This is ACTG A5380 Primary SAP Version 1.5 with names of authors, names of publication writing team members and analysis timeline redacted.

A5380

A Phase II Trial of Glecaprevir/Pibrentasvir Fixed-Dose Combination Treatment for Acute Hepatitis C Virus Infection (PURGE-C)

Protocol Version 1.0

ClinicalTrials.gov Identifier: NCT04042740

Primary Statistical Analysis Plan

Version 1.5

October 20, 2020

Created by: A5380 Study Statisticians

ACTG Statistical and Data Analysis Center

Harvard T.H. Chan School of Public Health

Table of Contents

Version History

Version	Changes Made	Date Finalized
1.0	Original Version per Protocol Version 1.0	July 11, 2019
1.1	Protocol amendment review (V1.0, LOA #1)	January 2, 2020
1.2	Changes due to the study visits affected by COVID-19 outlined in CM #2. Correction of typos.	April 24, 2020
1.3	Protocol amendment review (V1.0, LOA #2)	August 19, 2020
1.4	Protocol amendment review (V1.0, LOA #3)	September 21, 2020
1.5	Protocol amendment review (V1.0, LOA #4)	October 20, 2020

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcome measures and additional outcome measures of the A5380 study that will be included in the primary manuscript. They address the major primary and secondary objectives of the study. The Primary SAP outlines the general statistical approaches that will be used in the analysis of the study. It has been developed to facilitate discussion of the statistical analysis components and to provide agreement among the study team members regarding the statistical analyses to be performed and presented in the primary analysis report. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov.

Detailed outlines of tables, figures, and coding descriptions that will be included in the Primary Analysis Report are included in the Analysis Implementation Plan (AIP).

Analyses for the Primary Analysis Report will be finalized once the last participant has completed the Week 28 study visit (primary completion date, PCD), all queries have been resolved, and the study database closure/data lock has been completed.

Outlines of analyses for other objectives and outcome measures not included in the Primary SAP, including outcome measures after the Week 28 study visit, will be provided in a separate SAP for Other Objectives.

1.2 Version History

- Version 1.0 was developed based on Protocol Version 1.0, dated June 07, 2019.
- No changes after review of Protocol Version 1.0, Letter of Amendment #1, dated December 18, 2019.
- Changes due to the study visits affected by COVID-19 outlined in CM #2, dated April 20, 2020. Changes were made in Section 2.5 (HCV interim monitoring), Section 3.1.1 (about primary outcome on SVR12 HCV RNA), Section 3.1.2 (clarification of timeframe) and Section 4.2 first bullet (about HCV RNA data for SVR12 analysis). Typos in 3.1 after asterisk were also corrected. Changes from Version 1.0 are in **bold text**.
- No changes after review of Protocol Version 1.0, Letter of Amendment #2, dated August 14, 2020.
- No changes after review of Protocol Version 1.0, Letter of Amendment #3, dated September 9, 2020.
- No changes after review of Protocol Version 1.0, Letter of Amendment #4, dated October 13, 2020.

2 Study Overview

2.1 Study Design

A5380 is a prospective, phase II, single-arm study in treatment of acute HCV infection in participants with and without HIV-1 coinfection. The minimum number of HIV-1 infected participants for the study is 10, and there is no maximum set for the study. The key study objective is to evaluate the efficacy of a 4-week treatment of a fixed-dose combination of glecaprevir/pibrentasvir (G/P), using SVR12 as the primary outcome measure. SVR12 (sustained virologic response 12 weeks post-treatment) is defined as unquantifiable HCV RNA at 12 weeks after treatment discontinuation (Week 16 visit).

The study is designed to conclude with reasonable evidence that the true SVR12 proportion is greater than 80% in the study population. This will be assessed by examining if a two-sided 90% confidence interval for the sample proportion is entirely above 80%. The study sample size of 44 is deemed to provide reasonable precision around the estimated SVR12 proportion to provide useful information in the treatment of acute HCV.

The primary analysis will occur when all the study participants can be evaluated for SVR12. Accounting for the possible imputation for the outcome measure (described in Section 3.1 below), the primary analysis is expected to be finalized upon completion of Week 28 study visits. The finalization of primary analysis may occur while the study follow-up is ongoing.

The study is monitored by an independent Study Monitoring Committee (SMC) appointed by the AIDS Clinical Trials Group (ACTG). In addition, HCV RNA results will be closely monitored by the protocol core team (including study chairs, medical officer and statisticians) in the first 10 participants who have such data for evaluability by the visit occurring 4 weeks after the end of treatment (Week 8). Interim HCV RNA monitoring for this purpose is described further in Section 2.5 below. If the guidelines described in Section 2.5 are met, then the SMC will review the study results to make recommendation on the future conduct of the study. The first planned SMC review will be held when the interim HCV RNA monitoring review can occur or one year after the enrollment of the first study participant, whichever occurs first. The study will undergo interim data review at least annually by the appointed SMC.

2.2 Hypotheses

The fixed dose combination (FDC) of glecaprevir/pibrentasvir (G/P) given for 4 weeks will achieve sustained virologic response 12 weeks post-treatment (SVR12) greater than 80% for the treatment of acute hepatitis C virus (HCV) infection, with an acceptable safety profile and shorter length of therapy than is currently recommended for chronic HCV infection.

2.3 Study Objectives

This Primary SAP addresses the following primary and secondary objectives listed in the study protocol. Other study objectives in the protocol will be addressed in subsequent analysis plans.

2.3.1 Primary Objectives

1. To evaluate acute HCV treatment response to G/P given for 4 weeks, as assessed by sustained virologic response 12 weeks post-treatment (SVR12, defined as HCV RNA <lower limit of quantification [LLOQ], either target detected [TD] or target not detected [TND]).
2. To evaluate the safety and tolerability of G/P given for 4 weeks in persons with acute HCV infection, regardless of genotype and HIV status.

2.3.2 Secondary Objectives

1. To evaluate the antiviral efficacy of G/P given for 4 weeks for the treatment of acute HCV infection, as measured by the proportion of participants with HCV RNA <LLOQ (TD or TND) at study weeks 1, 2, 4, 8 (SVR4), 12 (SVR8), and 28 (SVR24).
2. To evaluate evidence of virologic failure, defined as failure to achieve HCV RNA <LLOQ (TD or TND at the end of treatment) and confirmed increase in HCV RNA >1 $\log_{10}$ from on-treatment nadir.
3. To evaluate the antiviral efficacy of G/P given for 4 weeks by HIV status.

This SAP addresses the outcome measures obtained out to study week 28. For the outcome measures obtained after Week 28, a separate SAP will be drafted.

2.4 Overview of Sample Size Considerations

The study is designed to conclude with reasonable evidence that the true SVR12 proportion is greater than 80% in the study population. This will be assessed by examining if a two-sided 90% confidence interval (CI) for the sample proportion is entirely above 80%. This is equivalent to showing that the SVR12 proportion is higher than 80% in a one-sided test with a type I error of 5%. With 44 participants, there is at least 90% power to show that proportion achieving SVR12 is greater than 80% in a one-sided exact binomial test with a targeted significance level of 5%. The true SVR12 proportion is assumed to be 95%, when treated with 4 weeks of the G/P regimen. With a sample size of 44 participants, the Wilson confidence interval for the true SVR12 proportion will be entirely above 80% if 40 or more participants achieve SVR12 out of 44 participants.

2.5 Overview of Formal Interim Monitoring

The study will undergo interim review at least annually by an ACTG-appointed Study Monitoring Committee (SMC). The first interim review **was initially planned to** occur when the study week 8 data are available from the first 10 participants, or one year after the enrollment of the first study participant, whichever occurs first. **Due to the study visits affected by COVID-19 outlined in CM #2, the first SMC interim review will occur when SVR12 results are available from the first 10 participants.**

In this study, HCV RNA results will be closely monitored by the protocol core team in the first 10 participants with HCV RNA data available to assess early evidence of potential harm in the short treatment duration of 4 weeks. The following guideline will be used to assess evidence of an

unacceptable number of participants not achieving unquantifiable HCV RNA excluding reinfections (failures), based on early interim data on 10 participants that may trigger an SMC review. Failures include HCV RNA relapse and virologic failure, defined in protocol section 10.2.3.2 and 10.2.2.2, respectively.

If 3 or more of the first 10 participants experience failures, further enrollment will be suspended while the Core Team and the SMC review the data closely and determination is made on the future conduct of the study.

The HCV RNA outcome for interim monitoring **was initially planned to use** data out to 4 weeks after the end of treatment**. Due to** the **study visits affected by COVID-19,** HCV RNA **results may not be available until Week 16 (SVR12 visit) for some participants. If Week 8 results are not available, Week 16 results will be** used for the **purpose** of **assessing potential harm with** the **abbreviated treatment duration of 4 weeks**. Formal interim analysis on the primary outcome measure SVR12 is not planned for this study.

3 Outcome Measures

3.1 Primary Outcome Measures

1. [For Primary Objective 1] SVR12 defined as achieving unquantifiable HCV RNA (<LLOQ TD or TND) at the study visit occurring at 12 weeks after treatment discontinuation (week 16). The sample within the visit window for week 12, as defined in Protocol V1.0 Section 6.0, will be used. If a participant does not have any HCV RNA measurements in this time period, then the participant will be considered as SVR12 failure, unless there are preceding and subsequent HCV RNA measurements* that are both LLOQ (either TD or TND**), or the participants' visit schedule was affected by COVID-19 as outlined in CM #2.**
2. [For Safety in Primary Objective 2] Any reported AE occurring after initiation of study treatment through 4 weeks after the treatment **discontinuation**.
3. [For Tolerability in Primary Objective 2] Tolerability, defined as completion of 4 weeks of treatment without discontinuation due to AEs.

   * The scheduled HCV RNA visits that may be used for the SVR12 determination in case of the missed measurement in the Week **16** visit window are weeks 8, 12 and 28. Unscheduled HCV RNA visits may also be used, if applicable. See Section 4.2 below on the analysis approach to SVR12.

3.2 Secondary Outcome Measures

1. [For Secondary Objectives 1 and 3] HCV RNA <LLOQ (TD or TND) at study visits, using the visit windows as defined in Protocol Section 6.0.
2. [For Secondary Objective 2] Virologic failure, defined as failure to achieve unquantifiable HCV RNA and confirmed increase in HCV RNA >1 $\log_{10}$ from on-treatment nadir.

Outcomes at study visits after Week 28 will be obtained after the primary completion date (PCD) and will be addressed in a separate analysis plan. For the outcome measures obtained after PCD, the results will be posted to ClinicalTrials.gov after the initial results submission and no later than one year after the last participant's study completion.

4 Statistical Principles

4.1 General Considerations

- The analysis will include all participants who initiate the study treatment.
- Baseline refers to study evaluation closest to Week 0 prior to initiation of study treatment.
- For summaries of outcomes at specified study visits (e.g. HCV RNA at study visits for Secondary Outcome Measure 1), study visit windows as specified in Protocol Section 6.0 will be used, unless specified otherwise. In the event of multiple results within a study window, the result closest to the scheduled evaluation week based on the time since study entry randomization date will be used.
- Continuous variables will be summarized with min, Q1, median, Q3, and max, unless specified otherwise. Mean and standard deviation may also be reported, if there are sufficient numbers to make these statistics meaningful.

4.2 Analysis Approaches

- For the primary analysis:
  - As described in Section 3.1 above on Primary Outcome Measures, if a participant does not have any HCV RNA measurements in the SVR12 visit window, then the participant will be considered SVR12 failure, unless there are preceding and subsequent HCV RNA measurements that are both LLOQ (either TD or TND). The latest available preceding and the earliest available subsequent HCV RNA measurements around the targeted SVR12 visit window will be used**. If the participant's visit schedule was affected by COVID-19 as outlined in CM #2 and (1) only one HCV RNA sample is available after the study treatment, and (2) the sample is collected after the SVR12 visit window, then this result will be used as the primary outcome.**
  - Otherwise, not achieving unquantifiable HCV RNA at the study visit corresponding to the SVR12 evaluation will be considered failure for SVR12 determination in the primary analysis regardless of the reason. As such, early discontinuation of the study prior to the SVR12 visit and reinfection prior to the SVR12 visit will be considered a failure.
  - For the SVR12 analysis, a supplementary analysis will be conducted in the analysis set that excludes (1) participants who discontinued the study for reasons not related to the study treatment, and (2) participants who became re-infected with HCV prior to SVR12 visit. Reasons not related to study treatment may include, but are not limited to: participant moved away, participant cannot get to the clinic, participant cannot be located.
- All available data for the indicated study visits from the participants who initiate the study treatment will be used in the analysis, and the number of participants with available data will be specified for each analysis.
- Confidence intervals around proportions will be provided using the Wilson method for binomial data.

- Subgroup analyses based on the screening HIV infection status will be conducted for the HCV RNA analyses to address Secondary Objective 3.

5 Report Contents

Additional details will be provided in an Analysis Implementation Plan (AIP). In addition to results for primary and secondary outcome measures, key baseline characteristics and study status are reported in ClinicalTrials.gov.

1. CONSORT Diagram
2. Study history
    a. A summary of changes to and clarifications of the protocol.
    b. A brief summary of the SMC reviews.
3. Study entry
    a. Screening: Number of participants screened for the study
    b. Accrual: Tables of accrual by month and by site
4. Baseline characteristics
    a. Demographics: age, sex, IV drug use and race/ethnicity
    b. Weight and BMI
    c. HCV genotype
    d. HCV RNA viral load
    e. HIV status and for those HIV-infected: HIV-1 RNA level, ARV regimen, CD4+ and CD8+ T-cell count
    f. Liver function tests: total and direct bilirubin, INR, ALT/SGPT, AST/SGOT, albumin, alkaline phosphatase
5. Study status
    a. Listing of premature study discontinuations with reasons. For premature discontinuations, the number of weeks on study will be provided.
    b. Number of participants who did not start study treatment.
6. Study treatment status
    a. Listing of premature study treatment discontinuations with reasons. For premature discontinuations, the number of weeks on study treatment will be provided.
7. Adverse events and deaths
    a. Summary of all adverse events defined in Section 7.2 of the protocol by MedDRA system organ class (SOC) and preferred term (PT) and by grade.
    b. Summary of the participants who died, including primary cause of death with weeks from study entry.
    c. Listing and narratives of deaths.
8. Pregnancies
    a. Listing and description of all available information related to pregnancy and outcome
9. Analysis of Primary Outcome Measure 1 described in Section 3.1
    a. Primary Objective 1 described in Section 2.3.1 will be addressed by estimating the proportion of participants who achieve SVR12, using the approach described in Section 4.2. A two-sided 90% CI will be calculated around the estimated SVR12 proportion. If this CI is entirely above 80%, then it will be concluded that there is evidence that the underlying SVR12 proportion is greater than 80%.

   b. As a supplementary analysis, SVR12 will be assessed in the analysis set that excludes participants who discontinued the study early for reasons clearly not related to the study treatment and participants who became re-infected with HCV prior to SVR12 visit, as described in Section 4.2.

10. Analysis of Primary Outcome Measure 2 described in Section 3.1
    a. To address safety in Primary Objective 2 described in Section 2.3.1, the AEs occurring after initiation of study treatment through the study visit occurring 4 weeks after the treatment completion will be summarized. The proportion of study participants with AEs will be estimated with a two-sided 95% CI around the estimate.
    b. As a supplementary safety analysis, all reported AEs (which include events that occur after the time frame defined above for Primary) will be summarized. A two-sided 95% CI will also be provided for the proportion of study participants with AEs.
11. Analysis of Primary Outcome Measure 3 described in Section 3.1
    a. To address tolerability in Primary Objective 2 described in Section 2.3.1, tolerability failures will be listed and described.
    b. The tolerability failure listing will be accompanied by treatment duration and the associated AEs.
12. Analysis of secondary outcome measures
    a. To address Secondary Objective 1, HCV RNA measurements at study visits will be assessed with proportion estimates with two-sided 90% CI.
    b. To address Secondary Objective 2, virologic failures will be listed and described. Listings on virologic failure will be accompanied by HCV RNA results and any available information on HCV genotype/subtype, RAS and phylogenetic results.
    c. To address Secondary Objective 3, SVR12 analysis described above in 9.a will be presented separately by HIV-1 infection status. In addition, HCV RNA measurements at study visits described above will be assessed with proportion estimates with two-sided 90% CI for the subgroup consisting of HIV-1 infected participants.