day) for the duration that the subject was in the Treatment Period (date of the last dose of study treatment date of first dose of study treatment + 1). Study treatment interruptions recorded on the eCRF will not be subtracted from the duration. If the number of tablets returned is not available for one or more of the bottles dispensed to a subject, then compliance will not be calculated for that subject.

A subject is considered to be compliant if the percentage is between 80% and 120%. Compliance will be calculated for each subject and summarized with the number of subjects, mean, standard deviation, median, Q1 and Q3 of inter-quartile range, minimum, and maximum. The percentage of compliant subjects will be summarized based on the data as observed.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline characteristics, medical history, and previous, concomitant and post-treatment medications will be summarized for the ITT population. Demographics and baseline characteristics will also be summarized for the mITT-VF population. Categorical

variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing/non-unknown observations. Continuous variables will be summarized with descriptive statistics (number of non-missing/non-unknown observations, mean and standard deviation, median, Q1 and Q3 of inter-quartile range, minimum, and maximum).

7.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the following groups: adolescents (age < 18 years), adults (age ≥ 18 years), and overall. Summaries of demographics and baseline characteristics will also be presented for the following groups: current/recent PWID subjects and former/non-PWID subjects using PWID Status Classification 1 (see definitions below), subjects with a history of opiate substitution therapy use that was ongoing at start of study treatment, and subjects with either no history of opiate substitution therapy use or a history of opiate substitution therapy use that was not ongoing at start of study treatment.

Continuous demographic variables include age, weight, height, and body mass index (BMI). Categorical demographic variables include sex (male or female), race (white, black/African-American, Asian, [further categorized as Japanese, Chinese, Korean, Taiwanese, or other Asian], American Indian/Alaska native, or native Hawaiian/other Pacific Islander; black or non-black), ethnicity (Hispanic/Latino or not Hispanic/Latino), age (< 18, 18 to < 40, 40 to < 65, 65 to < 75, ≥ 75 years; < 18 or ≥ 18 years; < 65 or ≥ 65 years; < 75 or ≥ 75 years), BMI (< 30 or ≥ 30 kg/m^2), country, geographic region (North America, Europe, or rest of world [ROW]), tobacco use (current, former, never, or unknown), and alcohol use (current, former, never, or unknown).

Continuous baseline characteristics include baseline log_{10} HCV RNA level, ALT, aspartate aminotransferase (AST), bilirubin (total, direct, and indirect), alkaline phosphatase, serum creatinine, creatinine clearance (Cockcroft-Gault calculation), estimated glomerular filtration rate (eGFR; modification of diet in renal disease [MDRD]

equation), platelet count, serum albumin, international normalized ratio (INR), homeostasis model of assessment insulin resistance (HOMA-IR), GGT, LDL, HDL, FibroTest score, FibroScan score, aspartate aminotransferase to platelet ratio index (APRI), Fibrosis-4 (FIB-4), CD4 (for HCV/HIV co-infected subjects), estimated acute HCV infection duration, and time since acute HCV infection diagnosis.

Categorical baseline characteristics include:

- HCV genotype (GT) (1, 2, 3, 4, 5, or 6) and available subtype (as determined by the central laboratory);
- HCV genotype (GT) (1, 2, 3, 4, 5, or 6) and available subtype (final HCV genotype and subtype as defined in Section 9.7);
- Cirrhosis status (cirrhotic, non-cirrhotic, or unknown test results indeterminate);
- Baseline Child-Pugh score (for cirrhotic subjects or subjects with cirrhosis status unknown; 5, 6, or > 6)
- Screening Child-Pugh score (for cirrhotic subjects or subjects with cirrhosis status unknown; 5, 6, or > 6)
- Baseline fibrosis stage (equivalent to Metavir F0 F1, F2, F3, or F4);
- Baseline HCV RNA level (< LLOQ or ≥ LLOQ; < 800,000 or ≥ 800,000 IU/mL; < 1,000,000 or ≥ 1,000,000 IU/mL);
- Baseline ALT (≤ ULN, > ULN to ≤ 3 × ULN, > 3 × ULN to ≤ 5 × ULN, > 5 × ULN to ≤ 10 × ULN, or > 10 × ULN);
- Baseline total bilirubin (< 34.2 or ≥ 34.2 µmol/L);
- Baseline creatinine clearance (< 60, ≥ 60 to < 90, or ≥ 90 mL/min);
- Baseline eGFR (< 90 or ≥ 90 mL/min/1.73 m^2);
- Baseline platelet count (< 100 or ≥ 100 × 10^9/L; < 150 or ≥ 150 × 10^9/L);
- Baseline serum albumin (< 35 or ≥ 35 g/L);
- Baseline APRI (≤ 1, > 1 to ≤ 2, or > 2);
- Baseline HOMA-IR (< 2 or ≥ 2 mU × mmol/L^2);
- Baseline FibroTest (< 0.75 or ≥ 0.75);

- Baseline FIB-4 (< 1.45, ≥ 1.45 to ≤ 3.25, or > 3.25);
- Baseline AST/ALT ratio (≤ 1 or > 1);
- Baseline HCV/HIV co-infection status (HCV mono-infected or HCV/HIV-1 co-infected);
- History of diabetes (yes or no);
- History of prior HCV infection (yes or no);
- History (i.e., started prior to start of study treatment) of non-prescribed illicit drug use (yes, ongoing as of the end of study participation; yes, last dose after last dose of study treatment; yes, last dose during study treatment period; yes, last dose less than 6 months prior to start of study treatment; yes, last dose 6 to 12 months prior to start of study treatment; yes, last dose more than 12 months prior to start of study treatment; yes, timing of last dose unknown; or no);
- History (i.e., started prior to start of study treatment) of non-prescribed illicit injection drug use (yes, ongoing as of the end of study participation; yes, last dose after last dose of study treatment; yes, last dose during study treatment period; yes, last dose less than 6 months prior to start of study treatment; yes, last dose 6 to 12 months prior to start of study treatment; yes, last dose more than 12 months prior to start of study treatment; yes, timing of last dose unknown; or no);
- PWID Status Classification 1 PWID classification defined with respect to study treatment start (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID)
    - Current/recent PWID defined with non-prescribed illicit injection drug use as:
        - yes, started prior to start of study treatment and ongoing as of end of study participation (Current);
        - yes, started prior to start of study treatment with last dose after last dose of study treatment (Current);
        - yes, started prior to start of study treatment with last dose during study treatment period (Current);
        - yes, started prior to start of study treatment with last dose less than 6 months prior to start of study treatment (Recent);

- yes, started prior to start of study treatment with last dose 6 to 12 months prior to start of study treatment (Recent).

○ Former/Non-PWID defined with non-prescribed illicit injection drug use as:

- yes, started prior to start of study treatment with last dose more than 12 months prior to start of study treatment (Former);
- yes, started prior to start of study treatment and timing of last dose unknown (Former);
- yes, started during study treatment period (Non-PWID);
- yes, started after last dose of study treatment (Non-PWID);
- no (Non-PWID).

- PWID Status Classification 2 PWID classification defined with respect to study treatment period (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID)
  - ○ Current/Recent PWID defined with non-prescribed illicit injection drug use as:
    - yes, started prior to start of study treatment and ongoing as of end of study participation (Current);
    - yes, started prior to start of study treatment with last dose after last dose of study treatment (Current);
    - yes, started prior to start of study treatment with last dose during study treatment period (Current);
    - yes, started prior to start of study treatment with last dose less than 6 months prior to start of study treatment (Recent);
    - yes, started prior to start of study treatment with last dose 6 to 12 months prior to start of study treatment (Recent);
    - yes, started during study treatment period (Current).
  - ○ Former/Non-PWID defined with non-prescribed illicit injection drug use as:
    - yes, started prior to start of study treatment with last dose more than 12 months prior to start of study treatment (Former);

- yes, started prior to start of study treatment and timing of last dose unknown (Former);
- yes, started after last dose of study treatment (Non-PWID);
- no (Non-PWID).

- PWID Status Classification 3 PWID classification defined with respect to study participation (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID)
  - Current/Recent PWID defined with non-prescribed illicit injection drug use as:
    - yes, started prior to start of study treatment and ongoing as of end of study participation (Current);
    - yes, started prior to start of study treatment with last dose after last dose of study treatment (Current);
    - yes, started prior to start of study treatment with last dose during study treatment period (Current);
    - yes, started prior to start of study treatment with last dose less than 6 months prior to start of study treatment (Recent);
    - yes, started prior to start of study treatment with last dose 6 to 12 months prior to start of study treatment (Recent);
    - yes, started during study treatment period (Current);
    - yes, started after last dose of study treatment (Current).
  - Former/Non-PWID defined with non-prescribed illicit injection drug use as:
    - yes, started prior to start of study treatment with last dose more than 12 months prior to start of study treatment (Former);
    - yes, started prior to start of study treatment and timing of last dose unknown (Former);
    - no (Non-PWID).

- History of opiate substitution therapy use (yes, ongoing at start of study treatment; yes, less than 6 months prior to start of study treatment; yes, 6 to 12 months prior to start of study treatment; yes, more than 12 months prior to start of study treatment; yes, timing of last dose unknown; or no);
- Acute HCV infection criteria met (a. yes, negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening; b. yes, negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 11-month period prior to Screening; AND risk behavior within 6 months prior to positive HCV RNA or HCV core antigen; c. yes, clinical signs and symptoms compatible with acute hepatitis (ALT > 5 × ULN and/or jaundice) in the absence of a history of chronic liver disease or other cause of acute hepatitis and positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening; AND risk behavior within 6 months prior to positive HCV RNA or HCV core antigen; d. yes, negative anti-HCV antibody with a positive HCV RNA or HCV core antigen within a 5-month period prior to Screening; or, e. no criteria met);
- Risk behavior for acute HCV infection (shared drug-injection equipment, shared non-injection drug use equipment, unprotected sexual activity with multiple partners, unprotected sexual activity with other male(s), risky tattoos or body piercings, shared personal items possibly contaminated with blood, healthcare worker with occupational exposure, or other behavior);
- Grouped risk behavior for acute HCV infection Grouping 1 (contaminated needle or IV drug use, contact with infected individual, occupational exposure, or other behavior);
- Grouped risk behavior for acute HCV infection Grouping 2 (drug use, sexual transmission, contact by contaminated objects, occupational, or other behavior);
- Estimated acute HCV infection duration (< 3 months, ≥ 3 months to < 6 months, or ≥ 6 months) across all and by each acute HCV infection criteria;
- Time since acute HCV infection diagnosis (< 3 months or ≥ 3 months);

- Baseline HIV-1 treatment status (for HCV/HIV co-infected subjects: HIV Treatment-Naïve or HIV-Treated);
- Baseline CD4+ T-cell count (for HCV/HIV co-infected subjects: < 200, 200 to < 350, 350 to < 500, or ≥ 500 cells/mm^3);
- Baseline plasma HIV-1 RNA (for HCV/HIV co-infected subjects: < 20 or ≥ 20 copies/mL).

Estimated acute HCV infection duration (days) is an estimate of how long a subject has been infected with HCV at the time of start of study treatment. The derivation differs slightly for each acute infection criteria category. Derivations used for this study were adapted from derivations used in the Matthews (2021)[3] and Martinello (2019)[4] articles. For each definition below, the most recent (i.e., closest to study treatment start date) negative HCV test of those specified and the earliest (i.e., furthest from study treatment start date) positive HCV test of those specified will be used.

a. For acute infection criteria (a), estimated infection start date is defined as the midpoint between the HCV negative test and HCV positive test.
b. For acute infection criteria (b), estimated infection start date is defined as the midpoint between the HCV negative test and HCV positive test.
c. For acute infection criteria (c), estimated infection start date is defined as 6 weeks (42 days) prior to the date of the HCV positive test.
d. For acute infection criteria (d), estimated infection start date is defined as 6 weeks (42 days) prior to the date of the HCV positive test.

The estimated duration of infection is defined as (study treatment start date estimated infection start date) + 1, in days.

Because a subject may qualify for more than one definition of acute HCV infection, the estimated infection duration will be determined using the following priority order for each subject: acute infection criteria (d), criteria (a), criteria (b), or criteria (c). For example, if a subject meets acute infection criteria (a) and (c), the estimated infection duration

associated with criteria (a) will be used. This prioritization will also be used to determine which acute HCV infection criteria each subject's estimated duration of infection is summarized under.

For categorization of the estimated infection duration, 1 month 31 days (e.g., 3 months is 93 days and 6 months is 186 days).

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class (SOC) and preferred term (PT)) will be summarized. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC. Subjects reporting more than one PT within a SOC will be counted only once for that SOC.

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 treatment (GLE/PIB). A concomitant medication is defined as any medication that started prior to the date of the first dose of study treatment and continued to be taken on or after the first dose of study treatment or any medication that started on or after the date of the first dose of study treatment, but not after the date of the last dose of study treatment. A post-treatment medication for the treatment of HCV is defined as any medication started on or after the date of last dose of study treatment with the indication entered as "Hepatitis C."

Prior medications will be divided into the following categories:

- HCV medications taken for the most recent prior HCV infection;
- Prior HIV medications taken by subjects with HCV/HIV co-infection at baseline;

- Non-prescribed illicit drugs overall and by injection or non-injection route and specific route within injection and non-injection routes;
- Opiate substitution therapy medications;
- All other prior medications.

Concomitant medications will be divided into the following categories:

- Concomitant HIV medications taken by subjects with HCV/HIV co-infection at baseline;
- Non-prescribed illicit drugs overall and by injection or non-injection route and specific route within injection and non-injection routes;
- Opiate substitution therapy medications;
- All other concomitant medications.

The number and percentage of subjects taking prior medications, concomitant medications, and post-treatment HCV medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary. Opiate substitution therapy and non-prescribed illicit drugs will be summarized as reported.

8.0 Handling of Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The primary efficacy endpoint of achievement of SVR_{12} will be analyzed based on the ITT population, and any subject who discontinues the study with an unknown SVR_{12} status (after applying backward imputation) will be counted as a failure for SVR_{12}. The key secondary efficacy endpoint of achievement of SVR_{12} will be analyzed based on the mITT-VF population, and intercurrent events will not have an effect on this analysis.

9.0 Efficacy Analyses

9.1 General Considerations

All tests and CIs will be two-sided at an alpha level of 0.05.

All efficacy analyses will be performed on the ITT population, unless otherwise specified.

Missing data will be imputed as described in Section 9.2 for analyses of the HCV RNA endpoints of SVR and virologic failure and the patient reported outcomes (PROs) questionnaires.

If a subject starts another treatment for HCV, then all HCV RNA and PRO values for this subject measured on or after the start date of the new HCV treatment will be excluded from analyses. The subject will be considered a failure for summaries of SVR at all time points after the start of the new HCV treatment.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® Quantitative HCV 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.

Definitions for Efficacy Endpoints

A confirmed quantifiable value during treatment is defined as any two consecutive HCV RNA measurements ≥ LLOQ (or 100 IU/mL for **Breakthrough**), either both during treatment or at the final treatment measurement and the next consecutive post-treatment measurement. A confirmed quantifiable post-treatment value is defined as any two consecutive post-treatment HCV RNA measurements ≥ LLOQ.

Breakthrough confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during the Treatment Period; or confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir) at any time point during the Treatment Period. A single breakthrough value (≥ 100 IU/mL or > 1 $\log_{10}$ above nadir)

followed by lost to follow-up also will be considered a breakthrough (i.e., will not require confirmation).

EOT failure HCV RNA ≥ LLOQ at end of treatment with at least 6 weeks of treatment, where the HCV RNA value must be collected on or after Study Treatment Day 36 and study treatment duration ≥ 36 days.

On-Treatment Virologic Failure **Breakthrough or EOT Failure**; if a subject meets both definitions of **Breakthrough** and **EOT Failure**, he or she will be categorized as **Breakthrough** only.

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

SVR_{12} HCV RNA < LLOQ in the SVR_{12} window (12 weeks after the last actual dose of study treatment) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

$Relapse_{12}$ confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study treatment (up to and including the SVR_{12} assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment and has post treatment HCV RNA data available, excluding reinfection as described below.

$Relapse_{overall}$ confirmed HCV RNA ≥ LLOQ between end of treatment and up to and including the last HCV RNA measurement collected in the PT Period for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment and has post treatment HCV RNA data available, excluding reinfection as described below.

Virologic failure through Post-Treatment Week 12 SVR_{12} non-responders who experience on-treatment virologic failure or $Relapse_{12}$.

Only subjects who have at least one post-treatment HCV RNA value will be included in analyses of relapse. For relapse analyses, the completion of treatment is defined as a study treatment duration ≥ 52 days. If the last available post-treatment value is ≥ LLOQ, then the subject will be considered a relapse (i.e., will not require confirmation).

HCV reinfection is defined as confirmed HCV RNA ≥ LLOQ after the end of treatment in a subject who had HCV RNA < LLOQ at Final Treatment Visit, along with the 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. Reinfection 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 is not possible due to technical difficulties, HCV reinfection 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 (**Relapse$_{12}$** and **Relapse$_{overall}$**), and no genotype, subtype, or clade switch compared with baseline as determined by phylogenetic analysis of the NS3 or NS5A gene sequences. If phylogenetic analysis is not possible due to technical difficulties, the subject will be defined 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.

Reasons for SVR$_{12}$ Non-Response

Subjects who do not achieve SVR$_{12}$ (SVR$_{12}$ non-responders) will be categorized as having:

1. On-treatment virologic failure (see **On-treatment virologic failure** definition);
2. HCV reinfection (see definition described earlier);
3. Relapse$_{12}$ (see **Relapse$_{12}$** definition);

4. Prematurely discontinued study treatment with no on-treatment virologic failure (defined as any SVR_{12} non-responder who prematurely discontinued study treatment [study treatment duration < 52 days] and did not meet the **On-treatment virologic failure** or **HCV reinfection** definitions);
5. Missing follow-up data in the SVR_{12} window (defined as any subject who completed study treatment without data in the SVR_{12} window after applying the imputation rules and not meeting the definitions of [1], [2], [3], or [4]);
6. Other (defined as any SVR_{12} non-responder not meeting the definitions of [1] [5]).

For the reasons for SVR_{12} nonresponse defined above, subjects are only to be counted in 1 category. Specifically, subjects who were SVR_{12} non-responders meeting the definition of HCV reinfection will be counted in the reinfection category regardless of whether they meet the definition of prematurely discontinued study treatment or $Relapse_{12}$.

9.2 Handling of Missing Data

Missing Data Imputation for SVR

For analyses of SVR, subjects missing visit values will have backward imputation applied, if possible. For backward imputation, if the nearest HCV RNA value after the SVR window is unquantifiable or undetectable, then it will be used to impute the HCV RNA value in the SVR window. If a subject is missing an HCV RNA value within the appropriate SVR window after performing backward imputation, then this value will be imputed with an HCV RNA value from a local laboratory if present; otherwise, the HCV RNA value will be missing. A subject with missing HCV RNA data in the analysis window, after imputations, will be imputed as a failure.

Missing Data Imputation for Virologic Failure

If HCV RNA values from the central laboratory are missing but a local laboratory value 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.

Missing Data Imputation for PRO Questionnaires

The handling of missing data for PROs will be as follows. For EuroQol-5 Dimensions-5 Level (EQ-5D-5L) index and VAS scores, no imputation will be performed for missing items. The missing items of the Fatigue Severity Scale (FSS) questionnaire will be imputed with the average score of the answered items as long as more than 50% of the items on the FSS are answered.

9.3 Primary Efficacy Endpoint and Analyses

9.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the achievement of SVR_{12} (defined as HCV RNA < LLOQ 12 weeks after the last actual dose of study treatment) for each subject in the ITT population.

9.3.2 Main Analysis of Primary Efficacy Endpoint

The attributes of the estimand corresponding to the primary efficacy endpoint are summarized in Table 2.

Table 2. Summary of the Estimand Attributes Corresponding to the Primary Efficacy Endpoint

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Primary	GLE/PIB 8 Weeks	SVR_{12}	ITT	Subjects who discontinue the study with an unknown SVR_{12} status (after applying backward imputation) will be counted as a failure for SVR_{12}	Number and percentage of subjects who achieve SVR_{12} along with a two-sided 95% CI calculated using Wilson's score method[2]

The superiority of 8-week treatment with GLE/PIB in acute HCV infection to the weighted efficacy threshold described in Section 2.5, which is based on the historical ITT SVR_{12} rate of treatment with GLE/PIB in PWID and non-PWID subjects with chronic HCV infection, will be demonstrated if the lower bound of the two-sided 95% CI for the percentage of subjects achieving SVR_{12} is greater than the weighted efficacy threshold. For the calculation of the efficacy threshold, the proportions of PWID and non-PWID subjects in this study will be determined using PWID Status Classification 1 described in Section 7.1.

The number and percentage of subjects with each reason for SVR_{12} non-response will be provided. A listing of subjects who do not achieve SVR_{12} by reason for non-response will also be provided.

9.3.3 Supplementary Analyses of Primary Efficacy Endpoint

As a supplementary analysis of the primary endpoint (Supplementary Analysis 1), the number and percentage of subjects in the ITT population who achieve SVR_{12} along with a two-sided 95% CI calculated using Wilson's score method will be compared to the

efficacy threshold as calculated using the proportions of PWID and non-PWID subjects in this study and the PWID Status Classifications 2 and 3 as described in Section 7.1.

As a supplementary analysis of the primary endpoint (Supplementary Analysis 2), the number and percentage of subjects in the ITT population with baseline HCV RNA ≥ LLOQ who achieve SVR_{12} along with a two-sided 95% CI calculated using Wilson's score method will be compared to the efficacy threshold as calculated using the proportions of PWID and non-PWID subjects included in this analysis and the PWID Status Classifications 1, 2, and 3 as described in Section 7.1. Additionally, the number and percentage of subjects with each reason for SVR_{12} non-response will be provided as well as a listing of subjects who do not achieve SVR_{12} by reason for non-response.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the achievement of SVR_{12} for each subject in the mITT-VF population.

9.4.2 Main Analysis of Key Secondary Efficacy Endpoint

The attributes of the estimand corresponding to the key secondary efficacy endpoint are summarized in Table 3.

Table 3. Summary of the Estimand Attributes Corresponding to the Key Secondary Efficacy Endpoint

Estimand Label	Attributes of the Estimand				
	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Key Secondary	GLE/PIB 8 Weeks	SVR_{12}	mITT-VF	Not applicable	Number and percentage of subjects who achieve SVR_{12} along with a two-sided 95% CI calculated using Wilson's score method[2]

The superiority of 8-week treatment with GLE/PIB in acute HCV infection to the weighted efficacy threshold described in Section 2.5, which is based on the historical mITT-VF SVR_{12} rate of treatment with GLE/PIB for PWID and non-PWID subjects with chronic HCV infection, will be demonstrated if the lower bound of the two-sided 95% CI for the percentage of subjects achieving SVR_{12} is greater than the efficacy threshold. The key secondary hypothesis will be tested only if the primary efficacy hypothesis is demonstrated according to the fixed-sequence testing procedure described in Section 12.0. For the calculation of the efficacy threshold, the proportions of PWID and non-PWID subjects in this study will be determined using PWID Status Classification 1 described in Section 7.1.

The number and percentage of subjects with each reason for SVR_{12} non-response will be provided.

9.4.3 Supplementary Analyses of Key Secondary Efficacy Endpoint

As a supplementary analysis of the key secondary endpoint, the number and percentage of subjects in the mITT-VF population who achieve SVR_{12} along with a two-sided 95% CI calculated using Wilson's score method will be compared to the efficacy threshold as

calculated using the proportions of PWID and non-PWID subjects in this study and the PWID Status Classifications 2 and 3 as described in Section 7.1.

As a supplementary analysis of the key secondary endpoint, the number and percentage of subjects in the mITT-VF population with baseline HCV RNA ≥ LLOQ who achieve SVR_{12} along with a two-sided 95% CI calculated using Wilson's score method will be compared to the efficacy threshold as calculated using the proportions of PWID and non-PWID subjects included in this analysis and the PWID Status Classifications 1, 2, and 3 as described in Section 7.1. Additionally, the number and percentage of subjects with each reason for SVR_{12} non-response will be provided.

9.4.4 Supportive Secondary Efficacy Endpoints and Analyses

The supportive secondary efficacy endpoints are:

- On-treatment virologic failure (as defined in Section 9.1) for each subject in the ITT population;
- $Relapse_{12}$ (as defined in Section 9.1) for each subject in the ITT population who completed treatment as planned (defined as study treatment duration ≥ 52 days) with HCV RNA < LLOQ at EOT and with at least 1 post-treatment HCV RNA value;
- Post-treatment reinfection with HCV (as defined in Section 9.1) for each subject in the ITT population.

For the analysis of on-treatment virologic failure, $Relapse_{12}$, and post-treatment HCV reinfection, the number and percentage of subjects in the ITT population will be summarized along with a two-sided 95% CI calculated using Wilson's score method.[2]

Subject numbers of all virologic failures and subjects with post-treatment reinfection will be provided.

9.5 Additional Efficacy Analyses

The following additional efficacy endpoints will be summarized for the ITT population:

- At each post-baseline visit in the Treatment Period, achievement of HCV RNA < LLOQ (using data as observed);
- Achievement of SVR_4 (as defined in Section 9.1);
- Virologic failure through Post-Treatment Week 12 (as defined in Section 9.1);
- $Relapse_{overall}$ (as defined in Section 9.1).

For each of the endpoints above, the number and percentage of subjects meeting the endpoint will be calculated. For the endpoints of SVR_4 and virologic failure, a two-sided 95% CI will be calculated using Wilson's score method.[2] Imputations for missing data will be performed as described in Section 9.2 for analysis of SVR_4, where a missing response will be imputed as a failure after performing the described imputation. All other endpoints will be presented using data as observed.

A summary of the subjects in the ITT population who completed treatment and relapsed (defined as **$Relapse_{overall}$**) will be prepared displaying the number of subjects relapsing overall and by SVR visit window (within the SVR_4 or SVR_{12} window or after SVR_{12} window), including the subject number and the SVR visit window corresponding to the first HCV RNA value of those indicating the occurrence of relapse. A similar summary will be prepared for subjects in the ITT population who prematurely discontinued treatment and relapsed after having HCV RNA < LLOQ at their Final Treatment Visit.

A listing of subjects in the ITT population excluded from the relapse denominator (e.g., study treatment duration < 52 days or no post-treatment HCV RNA) will be provided, as applicable.

The concordance between SVR_4 and SVR_{12} will be assessed for the ITT population by the agreement between SVR_4 and SVR_{12} and the positive predictive value (PPV) and negative predictive value (NPV) of SVR_4 on SVR_{12}. The agreement between SVR_4 and SVR_{12} is a percentage defined as the number of subjects achieving both SVR_4 and SVR_{12} and the

number of subjects where both SVR_4 and SVR_{12} are not achieved. The PPV of SVR_4 on SVR_{12} is the proportion of subjects who achieve SVR_{12} out of all subjects who achieved SVR_4. The NPV of SVR_4 on SVR_{12} is the proportion of subjects who do not achieve SVR_{12} out of all subjects who did not achieve SVR_4.

9.6 Efficacy Subgroup Analyses

The number and percentage of subjects achieving SVR_{12} in the ITT and mITT-VF populations will be presented for the following subgroups:

- HCV GT (1, 2, 3, 4, 5, or 6) and available subtype (final HCV genotype and subtype as defined in Section 9.7);
- Sex (male or female);
- Age (< 18, 18 to < 40, 40 to < 65, 65 to < 75, ≥ 75 years; < 18 or ≥ 18 years; < 65 or ≥ 65 years; < 75 or ≥ 75 years);
- Race (white, black/African-American, Asian, or other) and (black or non-black);
- BMI (< 30 or ≥ 30 kg/m^2);
- Baseline HCV RNA level (< 800,000 or ≥ 800,000 IU/mL; < 1,000,000 or ≥ 1,000,000 IU/mL);
- Baseline platelet count (< 100 or ≥ 100 × 10^9/L);
- Baseline serum albumin (< 35 or ≥ 35 g/L);
- Baseline ALT (≤ ULN, > ULN to ≤ 3 × ULN, > 3 × ULN to ≤ 5 × ULN, > 5 × ULN to ≤ 10 × ULN, or > 10 × ULN);
- Baseline total bilirubin (< 34.2 or ≥ 34.2 µmol/L);
- Geographic region (North America, Europe, or ROW);
- Baseline creatinine clearance (< 60, ≥ 60 to < 90, or ≥ 90 mL/min);
- Baseline eGFR (< 90 or ≥ 90 mL/min/1.73 m^2);
- History of diabetes (yes or no);

- History of opiate substitution therapy use (yes, ongoing at start of study treatment; yes, less than 6 months prior to start of study treatment; yes, 6 to 12 months prior to start of study treatment; yes, more than 12 months prior to start of study treatment; yes, timing of last dose unknown; or no);
- History (i.e., started prior to start of study treatment) of non-prescribed illicit drug use (yes, ongoing as of the end of study participation; yes, last dose after last dose of study treatment; yes, last dose during study treatment period; yes, last dose less than 6 months prior to start of study treatment; yes, last dose 6 to 12 months prior to start of study treatment; yes, last dose more than 12 months prior to start of study treatment; yes, timing of last dose unknown; or no);
- History (i.e., started prior to start of study treatment) of non-prescribed illicit injection drug use (yes, ongoing as of the end of study participation; yes, last dose after last dose of study treatment; yes, last dose during study treatment period; yes, last dose less than 6 months prior to start of study treatment; yes, last dose 6 to 12 months prior to start of study treatment; yes, last dose more than 12 months prior to start of study treatment; yes, timing of last dose unknown; or no);
- PWID Status Classification 1 - with respect to study treatment start (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID);
- PWID Status Classification 2 - with respect to study treatment period (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID);
- PWID Status Classification 3 - with respect to study participation (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID);
- Baseline APRI (≤ 1, > 1 to ≤ 2, or > 2);
- Baseline FibroTest (< 0.75 or ≥ 0.75);
- Baseline FIB-4 (< 1.45, ≥ 1.45 to ≤ 3.25, or > 3.25);
- Baseline AST/ALT ratio (≤ 1 or > 1);

- Risk behavior for acute HCV infection (shared drug-injection equipment, shared non-injection drug use equipment, unprotected sexual activity with multiple partners, unprotected sexual activity with other male(s), risky tattoos or body piercings, shared personal items possibly contaminated with blood, healthcare worker with occupational exposure, or other behavior);
- Grouped risk behavior for acute HCV infection (contaminated needle or IV drug use, contact with infected individual, occupational exposure, or other behavior);
- Grouped risk behavior for acute HCV infection (drug use, sexual transmission, contact by contaminated objects, occupational, other behavior);
- Baseline HCV/HIV co-infection status (HCV mono-infected or HCV/HIV-1 co-infected);
- Estimated acute HCV infection duration (< 3 months, ≥ 3 months to < 6 months, or ≥ 6 months) across all and by each acute HCV infection criteria used to estimate infection duration;
- History of prior HCV infection (yes or no);
- Baseline fibrosis stage (equivalent to Metavir F0 F1, F2, F3, or F4);
- Baseline cirrhosis status (cirrhotic, non-cirrhotic, or unknown test results indeterminate);
- Treatment duration (< 52 days or ≥ 52 days);
- Study treatment compliance (yes or no).

The number and percentage of subjects with each reason for SVR_{12} non-response will be presented for the following subgroups:

- PWID Status Classification 1 - with respect to study treatment start (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID);
- History of opiate substitution therapy use (yes, ongoing at start of study treatment; yes, less than 6 months prior to start of study treatment; yes, 6 to 12 months prior to start of study treatment; yes, more than 12 months prior to start of study treatment; yes, timing of last dose unknown; or no).

The number and percentage of subjects with on-treatment virologic failure, $Relapse_{12}$, and post-treatment HCV reinfection in the ITT population will be presented for the following subgroups:

- Age (< 18, 18 to < 40, 40 to < 65, 65 to < 75, ≥ 75 years; < 18 or ≥ 18 years; < 65 or ≥ 65 years; < 75 or ≥ 75 years);
- PWID Status Classification 1 - with respect to study treatment start (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID);
- PWID Status Classification 2 - with respect to study treatment period (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID);
- PWID Status Classification 3 - with respect to study participation (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID);
- Baseline HCV/HIV co-infection status (HCV mono-infected or HCV/HIV-1 co-infected).
- History of opiate substitution therapy use (yes, ongoing at start of study treatment; yes, less than 6 months prior to start of study treatment; yes, 6 to 12 months prior to start of study treatment; yes, more than 12 months prior to start of study treatment; yes, timing of last dose unknown; or no);

The two-sided 95% confidence interval using Wilson's score method will be produced if there are at least 5 subjects in the subgroup.

9.7 Resistance Analyses

For all subjects, full length NS3/4A and NS5A from baseline samples will be sequenced by next generation sequencing (NGS). For subjects who experience virologic failure (on-treatment virologic failure or $Relapse_{overall}$ as defined in Section 9.1), full length NS3/4A and NS5A from the first sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS.

For all subjects who experience virologic failure for any reason, a listing by subject that includes HCV genotype/subtype, reason for non-response, baseline and post-baseline resistance data availability, and key baseline characteristics (e.g., sex, age, race, fibrosis stage, baseline HCV RNA (log_{10}), and treatment duration (days)) will be produced.

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore, if the HCV RNA level at the time of HCV virologic failure or treatment discontinuation is < 1000 IU/mL, the sample closest in time after HCV virologic failure/treatment discontinuation with an HCV RNA level ≥ 1000 IU/mL will be used.

For each DAA target, signature amino acid positions and a key subset of amino acid positions for the respective inhibitor class are listed in Table 4. Appropriate subtype-specific prototypic reference sequences will be used for comparison with sequences from samples.

Table 4. Signature Amino Acid Positions and the Key Subset of Amino Acid Positions

Target	Signature Amino Acid Positions	Key Subset of Amino Acid Positions
GT1 NS3	36, 43 (GT1a only), 54, 55, 56, 80, 107, 122, 132 (GT1a only), 155, 156, 158, 168, 170, 175 (GT1b only)	155, 156, 168 (all GTs)
GT2, 3, 4, 5, 6 NS3	36, 43, 54, 55, 56, 80, 155, 156, 166 (GT3 only), 168	
GT1 NS5A	24, 28, 29, 30, 31, 32, 54 (GT1b only), 58, 62, 92, 93	24, 28, 30, 31, 58, 92, 93 (all GTs)
GT2, 3, 4, 5, 6 NS5A	24, 28, 29, 30, 31, 32, 58, 92, 93	

The following definitions will be used in the resistance analyses:

- Baseline polymorphism: a polymorphism by NGS in a baseline sample at a detection threshold of ≥ 2% or ≥ 15% (depending on the threshold utilized) within a subject's viral population that was not present in the appropriate prototypic reference amino acid sequence for a given DAA target (NS3 or NS5A).
- Substitution at signature amino acid position: substitution (relative to reference) present at a detection threshold of ≥ 2% within a subject's viral population in a baseline or a post-baseline sample at a signature amino acid position.
- Post-baseline substitution: an amino acid substitution in a post-baseline time point sample that was not detected at baseline (< 2%) in the subject and is detectable in ≥ 2% of the sequences from the post-baseline sample.
- Enriched polymorphism: polymorphism present in both the baseline and a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post baseline % baseline %) ≥ 20].
- Treatment-emergent substitution: A post-baseline substitution or an enriched polymorphism.

The following will be provided:

- Listing by subject of all baseline polymorphisms at signature amino acid positions for each DAA target (NS3 and NS5A) at detection threshold of 2% for subjects in the ITT population.
- The number and percentage of subjects in the ITT population with baseline polymorphisms at signature amino acid positions at detection threshold of 2% and 15%. This table includes prevalence of each baseline polymorphism, and a summary of number of subjects with polymorphisms in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, and any in NS3 + NS5A.

- The number and percentage of subjects in the ITT population with baseline polymorphisms at a key subset of amino acid positions in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, and any in NS3 + NS5A, by subtype, and total (across all subtypes).
- Listing by subject (and time point) of all treatment-emergent substitutions relative to the baseline amino acid sequences for each DAA target (NS3 and NS5A) for subjects in the ITT population who experience virologic failure.
- Listing by subject (and time point) of substitutions at signature amino acid positions (relative to reference sequence) for each DAA target (NS3 and NS5A) for subjects in the ITT population who experience virologic failure.

HCV Genotype/Subtype

Phylogenetic analysis will be conducted on HCV NS3/4A and/or NS5A sequences from baseline samples from all subjects in order to accurately determine genotype/subtype. If the phylogenetic analysis is not available, then the result from Sanger sequencing of a region of NS5B by AbbVie or by the central laboratory will be used to determine the subject's HCV genotype/subtype, if available. Finally, if neither the phylogenetic analysis result nor the Sanger sequencing assay result is available, then the Inno-LiPA assay result from the central laboratory will be used to categorize the subject. This genotype/subtype category (referred to as final genotype/subtype) will be used in efficacy subgroup analyses.

In addition, the final genotype/subtype as well as the results from the central laboratory (Sanger sequencing or Inno-LiPA 2.0 Assay [if Sanger sequencing not available]) will be summarized as part of the baseline characteristics. A summary of HCV genotype subtype as provided by the central laboratory (Sanger sequencing or Inno-LiPA 2.0 Assay [if Sanger sequencing not available]) versus phylogenetic analysis also will be provided. Listings of HCV genotype and subtype will be provided separately for central laboratory results and phylogenetic analysis results.

9.8 Patient Reported Outcomes

The following instruments will be used to collect PROs: EuroQol-5 Dimensions-5 Level (EQ-5D-5L) and Fatigue Severity Scale (FSS). Missing data for each measurement will be handled as described in Section 9.2.

The EQ-5D-5L is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-5L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on 5 levels of severity. Responses to the 5 items encode a discrete health state which is mapped to a preference (utility) specific for different societies. Subject's responses to the EQ-5D-5L will be combined into a unique health state using a 5-digit code with 1 digit from each of the 5 dimensions. The EQ-5D-5L states will be converted into a single preference-weighted health utility index score by applying weights.[5,6] Subjects also rate their perception of their overall health on a separate visual analogue scale (VAS). The VAS score will be analyzed separately. Higher health index and VAS scores indicate better health. For EQ-5D-5L index and VAS scores, no imputation will be performed for missing items.

The FSS measures the impact of fatigue over the past week on specific types of functioning. The survey consists of 9 questions using a 7-point Likert scale. A total score is calculated as the average of the individual item responses (adding up all the answers and dividing by nine). Higher FSS scores indicate a higher degree of impact of fatigue. Imputation will be applied to the total score as described in Section 9.2. If a subject starts another treatment for HCV, then all PRO values for this subject measured on or after the start date of the new HCV treatment will be excluded from analyses.

Summary statistics (number of subjects and mean) at each protocol-specified visit and for the change from baseline (number of subjects, mean, SD, minimum and maximum) to each applicable post-baseline timepoint will be provided for EQ-5D-5L health index score and VAS score and for the FSS total score.

The following analysis of PROs also will be performed:

- Number and percentage of subjects who have ever experienced a decrease from baseline up through each applicable time point of greater than or equal to 0.7 in the FSS total score will be calculated along with a two-sided 95% CI based on Wilson's score method.[2]

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Safety Analysis Set.

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific AEs will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same AE occurs multiple times within a subject, the highest severity and level of relationship to GLE/PIB will be reported.

Participants in clinical trials with HIV-1 may develop infections typically associated with acquired immune deficiency syndrome (AIDS). Adverse events that are considered to be AIDS-associated opportunistic infections (OIs) as identified by the investigators on the AE eCRF will not be included in any analyses of AEs as they will be summarized separately (see Section 10.2.6).

Adverse events and AIDS-associated OIs will be summarized for the following groups: adolescents (age < 18 years), adults (age ≥ 18 years), and overall.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AE with an onset date that is after the first dose of study treatment and no more than 30 days after the last dose of study treatment. Events where the onset date is the same as the study treatment start date are assumed to be treatment-emergent. If an incomplete onset date was collected for an AE, 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 treatment start date).

10.2.2 Adverse Event Overview

An overview of AEs will be presented consisting 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 DAAs (GLE/PIB);
- Treatment-emergent AEs of Grade 3 or higher;
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (GLE/PIB);
- Treatment-emergent AEs leading to discontinuation of study treatment;
- DAA-related treatment-emergent AEs leading to discontinuation of study treatment;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to DAAs (GLE/PIB);
- Serious treatment-emergent AEs leading to discontinuation of study treatment;
- Treatment-emergent AEs leading to interruption of study treatment;
- Treatment-emergent AEs leading to death;
- Deaths.

The following listings of AEs will be prepared:

- All serious AEs (from the time the subject signed the study-specific informed consent through the end of the study);
- Treatment-emergent serious AEs;
- Treatment-emergent AEs leading to death;
- Treatment-emergent AEs leading to discontinuation of study treatment;
- Treatment-emergent AEs leading to study treatment interruption.

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

The number and percentage of subjects with treatment-emergent AEs will be tabulated by primary MedDRA SOC and PT. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

Subjects reporting more than one AE for a given PT will be counted only once for that term (most severe/highest grade incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one AE within a SOC will be counted only once for that SOC. Subjects reporting more than one AE will be counted only once in the overall total.

The following summaries of AEs by SOC and PT will be generated:

- Treatment-emergent AEs;
- Treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (GLE/PIB);
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (GLE/PIB);
- Grade 3 or higher treatment-emergent AEs;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to DAAs (GLE/PIB);

- Treatment-emergent AEs leading to discontinuation of study treatment;
- DAA-related treatment-emergent AEs leading to discontinuation of study treatment;
- Serious treatment-emergent AEs leading to discontinuation of study treatment;
- Treatment-emergent AEs leading to interruption of study treatment;
- Treatment-emergent AEs leading to death.

A listing of treatment-emergent AEs grouped by SOC and PT with subject numbers will be created.

The number and percentage of subjects experiencing treatment-emergent AEs will be tabulated according to PT and sorted by overall frequency. Similar summaries will be provided for Grade 3 or higher treatment-emergent AEs, DAA-related treatment-emergent AEs, DAA-related Grade 3 or higher treatment-emergent AEs, and DAA-related treatment-emergent serious AEs.

Treatment-emergent AEs and DAA-related treatment-emergent AEs will be summarized by maximum severity grade level of each PT, where each AE will be assigned a grade level (Grade 1, 2, 3, 4, or 5) by the investigator. Additionally, of the subjects who reported at least one treatment-emergent AE, the number and percentage of subjects reporting events with a maximum severity of Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5 will be calculated.

Treatment-emergent AEs also will be summarized by maximum relationship of each PT to study treatment (DAAs), as assessed by the investigator.

10.2.4 SAEs (Including Deaths) and Adverse Events Leading to Study Treatment Discontinuation

SAEs (including deaths) and AEs leading to study treatment discontinuation will be summarized by SOC and PT and in listing format as described in Section 10.2.2 and Section 10.2.3.

10.2.5 Adverse Events of Special Interest

For the hepatic decompensation/hepatic failure AE of special interest defined below, the number and percentage of subjects experiencing at least one treatment-emergent AE in the search will be presented overall and by SOC and PT. In addition, a listing of treatment-emergent AEs for subjects meeting the search criterion will be provided. For the hepatocellular carcinoma AE of special interest, a listing of all AEs meeting the search criterion will be provided.

Hepatic decompensation and hepatic failure:

- Treatment-emergent events only
- Product MedDRA Query (PMQ) of "Hepatic decompensation and hepatic failure"

Hepatocellular carcinoma:

- All post-baseline cases, treatment-emergent and non-treatment emergent
- Search based on specific MedDRA PTs of hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, hepatic cancer metastatic, and hepatic cancer recurrent.

10.2.6 AIDS-Associated Opportunistic Infections

The number and percentage of subjects experiencing treatment-emergent AIDS-associated OIs will be tabulated according to SOC and PT for the HCV/HIV co-infected subjects. Subjects reporting more than one AIDS-associated OI for a given PT will be counted only once for that term. Subjects reporting more than one AIDS-associated OI within a SOC will be counted only once for that SOC. Subjects reporting more than one AIDS-associated OI will be counted only once in the overall total. A listing of treatment-emergent AIDS-associated OIs will also be generated.

10.3 Analysis of Laboratory Data

The hematology (including coagulation parameters), clinical chemistry, urinalysis (specific gravity and pH only), and total insulin laboratory tests defined in the protocol operations manual will be summarized.

The baseline value for clinical laboratory tests will be the last non-missing measurement on or before the day of the first dose of study treatment. Values on Day 1 must also be before the time of first dose if time is available. The same baseline value will be used for change to Treatment Period visits and change to Post-Treatment Period visits.

Each laboratory variable will be summarized for all protocol-specified time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, Q1 and Q3 of inter-quartile range, minimum and maximum. Mean change from baseline to each applicable visit, including applicable post-treatment visits, will also be summarized for the laboratory parameters of ALT, AST, bilirubin (total, direct, and indirect), and alkaline phosphatase, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard deviation, median, Q1 and Q3 of inter-quartile range, minimum and maximum will be presented for the mean change from baseline.

Changes in hematology (including coagulation parameters), clinical chemistry, and urinalysis laboratory parameters will be tabulated using shift tables. Laboratory data values will be categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline to minimum value and maximum value during the Treatment Period will be created. In this shift table, the number and percentage of subjects with baseline values within or above the normal range (baseline high or normal) and a minimum value below the normal range (post-baseline low) and the number and percentage of subjects with baseline values within or below the normal range (baseline low or normal) and a maximum value above the normal range (post-baseline high) will be summarized.

Summaries of graded laboratory parameters and shift from baseline grade (see below) will be summarized for the following groups: adolescents (age < 18 years), adults (age ≥ 18 years), and overall.

The laboratory parameters listed in Appendix B 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 the baseline value and for values during the Treatment Period for subjects with both a baseline value and at least one post-baseline value during the Treatment Period. To be counted, the post-baseline value must have a toxicity grade that is more extreme than the toxicity grade corresponding to the baseline value. The summary will also include the number and percentage of subjects with a maximum of at least Grade 3 for all laboratory parameters in Appendix B. A listing of all relevant laboratory parameters will be provided for each subject who had an increase to Grade 2 or higher for any laboratory variable in Appendix B.

Shift tables from baseline to maximum value during the Treatment Period will be created for ALT and total bilirubin values categorized by toxicity grade. For each baseline grade, the frequency and percentage of subjects with maximum Grades of 0, 1, 2, 3, and 4 during treatment will be calculated. The number and percentage of those subjects who improved from baseline, were the same as baseline, or who worsened from baseline will also be calculated.

Shift tables from baseline to the Week 4 and Final Treatment Visits will be created for ALT and total bilirubin categorized by toxicity grade. For each baseline grade, the frequency and percentage of subjects with Grades of 0, 1, 2, 3, and 4 at the Week 4 and Final Treatment Visits will be calculated. The number and percentage of those subjects who improved from baseline, were the same as baseline, or who worsened from baseline will also be calculated.

Assessment of Hepatic Laboratory Values

The number and percentage of subjects with laboratory values meeting the following criteria during treatment will be summarized for adolescents (age < 18 years), adults (age ≥ 18 years), and overall:

- Post-nadir (preceding value is lower than the subsequent value) ALT > 5 × ULN (regardless of grade change);
- Total bilirubin ≥ 2 × ULN and > baseline (i.e., a post-baseline value must be more extreme than the baseline value to be considered);
- Post-nadir ALT > 3 × ULN and total bilirubin > 2 × ULN;
- Post-nadir ALT > 3 × ULN and total bilirubin ≤ 2 × ULN.

Four listings (one for each bullet above) of all liver function tests including 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 the criterion defined above.

Hepatic Laboratory Abnormalities of Interest

Among the events assessed under "Assessment of Hepatic Laboratory Values," the following criteria are of interest:

- Confirmed post-nadir ALT > 5 × ULN;
- Post nadir ALT > 3 × ULN and a concurrent total bilirubin > 2 × ULN with a direct bilirubin:total bilirubin ratio > 0.4.

To support the assessment of hepatic laboratory abnormalities of interest, the following potential events will be summarized for adolescents (age < 18 years), adults (age ≥ 18 years), and overall:

- Confirmed post-nadir ALT > 5 × ULN;
- Post-nadir ALT > 3 × ULN and total bilirubin > 2 × ULN with a direct bilirubin:total bilirubin ratio > 0.4.

Two listings (one for each bullet) of all liver function tests including 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 the criterion defined above.

The assessments of hepatic laboratory values and hepatic laboratory abnormalities of potential interest will include subjects who have a baseline and at least one post-baseline value during the Treatment Period for the respective parameter. Criteria that include both ALT and total bilirubin require both parameters to have a baseline and at least one value during the Treatment Period. The maximum ratio relative to the ULN will be used to determine if subjects meet any of the criteria listed above. The ALT and total bilirubin values do not need to be concurrent in order to meet the defined criteria in statistical summaries. 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), except where noted in the criteria above. A confirmed post-nadir increase in ALT is defined as two consecutive values of ALT > 5 × ULN after nadir, either both during treatment or at the final treatment measurement and the next consecutive post-treatment measurement. A single post-nadir ALT value of greater than 5 × ULN followed by lost to follow-up (no additional ALT values) also will be considered as confirmed (i.e., will not require confirmation). The ratio of direct to total bilirubin will be calculated using the same date/time sample corresponding to the total bilirubin elevation.

10.4 Analysis of Vital Signs

Vital sign variables are body temperature, sitting systolic blood pressure, sitting diastolic blood pressure, heart rate, and body weight.

The baseline value for vital signs will be the last measurement on or before the day of the first dose of study treatment. The same baseline value will be used for change to Treatment Period visits and change to Post-Treatment Period visits.

Each vital sign variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, Q1 and Q3 of inter-quartile range, minimum and maximum. Mean change from baseline to each applicable visit, including applicable post-treatment visits, will also be summarized, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard deviation, median, Q1 and Q3 of inter-quartile range, minimum and maximum will be presented for the mean change from baseline.

Vital sign variables will be evaluated based on the potentially clinically significant (PCS) criteria presented in Appendix B.

The number and percentage of subjects with on-treatment values meeting the specified criteria for PCS vital sign values will be summarized. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. A separate listing will be provided that presents all vital sign values for the subjects meeting PCS criteria during treatment.

10.5 Safety Subgroup Analyses

The following safety summaries will be performed as described above (by adolescents (age < 18 years), adults (age ≥ 18 years), and overall) for specific subgroups:

- Adverse event overview (see Section 10.2.2);
- Treatment-emergent AEs sorted by descending frequency of MedDRA PT (see Section 10.2.3);
- Treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (GLE/PIB) sorted by descending frequency of MedDRA PT (see Section 10.2.3);
- Serious treatment-emergent AEs by MedDRA SOC and PT (see Section 10.2.3);
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (GLE/PIB) by MedDRA SOC and PT (see Section 10.2.3);

- Treatment-emergent AEs leading to discontinuation of study treatment by MedDRA SOC and PT (see Section 10.2.3);
- Treatment-emergent hepatic decompensation/hepatic failure events by MedDRA SOC and PT (see Section 10.2.5);
- ALT and total bilirubin elevations of the NCI-CTCAE v4.03 Grade 1, 2, 3, or 4 during the Treatment Period with grade increased from baseline (see Section 10.3);
- Shift from baseline to maximum value during the Treatment Period for ALT and total bilirubin categorized by toxicity grade (see Section 10.3);
- Shift from baseline to Week 4 and Final Treatment Visits for ALT and total bilirubin categorized by toxicity grade (see Section 10.3);
- Assessment of hepatic laboratory values during the Treatment Period (see Section 10.3);
- Hepatic laboratory abnormalities of interest during the Treatment Period (see Section 10.3).

The safety summaries above will be presented for the following subgroups:

- Baseline HCV RNA (< LLOQ or ≥ LLOQ);
- Age (< 65, ≥ 65 years);
- Baseline HCV/HIV co-infection status (HCV mono-infected or HCV/HIV-1 co-infected);
- History of opiate substitution therapy use (yes, ongoing at start of study treatment; yes, less than 6 months prior to start of study treatment; yes, 6 to 12 months prior to start of study treatment; yes, more than 12 months prior to start of study treatment; yes, timing of last dose unknown, or no);
- History (i.e., started prior to start of study treatment) of non-prescribed illicit drug use (yes, ongoing as of the end of study participation; yes, last dose after last dose of study treatment; yes, last dose during study treatment period; yes, last dose less than 6 months prior to start of study treatment; yes, last dose 6 to 12 months prior to start of study treatment; yes, last dose more than 12 months prior to start of study treatment; yes, timing of last dose unknown; or no);

- History (i.e., started prior to start of study treatment) of non-prescribed illicit injection drug use (yes, ongoing as of the end of study participation; yes, last dose after last dose of study treatment; yes, last dose during study treatment period; yes, last dose less than 6 months prior to start of study treatment; yes, last dose 6 to 12 months prior to start of study treatment; yes, last dose more than 12 months prior to start of study treatment; yes, timing of last dose unknown; or no);
- PWID Status Classification 1 - with respect to study treatment start (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID);
- PWID Status Classification 2 - with respect to study treatment period (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID).

11.0 Interim Analyses

No interim analysis is planned for this study.

12.0 Overall Type-I Error Control

In order to control the family-wise Type-I error rate, a fixed-sequence testing procedure[7] will be used for the primary and key secondary efficacy analyses of SVR_{12} listed below. The fixed-sequence testing procedure will utilize the sequence of the primary analysis followed by the key secondary analysis.

The multiplicity-controlled efficacy analyses will be performed sequentially in the following order:

1. Primary: Superiority of the SVR_{12} rate of 8-week treatment with GLE/PIB for subjects in the ITT population to the efficacy threshold. If superiority is demonstrated, then proceed to the key secondary efficacy analysis. If superiority is not demonstrated in the primary analysis, then stop the testing procedure (i.e., do not perform the key secondary analysis).

2. Key Secondary: Superiority of the SVR_{12} rate of 8-week treatment with GLE/PIB for subjects in the mITT-VF population to the efficacy threshold. If superiority is demonstrated, then declare superiority for both the mITT-VF and ITT populations. If not, then declare that superiority was demonstrated only for the ITT population.

13.0 Version History

Table 5. SAP Version History Summary

Version	Date	Summary
1.0	13 October 2021	Initial version
2.0	15 November 2023	Version 2.0
3.0	02 July 2024	Version 3.0
4.0	12 August 2024	Version 4.0

13.1 Summary of Changes

The following is a summary of changes **between the protocol (protocol version 3.0 dated 23 April 2021) and SAP version 1.0.** These changes were made to provide additional information for the specified groups of subjects.

Summaries for adolescents and for adults were added for:

- Demographics and baseline characteristics summaries;
- Subgroup analyses of supportive secondary efficacy endpoints;
- Adverse events summaries.

The following subgroups were added for the summaries of SVR_{12}:

- Baseline total bilirubin (< 34.2 or ≥ 34.2 µmol/L);
- PWID status (current/recent PWID or former/non-PWID);
- Baseline fibrosis stage (equivalent to Metavir F0 - F1, F2, F3, or F4);
- Baseline cirrhosis status (cirrhotic or non-cirrhotic);

- Treatment duration (< 52 days or ≥ 52 days);
- Study treatment compliance (yes or no).

The following subgroup was added for the summaries of the supportive secondary endpoints:

- PWID status (current/recent PWID or former/non-PWID).

The following is a summary of changes **between SAP version 1.0 and SAP version 2.0.**

- Throughout
  - Added that Q1 and Q3 of inter-quartile range will be included in numerical summaries
    - Rationale: To provide additional summary statistics
- Section 5.0
  - Clarified that the subjects who failed to enroll in the study are those who failed to receive at least one dose of study treatment
    - Rationale: For clarification
- Section 7.0
  - Added demographics and baseline disease characteristics summaries for mITT-VF population
    - Rationale: To provide this information for the key secondary efficacy analysis population
- Section 7.1
  - Added demographics and baseline characteristics summaries to be by adult, adolescent, and overall
    - Rationale: To provide this information for the adolescent and adult subjects separately
  - Updated cirrhosis status categories to include "unknown test results indeterminate" and clarified that screening and baseline Child-Pugh score includes subjects with cirrhosis status unknown
    - Rationale: To align with protocol-allowed cirrhosis status

- Updated categories for baseline HCV RNA level and baseline APRI
  - Rationale: To correct typos
- Updated history of non-prescribed illicit drug use categories, history of non-prescribed illicit injection drug use categories, and PWID status categories
  - Rationale: To align with data collection and provide multiple definitions of PWID status
- Added another set of grouped risk behaviors for summarization
  - Rationale: To provide additional information based on different groupings of risk behaviors
- Provided details for calculation of estimated acute HCV infection duration
  - Rationale: To provide details

- Section 7.3
  - Clarified that any prior and concomitant HIV ART medications will be summarized for subjects who are HCV/HIV co-infected at baseline, not only those receiving ART at baseline
    - Rationale: For clarification
  - Clarified that opiate substitution therapy and non-prescribed illicit drugs will be summarized as reported rather than by generic drug name based on the WHO Drug Dictionary
    - Rationale: For clarification
- Section 9.3.3 and Section 9.4.3
  - Added section describing supplementary analyses of primary endpoint and key secondary endpoint
    - Rationale: To add analyses with comparisons to efficacy thresholds based on different definitions of PWID status
- Section 9.6
  - Updated subgroups based on age, baseline HCV RNA level, history of non-prescribed illicit drug use, history of non-prescribed illicit injection drug use, PWID status, grouped risk behavior categories, HCV/HIV co-infection status, and baseline cirrhosis status for summaries of SVR_{12}

- Rationale: To align with Section 7.1

- Updated subgroups based on age and PWID status for summaries of the secondary efficacy endpoints
  - Rationale: To align with Section 7.1
- Updated the subgroup analyses of secondary endpoints to include summaries by HCV/HIV co-infection status
  - Rationale: To provide additional information for subjects with and without HIV co-infection

- Section 10.3
  - Clarified that hematology laboratory parameters include coagulation parameters and that summaries of laboratory variables over time would include summaries for all protocol-specified timepoints
    - Rationale: For clarification
  - Clarified which laboratory parameters would be tabulated using shift tables
    - Rationale: For clarification
  - Added that the summaries of graded laboratory parameters, shifts from baseline in graded laboratory parameters, and assessments of hepatic laboratory values and hepatic laboratory abnormalities of interest will be summarized for adult, adolescent, overall
    - Rationale: To provide this information for the adolescent and adult subjects separately
  - Added additional shift tables for baseline to maximum on-treatment, Week 4, and Final Treatment Visit values for ALT and total bilirubin categorized by toxicity grade
    - Rationale: To provide additional assessments of on-treatment ALT and total bilirubin
- Section 10.5
  - Added Section 10.5 Safety Subgroup Analyses; added analyses of key AE and laboratory summaries to be done by adult, adolescent, overall, and by subgroups of age, baseline HCV/HIV co-infections status, history of non-prescribed illicit drug use, history of non-prescribed illicit injection drug use, and PWID status

- Rationale: To provide assessments of safety for subgroups of interest

- Appendix B, Table B-1
  - Added eGFR
    - Rationale: To correct omission

The following is a summary of changes between **SAP version 2.0 and SAP version 3.0.**

- Section 2.5
  - Clarified that for calculation of the efficacy thresholds, PWID is defined as current/recent PWID, and non-PWID is defined as former/non-PWID
    - Rationale: For clarification
- Section 6.0
  - Clarified that if the number of tablets returned is not available for one or more of the bottles dispensed to a subject, then compliance will not be calculated for that subject
    - Rationale: For clarification
  - Added that Q1 and Q3 of inter-quartile range will be included in numerical summaries
    - Rationale: To correct omission
- Section 7.1
  - Added demographics and baseline characteristics summaries for groups of subjects based on PWID Status Classification 1 and history of opiate substitution therapy use
    - Rationale: To provide additional information for these groups of subjects
  - Added categories of < LLOQ and ≥ LLOQ for baseline HCV RNA level
    - Rationale: To provide a summary of subjects who had unquantifiable or undetectable HCV RNA at baseline
  - Removed antiretroviral (ART) requirement from baseline characteristic summary of HIV treatment status

- Rationale: To remove limitation to include only ART medications for coinfected subjects

- Section 7.3
  - Removed restriction to include only ART medications in the summaries of HIV medications
    - Rationale: To align with baseline characteristics summary
- Section 9.3.3 and Section 9.4.4
  - Added supplementary analyses of primary and key secondary endpoints excluding those subjects who had baseline HCV RNA < LLOQ
    - Rationale: To provide assessments in subjects who had quantifiable HCV RNA at baseline
- Section 9.6
  - Updated the subgroup analyses of secondary endpoints to include summaries by history of opiate substitution therapy
    - Rationale: To provide additional information for subjects with and without a history of opiate substitution therapy
  - Added subgroup analyses of reasons for SVR_{12} non-response for PWID status and history of opiate substitution therapy
    - Rationale: To provide additional information for subjects based on PWID status and history of opiate substitution therapy
  - Updated subgroup description of estimated infection duration to include summaries across all and by each acute HCV infection criteria
    - Rationale: To align with Section 7.1
- Section 10.3
  - Clarified the data requirements for subjects to be included in the summaries of graded laboratory parameters and assessments of hepatic laboratory values and hepatic laboratory abnormalities of interest
    - Rationale: For clarification
- Section 10.5
  - Added baseline HCV RNA < LLOQ or ≥ LLOQ as a safety subgroup variable

- Rationale: To provide assessments of safety in subjects who had quantifiable HCV RNA at baseline and those who did not

- Added history of opiate substitution therapy as a safety subgroup variable
  - Rationale: To provide assessments of safety in subjects who had a history of opiate substitution therapy and those who did not

The following is a summary of changes between **SAP version 3.0 and SAP version 4.0.**

- Section 7.1
  - Removed "followed by initiating GLE/PIB treatment" from acute HCV infection criteria description
    - Rationale: To align with text in protocol

14.0 References

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15.0 Appendices

Appendix A. Protocol Deviations

Protocol deviations will be categorized as follows:

- Subject entered into the study even though they did not satisfy eligibility criteria;
- Subject developed withdrawal criteria during the study and was not withdrawn;
- Subject received the wrong treatment or incorrect dose of study treatment;
- Subject took a prohibited concomitant medication.

Appendix B. Laboratory Toxicity Grades and Potentially Clinically Significant Criteria for Vital Sign Values

Table B-1. 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	--
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	--
Creatinine clearance	< LLN – 60 mL/min	< 60 – 30 mL/min	< 30 – 15 mL/min	< 15 mL/min
eGFR	< 90 – 60 mL/min/1.73 m^2	< 60 – 30 mL/min/1.73 m^2	< 30 – 15 mL/min/1.73 m^2	< 15 mL/min/1.73 m^2
Albumin	< LLN – 30 g/L	< 30 – 20 g/L	< 20 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
Lymphocyte	< LLN – 0.8 × 10^9/L	< 0.8 – 0.5 × 10^9/L	< 0.5 – 0.2 × 10^9/L	< 0.2 × 10^9/L
GGT	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Glucose (high)	> ULN – 8.9 mmol/L	> 8.9 – 13.9 mmol/L	> 13.9 – 27.8 mmol/L	> 27.8 mmol/L
Glucose (low)	< 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
Cholesterol	> ULN – 7.75 mmol/L	> 7.75 – 10.34 mmol/L	> 10.34 – 12.92 mmol/L	> 12.92 mmol/L
Triglycerides	> 1.71 – 3.42 mmol/L	> 3.42 – 5.7 mmol/L	> 5.7 – 11.4 mmol/L	> 11.4 mmol/L

Table B-1. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values (Continued)

Test	Grade 1	Grade 2	Grade 3	Grade 4
Sodium (low)	< LLN – 130 mmol/L	--	< 130 – 120 mmol/L	< 120 mmol/L
Sodium (high)	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L	> 160 mmol/L
Potassium (low)	< LLN – 3.0 mmol/L	--	< 3.0 – 2.5 mmol/L	< 2.5 mmol/L
Potassium (high)	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L	> 7.0 mmol/L
Magnesium (low)	< LLN – 0.5 mmol/L	< 0.5 – 0.4 mmol/L	< 0.4 – 0.3 mmol/L	< 0.3 mmol/L
Magnesium (high)	> ULN – 1.23 mmol/L	--	> 1.23 – 3.30 mmol/L	> 3.30 mmol/L

Note: Criteria from National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Table B-2. Criteria for Potentially Clinically Significant Vital Sign Values

Test/Measurement	Very Low (VL)	Very High (VH)
Systolic Blood Pressure	≤ 90 mmHg AND A decrease of ≥ 20 mmHg from baseline	≥ 180 mmHg AND An increase of ≥ 20 mmHg from baseline
Diastolic Blood Pressure	≤ 50 mmHg AND A decrease of ≥ 15 mmHg from baseline	≥ 105 mmHg AND An increase of ≥ 15 mmHg from baseline
Heart Rate	≤ 50 bpm AND A decrease of ≥ 15 bpm from baseline	≥ 120 bpm AND An increase of ≥ 15 bpm from baseline
Weight	A decrease of ≥ 15% from baseline	An increase of ≥ 15% from baseline
Body Temperature		> 38.3°C AND An increase of ≥ 1.1°C from baseline