A5360

Primary Statistical Analysis Plan

Version 2.0

A Single-arm Study to Evaluate the Feasibility and Efficacy of a Minimal Monitoring Strategy to Deliver Pan-genotypic Ribavirin-free HCV Therapy to HCV Infected Populations who are HCV Treatment Naïve with Evidence of Active HCV Infection: The MINMON Study

Protocol Version 1.0 LOA #3

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Created by:

[REDACTED]

SDAC/Harvard T.H. Chan School of Public Health

1 Version History Table

Version	Changes Made	Rationale	Effective Date
1	Original Version (including protocol revisions including LOAs #1, #2 and #3)	Initial version	5/16/2019
2	Edited exploratory outcomes; defined reference start dates; adjusted post MINMON visit windows; added HCV genotype to analysis approaches; updated report contents	Report will focus on the week 24 analysis objectives, and therefore will only include exploratory outcomes related to this timeframe.	4/29/2020

2 Introduction

2.1 Purpose and Scope

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcome measures and additional outcome measures of the A5360 study that will be included in the primary manuscript, and which address, at a minimum, 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 among the study team, and to provide agreement between the study team and statisticians 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 a separate document called the Primary Analysis Implementation Plan (AIP).

Analyses for the Primary Analysis Report will be triggered by the study's primary completion date (PCD) which is defined as the date when the Sustained Virologic Response (SVR) evaluation visit has occurred for all participants enrolled. The SVR evaluation visit is the first clinic visit occurring more than 22 weeks post study entry (and up to 76 weeks post entry), where samples for HCV RNA were collected). These analyses will be finalized after all queries have been resolved.

Analyses not included in this document (i.e. those planned for manuscripts subsequent to the primary one), will be outlined in a separate, Secondary Statistical Analysis Plan, and parallel Secondary AIP.

2.2 Summary of Major Changes

Throughout this document, major updates will be in **bold** face type.

3 Study Overview

3.1 Study Design

Copied from Schema:

DESIGN

This is a phase IV open-label, multicenter, prospective study to assess the feasibility and efficacy of a minimal monitoring (MINMON) approach in active hepatitis C virus (HCV)-infected, treatment naïve participants, with and without HIV-1 co-infection, and with no cirrhosis or with compensated cirrhosis only. This study will enroll a cohort of participants with active HCV-infection to follow a minimal monitoring protocol, at US and non-US sites:

1) *No pre-treatment HCV genotyping;*
2) *Entire treatment course (84 tablets) given to participants at entry;*
3) *No scheduled on-treatment laboratory monitoring or clinic visits;*
4) *Remote contact with participants at week 4 (adherence counseling and locator update) and week 22 (scheduling of SVR visit and locator update).*
5) *Participants will receive the fixed-dose combination (FDC) of sofosbuvir/velpatasvir (SOF/VEL) for 12 weeks.*

DURATION *72 weeks*

SAMPLE SIZE *400 participants*

POPULATION *Men and women aged 18 years or older with active HCV-infection of any genotype, HCV treatment naïve, with or without HIV-1 co-infection. Persons with either compensated cirrhosis or without evidence of cirrhosis are eligible.*

STRATIFICATION *The study will use stratification factors to limit enrollment by certain subgroups. These stratification factors include geographical location (limited to no more than 132 participants enrolled from sites in the US within the overall study sample), HIV-1 infection (limited to no more than 200 participants being HIV-1 positive within the overall study sample), and cirrhosis status (limited to no more than 80 participants within the overall study sample having compensated cirrhosis). There are no additional restrictions regarding participants who are both HIV-co-infected and have compensated cirrhosis, and or/geographical distribution of those participants.*

3.2 Hypotheses

A MINMON strategy to deliver interferon and ribavirin (RBV)-free pan-genotypic therapy to participants with active HCV infection who are HCV treatment-naïve, globally, will be efficacious and safe.

3.3 Study Objectives

This Primary SAP addresses the following primary, secondary and selected exploratory objectives listed in the study protocol. Other study objectives in the protocol will be addressed in separate analysis plan documents.

3.3.1 Primary Objectives

1. To estimate SVR (defined as HCV RNA < lower limit of quantification [LLOQ] at least 10 weeks after the end of treatment [EOT] [which is at least 22 weeks from the study entry visit date]).

2. To summarize the occurrence of serious adverse events (SAEs) within 24 weeks following study entry.

3.3.2 Secondary Objectives

1. To estimate the proportion of participants with unplanned clinic visits prior to SVR evaluation.

2. To summarize the occurrence of adverse events, other than SAEs, within 24 weeks following study entry.

3. To estimate the proportion of participants who prematurely discontinue HCV treatment.

3.3.3 Exploratory Objectives (only the objectives addressed in the primary analysis are listed here)

1. *To describe the number and types of evaluations performed at unplanned visits.*

2. *To estimate the prevalence of HCV resistance-associated substitutions (RASs) among participants who do not achieve SVR [if data available].*

3.4 Overview of Sample Size Considerations

The sample size of 400 participants in this single-arm study was chosen for statistical properties regarding the use of efficacy data from this study to inform the utility and feasibility of future studies of the MINMON approach, and the precision (based on confidence interval (CI) width) about sustained virologic response (SVR) efficacy outcome estimates. A high benchmark is defined when the lower confidence limit of the 2-sided 95% CI about the SVR estimate is strictly greater than 96%. If a high benchmark is observed in A5360, then SVR for the MINMON strategy exceeds 96%--and future randomized clinical trials may not be needed. A low benchmark is defined as when the upper confidence limit of the 2-sided 95% CI about the SVR estimate is

strictly less than 95%. If neither benchmark is met, then it may be desirable to use the MINMON approach versus SOC in future RCT considering the efficacy estimates from this study. For additional details on sample size considerations, refer to protocol section 10.4.

3.5 Overview of Formal Interim Monitoring

Timing and triggers for reviews: The study will undergo interim review at least annually by an ACTG-appointed Study Monitoring Committee (SMC). The first interim review will occur no more than one year after the enrollment of the first study participant or approximately 6 months after 25% of the study sample (100 participants) have completed 12 weeks on study, whichever occurs earlier. An unplanned interim review will be triggered if, at any time, more than 20 persons are not evaluable for the SVR outcome before study discontinuation or 76 weeks following study enrollment. Another trigger for an unplanned interim review is if, at any time, the number of participants experiencing an SAE exceeds 5% of the interim analysis dataset, and the absolute number of participants with SAEs is at least 10. An interim review may also be convened if a concern is identified by the DAIDS clinical representative, the study chairs, or study statistician in consultation with the team.

Scope of reports: Items for SMC interim review include the following: screening and accrual, baseline characteristics of study sample, data (and specimen) completeness, premature study treatment and study discontinuation, unplanned study visits, safety (serious and other adverse events), evaluability for primary efficacy outcome, and for interim reviews including efficacy outcome: SVR outcome estimation.

Interim looks at efficacy and modification guidelines: A planned interim review for efficacy will be triggered when SVR outcomes are available for approximately 100 participants, but could occur earlier (under case of a faster than anticipated accrual rate). The team wishes that the interim look at efficacy occur while the study is still accruing, so that if SVR rate is unacceptably low (ie, futility), that there is still an opportunity to intervene before accrual to the study is completed. If the analysis sample for the initial planned review for efficacy as outlined above includes fewer than 40% participants from non-US clinical research sites, then a second planned review of efficacy will be triggered when SVR outcomes are available on approximately 230 participants (with the upper limit of US participants of 132, this estimates at least 40% non-US representation in the 2nd efficacy look interim analysis sample). The same analysis plan and monitoring bounds as defined in the first look as described below would be applied to this second look at SVR.

Consideration would be given to closer monitoring or stopping the study if there is early and strong evidence to exclude the SVR rate from being 95% or higher (ie, upper confidence bound on a 1-sided 99.9% CI is lower than 95%). With 100 participants, this boundary would be met if the observed SVR rate were 86% or lower (which corresponds to 14 or more SVR non-responders out of 100). For additional information, SVR estimates will be provided separately for subgroups such as defined by geographical location (i.e. by country), by HIV-coinfection status, and by cirrhosis status.

However, if the SMC sees early benefit of the MINMON intervention, the team intends the study to proceed with full accrual and follow-up in order to confirm early evidence, and gain precision on the efficacy outcome estimate and other outcomes.

4 Outcome Measures

Note: Information below in *italics* has been formatted according to the results format specifications in clinicaltrials.gov. All primary and secondary outcomes are anticipated to be reported with the initial results submission.

4.1 Primary Outcome Measures

4.1.1 Primary Efficacy Outcome Measure

***Measure Title**: Percentage of Participants with Sustained Virologic Response 12 (SVR12)*

***Measure Description**: SVR12 was defined as plasma HCV RNA less than the lower limit of quantification (LLOQ) from the earliest sample drawn at least 22 weeks following study treatment initiation (i.e. at a visit scheduled at least 10 weeks after scheduled end of study treatment). Participants without any HCV RNA result at least 22 weeks after treatment initiation will be considered as having HCV RNA greater than the LLOQ.*

A two-sided 95%, confidence interval was calculated for this percentage using the Wilson (score) method.

***Time Frame**: At least 22 weeks and up to 76 weeks from treatment initiation.*

***Population Description**: Participants who enrolled and received first dose of study medication.*

Associated study objective: "To estimate SVR (defined as HCV RNA < lower limit of quantification [LLOQ] at least 10 weeks after the end of treatment [EOT] [which is at least 22 weeks from the study entry visit date])."

Details: Due to the definition of SVR outcome measure, missing HCV RNA results will lower the overall percentage of participants with SVR. Therefore, various reasons for non-SVR (e.g., discontinued treatment early due to various reasons including intolerability, observed HCV RNA $\geq$ LLOQ, missing evaluation for SVR (and reasons as known), and the number of participants meeting each reason for non-SVR, will be presented in order to interpret the overall SVR sample estimate.

For interim analyses: Interim analysis is planned when SVR outcomes are available for approximately 100 participants. At interim reviews, SVR will be calculated only among those with potential to contribute to SVR (by having at least 22 weeks elapsed since study entry). Imputation of missing SVR evaluation as non-SVR response will only occur for participants for whom more than 76 weeks since study enrollment has elapsed. In other words, early study discontinuations prior to week 22 will not be counted in SVR estimation at interim review, as these could bias the estimation of SVR towards futility. Instead, these early study discontinuations prior to week 22 (before available for SVR evaluation), and others missing SVR evaluation, will contribute to the interim monitoring

trigger. For more details, refer to Overview of Formal Interim Monitoring of section 3.5 above.

4.1.2 Primary Safety Outcome Measure

***Measure Title**: Percentage of Participants with an Occurrence of Serious AEs According to ICH Criteria*

***Measure Description**: Serious adverse events (SAEs) as defined by International Council for Harmonization (ICH) guidelines occurring from treatment initiation until 28 weeks following treatment initiation (end of week 24 visit window)*

A two-sided, 95% confidence interval was calculated for the percentage using the Wilson (score) method.

***Time Frame**: Within 28 weeks following treatment initiation.*

***Population Description**: Participants who received first dose of study medication and had at least one post-entry evaluation for adverse events.*

Associated study objective: "To summarize the occurrence of serious adverse events (SAEs) within 24 weeks following study entry."

Details: All SAEs meeting this outcome measure will be summarized and described. Note, the timing above applies to the timing of the event occurrence, and not to when the event was reported. For example, an event occurring at week 23 might not be reported until the week 48 clinic visit. Also, a clinic visit is not required for "evaluation for adverse events''; the reporting of an AE qualifies as meeting this criterion. This allows exclusion of participants who are lost after initial dose with no information on AEs following initiation of study treatment.

4.2 Secondary Outcome Measures

4.2.1 Secondary Outcome Measure #1 – Unplanned clinic visits

***Measure Title**: Percentage of Participants with at Least One Unplanned Clinic Visit Prior to SVR12 Evaluation*

Measure Description: *According to the study minimal monitoring intervention, there were no planned clinic visits prior to study week 24, when SVR12 was scheduled to be evaluated.*

A two-sided, 95% confidence interval was calculated for the percentage using the Wilson (score) method.

***Time Frame**: From treatment initiation to week 22.*

***Population Description**: Participants who enrolled and received first dose of study medication.*

Associated study objective: "To estimate the proportion of participants with unplanned clinic visits prior to SVR evaluation."

Details: Number, reasons for and timing of unplanned clinic visits will also be summarized.

4.2.2 Secondary Outcome Measure #2 – Other AEs

***Measure Title**: Percentage of Participants with an occurrence of one or more non-serious, Grade >= 3 Adverse Event, or treatment limiting AE.*

***Measure Description**: AEs included all primary diagnoses, primary signs/symptoms, and primary laboratory abnormalities that either had severity grade ≥ 3 or led to a change in study medication. SAEs by ICH criteria were excluded as they contributed to the primary safety outcome measure.*

A two-sided, 95% confidence interval was calculated for the percentage using the Wilson (score) method.

***Time Frame**: Within 28 weeks following treatment initiation.*

***Population Description**: Participants who received first dose of study medication and had at least one post-entry evaluation for adverse events.*

Associated study objective: "To summarize the occurrence of adverse events, other than SAEs, within 24 weeks following study entry."

Details: All AEs meeting this outcome measure will be enumerated, and summarized by MeDdRA categorization (SOC and HLT).

Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, used for severity grading.

Note, the timing above applies to the timing of the event and not to when the event was reported. For example, an event occurring at week 23 might not be reported until a week 48 clinic visit. Also, a clinic visit is not required for "evaluation for adverse events''; the reporting of an AE qualifies as meeting this criterion. This allows exclusion of participants who are lost after initial dose with no information on AEs following initiation of study treatment.

4.2.3 Secondary Outcome Measure #3 – Premature Discontinuation of HCV medications

***Measure Title**: Percentage of Participants who Prematurely Discontinued HCV Study Medications*

***Measure Description**: Premature discontinuation was defined by participant self-report, as there were no planned clinic visits during the 12 week study medication period. Participants discontinuing study follow-up without information about completion of HCV study medications were counted as having prematurely discontinued medications.*

A two-sided, 95% confidence interval was calculated for the percentage using the Wilson (score) method.

***Time Frame**: From treatment initiation to SVR12 evaluation.*

***Population Description**: Participants who enrolled into study and received first dose of study medication.*

Associated study objective: "To estimate the proportion of participants who prematurely discontinue HCV treatment."

Details: Since participant reporting of the timing of stopping study treatment may be by participant recall more than 12 weeks after the fact, premature discontinuation will be defined by the final treatment dose date being fewer than 11 weeks (or fewer than 77 days) post initial dose accounting for reported treatment interruptions. The timing and reasons for premature discontinuation will be summarized, as those details are available in the study database. As available, any other details on the disposition of study treatment (e.g. treatment interruptions), will be summarized.

4.3 Other Outcome Measures

4.3.1 Types of evaluations at unplanned clinic visits

This will be a descriptive analysis to summarize the nature of evaluations at unplanned clinic visits, e.g. whether and number of lab tests.

4.3.2 Prevalence of HCV resistance-associated substitutions (RASs) among participants who do not achieve SVR [if RAS data are available at time of analysis report]

Measure Title*: Percentage of Participants with HCV resistance-associated substitutions (RASs) among non-SVR Participants*

Measure Description*: HCV resistance-associated substitutions (RASs) were defined as amino acid substitution that confer reduced susceptibility to a direct-acting antiviral (DAA) and may contribute to virology failure. Non-SVR responders were assessed for RASs by comparing SVR12 sequence data with baseline to assess amino acid changes in the NS5A and NS5B gene regions.*

Time Frame*: At time of SVR12 evaluation.*

Population Description*: Participants who do not achieve SVR.*

Associated study objective: "To estimate the prevalence of HCV resistance-associated substitutions (RASs) among participants who do not achieve SVR."

Details: Those who do not achieve SVR with an observed HCV RNA >LLOQ will have both baseline and SVR specimens tested for HCV RASs by sequencing the NS5A and NS5B regions. Participants in this sub-set with HCV RASs present in their SVR specimen that were not present in their baseline specimen will be enumerated along with the relative frequencies of new RASs. A description of the observed RASs will also be provided.

Note: This outcome will only be included in the analysis report if data on RASs is available to the statistician and ready for analysis.

5 Statistical Principles

5.1 General Considerations

5.1.1 Definitions

Baseline: Any characteristic measured or evaluated prior to the first dose of study medication (including information collected at screening) can be used as a 'baseline' characteristic. Areas where use of screening could induce bias (due to eligibility criteria) will be noted in any analysis, as applicable.

SVR: Target not detected (TND) result is a valid that also qualifies as <LLOQ and will be counted as an SVR responder. When handling of multiple HCV RNA results, the valid result from the earliest sample drawn within the SVR evaluation window (starting 22 weeks post study treatment initiation) will be used for analysis.

Reference Start Dates:

- Study enrollment date: Date participant was enrolled on study.
- Treatment start date: Date participant took first dose of study treatment.

5.1.2 Clinic Study Visit Windows

MINMON intervention EPOCH [Step 1]: The first follow-up clinic visit at study week 24, for primary outcome SVR evaluation has a window of -14 days to +28 days. If week 24 study visit is missed, this "primary SVR evaluation" visit can occur anytime up to study week 72 which is the end of study follow-up.

Post SVR, post MINMON, or follow-up EPOCH [Step 2]: Two clinic visits are scheduled post SVR at week 48 and 72. The ranges of week 48 clinic visits were examined and the observed range is used for visit window; weeks 48 has a window of -28/+60 days. Week 72 has a window of ± 28 days.

5.1.3 Analysis Sets

Enrolled participants who do not start study medication will be excluded from all analyses. Note that per protocol instructions, the first dose of study medication is to be observed in the study clinic during the entry evaluation visit.

Full analysis sample (= Efficacy analysis sample at final analysis): Participants who started study medication. For the efficacy analysis sample for interim reviews, refer to section: 4.1.1 Primary Efficacy Outcome Measure. At interim analyses, the efficacy analysis sample will differ from the full analysis sample as follows: participants missing HCV RNAs for SVR evaluation will not be counted as SVR non-responders unless they enrolled more than 76 weeks prior to dataset finalization. Thus, the efficacy analysis sample at interim reviews will be based on observed HCV RNAs in the SVR evaluation window plus participants who both left the study without a result for SVR evaluation and who enrolled more than 76 weeks ago (and thus can no longer be evaluated for SVR on study).

Safety analysis sample: Participants who started study medication and who were evaluated for AEs for the time period after first dose of study treatment through up to 24 week later. This criterion will be met for any participant having an unscheduled visit prior to week24/SVR evaluation, or any participant having a week 24 or SVR evaluation visit. At interim analysis, due to no planned study clinic visits prior to study week 24, this analysis sample include all participants who started treatment, and only exclude those who were both known lost to all follow-up and without any follow-up for AEs. This sample will be split into subgroups defined by those having week 24/SVR evaluation visit versus not.

5.1.4 Analysis Approaches

The analysis of each objective addressed in this SAP will be conducted using the appropriate analysis sample as defined in section 4.1.

As this is a single arm study, the primary descriptive and statistical inference on outcomes will be performed on the entire specified analysis sample as a single group, and focus on estimation. However, as there exist key subgroups upon which separate estimates for outcomes is desired, analyses will often (as specified below) be repeated within subgroups defined by the following:

- **Country** (to help inform each MOH or other, policy groups, as well as serving as an imperfect surrogate for HCV genotype)
- **Cirrhosis status** *(*compensated cirrhotic and non-cirrhotic by classification by FIB-4 score)
- **HIV-1 infection status** (positive and negative)
- **Sex assigned at birth** (female and male)
- **If data are available, by HCV genotype**

However, there are no plans to perform formal hypothesis testing for differences in outcomes among subgroups.

All statistical hypothesis testing at final analysis, will use the nominal significance level of 0.05. See detailed specifications at interim reviews for alternative significance levels.

6 Report Contents

Detailed descriptions of the content of each of the following sections are given in the AIP:

1. CONSORT Diagram (final analysis only)
2. Accrual
3. Baseline characteristics
4. Study conduct
    a. Study status and follow-up
    b. Study medication disposition
    c. Remote contact at week 4
    d. Adherence of medication, premature discontinuation of study treatment
    e. Remote contact at week 22
    f. Data and specimen availability (other than for SVR evaluation)
    g. Unplanned Clinic Visits (number/reasons)
5. Safety
    a. Primary Safety Outcome Measure: SAEs within 24 weeks
    b. Secondary Safety Outcome Measure: other AEs within 24 weeks
    c. Summary of other AEs (all AEs after 24 weeks)
    d. Summary of pregnancies that occur during study participation
    e. Summary of HIV-1 RNA among PLWH at Week 24/SVR visit
6. Efficacy
    a. Study visit of SVR collection
    b. SVR12 estimation
        i. Summary of details (e.g assay, LLOQ, lab) used to evaluate SVR
        ii. Estimation within subgroups
        iii. Reasons for non-SVR
        iv. Summary of participants not achieving SVR (baseline characteristics, study/treatment disposition, safety and tolerability information)
    c. Summary of HCV RASs among participant not achieving SVR [if data available]