A5360

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

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

NIAID CRMS # 30103

This file contains the current ACTG A5360 protocol, which includes the following document:

- Letter of Amendment #5, dated 28 July 2020
- Letter of Amendment #4, dated 22 June 2020
- Clarification Memorandum #3, dated 09 April 2020
- Clarification Memorandum #2, dated 23 September 2019
- Clarification Memorandum #1, dated 26 March 2019
- Letter of Amendment #3, dated 11 February 2019
- Letter of Amendment #2, dated 08 August 2018
- Letter of Amendment #1, dated 15 June 2018
- Protocol Version 1.0, dated 10 January 2018

Letter of Amendment #5 for:

A5360

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

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

NIAID CRMS # 30103

Letter of Amendment Date: 28 July 2020

ACTG NETWORK COORDINATING CENTER
Social & Scientific Systems, a DLH Company
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3000
Fax: 301-628-3302

LETTER OF AMENDMENT #5

DATE: July 28, 2020

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5360 Protocol Team

SUBJECT: Letter of Amendment #5 for Protocol A5360

The following information affects the A5360 study and must be forwarded to each site's institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by the IRB/EC before implementation.

The following information may also affect the Sample Informed Consent. The IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies

that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory file.

The main reason for this LOA is to provide additional guidance for the resumption of study visits for non-US sites, in the midst of the ongoing COVID-19 pandemic and in follow-up to the COVID-19-related LOA #4, dated 06/22/20.

This LOA is being implemented for the following reason:

- Given the evolving pandemic in non-US settings, a team decision has been made to extend the upper window for the week 72 in-person visit for non-US sites to February 28, 2021, which is the last date for which this visit can be completed. If non-US sites are unable to complete the week 72 in-person visit by this date, this will be considered a missed visit. In response, the following sections have been updated: Table 6.1-2, section 6.2.4, and section 6.2.5.

The following are changes (noted in bold or strikethrough) to A5360, Version 1.0, dated 01/10/18, titled "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." These changes will be included in the next version of the A5360 protocol if it is amended at a future date. Changes that have already been made (either by LOA or by CM) have been incorporated in the excerpted text shown below (and are no longer presented in bold or strikethrough).

1. Table 6.1-2 (Schedule of Evaluations: Step 2 Visits Post SVR Evaluation), the visit windows for weeks 48 and 72 have been updated as shown in the excerpt from the table below.

	Weeks			
	42	48	68	72
Evaluation	Window ±28 days, except for the following: • In-person week 48 for non-US participants ONLY: Window is -28/ +56 days • In-person week 72 for US participants ONLY: Window is -28 days through October 31, 2020 (see Notes A, B, and C). • **In-person week 72 for non-US participants ONLY: Window is -28 days through February 28, 2021 (see Notes D and E).**			

NOTE A: The extension in the week 72 visit for US participants applies only to study participants with completed week 24/SVR visit by the date of the A5360 Version 1.0 Clarification Memo #3, dated 04/09/20.

NOTE B: The extension in the week 72 visit also covers **US** participants who time out of the week 72 window (implemented via CM #3, dated 04/09/20), before the approval of A5360 Version 1.0 LOA #4, dated 06/22/20.

NOTE C: If the week 72 in-person visit for US participants cannot be completed by October 31, 2020, this will be considered a missed visit.

NOTE D: The extension in the week 72 visit also covers non-US participants who time out of the week 72 window before the approval of A5360 Version 1.0 LOA #5, dated 07/28/20.

NOTE E: If the week 72 in-person visit for non-US participants cannot be completed by February 28, 2021, this will be considered a missed visit.

2. Section 6.2.4, Post-Entry Evaluations, the following subsection has been added:

   Alternate Completion of Post-Entry Evaluations

   - Post-SVR week 48 visit:

     1) For non-US participants: The post-SVR week 48 in-person visit may be scheduled to occur up to and including 56 days after the week 48 ideal visit date. Complete the week 48 visit per Table 6.1-2 (Schedule of Evaluations: Step 2 - Visits Post SVR Evaluation).

     2) For all participants: If a week 48 in-person visit cannot be completed before the visit window closes, enter the visit as, "Participant unable to come to clinic due to COVID-19," using the instructions provided by the Data Management Center (DMC), entitled, "COVID-19 DMC Updates-FINAL."

   - Post-SVR week 72 visit:

     1) For US participants: The post-SVR week 72 in-person visit may be scheduled through October 31, 2020. Complete the week 72 visit per Table 6.1-2 (Schedule of Evaluations: Step 2 - Visits Post SVR Evaluation).

        NOTE: If a week 72 in-person visit cannot be completed for a US participant by October 31, 2020, this will be considered a missed visit.

     2) For non-US participants: ~~If a week 72 in-person visit cannot be completed before the visit window closes, contact the A5360 core team (actg.coreA5360@fstrf.org) for further guidance.~~ **The post-SVR week 72 in-person visit may be scheduled through February 28, 2021. Complete the week 72 visit per Table 6.1-2 (Schedule of Evaluations: Step 2 - Visits Post SVR Evaluation).**

        NOTE: If a week 72 in-person visit cannot be completed for a non-US participant by February 28, 2021, this will be considered a missed visit.

3. Section 6.2.5, Study Completion Evaluations, the first paragraph has been updated as follows:

   For Step 2, week 72 **in-person visit** (± **-**28 days, **through February 28, 2021 for non-US participants;** -28 days, through October 31, 2020, for US participants) will be the final study visit for all participants, independent of the entry week for Step 2.

4. Protocol Signature Page

   A Protocol Signature Page (PSP) is appended for submission to the DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

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

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

Letter of Amendment #4 for:

A5360

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

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

NIAID CRMS # 30103

Letter of Amendment Date: 22 June 2020

ACTG NETWORK COORDINATING CENTER
Social & Scientific Systems
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3000
Fax: 301-628-3302

LETTER OF AMENDMENT #4

DATE: June 22, 2020

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5360 Protocol Team

SUBJECT: Letter of Amendment #4 for Protocol A5360

The following information affects the A5360 study and must be forwarded to each site's institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by the IRB/EC before implementation.

The following information may also affect the Sample Informed Consent. The IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received

and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory file.

The main reason for this LOA is to provide guidance for the resumption of study visits in follow-up to the COVID-19-related Clarification Memo #3 (CM #3), dated 04/09/20, as US and Non-US sites begin to open to research visits. This LOA is formal notification that the temporary pause of all study visits as stated in CM #3 is now lifted. All sites should contact study participants when sites are able to resume in-person research visits to schedule the participant's next visit. This contact can be considered the remote contact corresponding to week 42 or week 68 and must be documented in the participant's study file.

This LOA is being implemented for the following reasons:

- A team decision has been made to extend the upper window for the week 72 in-person visit for US sites, to October 31, 2020, which is the last date for which this visit can be completed. If US sites are unable to complete the week 72 in-person visit by this date, this will be considered a missed visit. In response, the following sections have been updated: Table 6.1-2, section 6.2.4, and section 6.2.5.

- Per DAIDS directive, COVID-19-related changes made via CM #3 have been incorporated. In response, the following sections have been updated: Table 6.1-2, section 6.2.4, and section 6.2.5.

The following are changes (noted in bold or strikethrough) to A5360, Version 1.0, dated 01/10/18, titled "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." These changes will be included in the next version of the A5360 protocol if it is amended at a future date. Changes that have already been made (either by LOA or by CM) have been incorporated in the excerpted text shown below (and are no longer presented in bold or strikethrough).

1. Table 6.1-2 (Schedule of Evaluations: Step 2- Visits Post SVR Evaluation), the visit windows for weeks 48 and 72 have been updated as shown in the excerpt from the table below.

	Weeks			
	42	48	68	72
Evaluation	**Window ±28 days, except for the following:** • **In-person week 48 for non-US participants ONLY: Window is -28/ +56 days** • **In-person week 72 for US participants ONLY: Window is -28, ~~/+84~~ days through October 31, 2020 (see Notes A, B, and C).**			

NOTE A: The extension in the week 72 visit for US participants applies only to study participants with completed week 24/SVR visit by the date of the A5360 Version 1.0 Clarification Memo #3, dated 04/09/20.

NOTE B: The extension in the week 72 visit also covers participants who time out of the week 72 window (implemented via CM #3, dated 04/09/20), before the approval of A5360

Version 1.0 LOA #4, dated 06/22/20.

NOTE C: If the week 72 in-person visit for US participants cannot be completed by October 31, 2020, this will be considered a missed visit.

2. Section 6.2.4, Post-Entry Evaluations, the following sentence has been added at the end of the first paragraph in the Step 2 Registration subsection:

   Refer to the Alternate Completion of Post-Entry Evaluations subsection for the instructions on completing study visits when an in-person visit cannot be safely conducted.

3. Section 6.2.4, Post-Entry Evaluations, the following subsection has been added:

   Alternate Completion of Post-Entry Evaluations

   - **Post-SVR week 48 visit:**
     1) **For non-US participants: The post-SVR week 48 in-person visit may be scheduled to occur up to and including 56 days after the week 48 ideal visit date. Complete the week 48 visit per Table 6.1-2 (Schedule of Evaluations: Step 2 - Visits Post SVR Evaluation).**
     2) **For all participants: If a week 48 in-person visit cannot be completed before the visit window closes, enter the visit as, "Participant unable to come to clinic due to COVID-19," using the instructions provided by the Data Management Center (DMC), entitled, "COVID-19 DMC Updates-FINAL."**
   - **Post-SVR week 72 visit:**
     1) **For US participants: The post-SVR week 72 in-person visit may be scheduled through October 31, 2020 ~~84 days after the week 72 ideal visit date~~. Complete the week 72 visit per Table 6.1-2 (Schedule of Evaluations: Step 2 - Visits Post SVR Evaluation).**

        NOTE: If a week 72 in-person visit cannot be completed for a US participant by October 31, 2020, this will be considered a missed visit.
     2) **For non-US participants: If a week 72 in-person visit cannot be completed before the visit window closes, contact the A5360 core team (actg.coreA5360@fstrf.org) for further guidance.**

4. Section 6.2.5, Study Completion Evaluations, the first paragraph has been updated as follows:

   For Step 2, week 72 **in-person visit** (±28 days **for non-US participants, -28~~/+84~~ days, through October 31, 2020, for US participants)** will be the final study visit for all participants, independent of the entry week for Step 2.

5. Protocol Signature Page

   A Protocol Signature Page (PSP) is appended for submission to the DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

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

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

Clarification Memo #3 for:

A5360

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

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

NIAID CRMS # 30103

Clarification Memo Date: 09 April 2020

ACTG NETWORK COORDINATING CENTER
Social & Scientific Systems
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3000
Fax: 301-628-3302

CLARIFICATION MEMO

DATE: April 9, 2020

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5360 Protocol Team

SUBJECT: Clarification Memo #3 for Protocol A5360 (COVID-19)

This clarification memo (CM) does not result in a change in the protocol informed consent document. The Division of AIDS (DAIDS) has determined that these protocol changes and clarifications should be implemented immediately in response to the COVID-19 pandemic, which poses a safety risk to participants and site staff. Sites do not need institutional review board (IRB) approval prior to implementing this CM.

DAIDS does not require sites to forward this CM to their IRB; however, sites must follow their IRB's policies and procedures. If IRB review of CMs is required at a site, that site must submit this document for review.

Each site should file a copy of this CM with the protocol for reference.

The main reason for this CM is to provide guidance for study visits during the COVID-19 pandemic. The instructions in this CM supersede the instructions that were in the memo released by the A5360 Protocol Team on 03/23/20 with subject "COVID-19: Temporary Pause for Protocol A5360 (MINMON Study) and Guidance for Enrolled Participants."

All sites should contact study participants to inform them of the temporary pause in all study visits and that they will be contacted to schedule their next visit when the pause is lifted. This contact must be documented in the participant's study file but does NOT need to be recorded on the eCRFs and reported to the A5360 core team.

When the temporary pause on study visits is lifted, sites should contact study participants to schedule their next visit. This contact can be considered the remote contact corresponding to week 42 or week 68. This contact must be documented in the participant's study file.

The A5360 Protocol Team is closely monitoring the situation concerning the COVID-19 pandemic. New guidance will be released in the beginning of May 2020, if needed.

The following are clarifications (noted in bold or strikethrough) to Protocol A5360, Version 1.0, 01/10/18, titled "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." These clarifications will be included in the next version of the A5360 protocol if it is amended at a future date.

1. In section 6.1, Table 6.1-2 (Schedule of Evaluations: Step 2- Visits Post SVR Evaluation), the visit windows for weeks 48 and 72 have been updated as shown in the excerpt from the table below.

	Weeks			
	42	48	68	72
Evaluation	Window ±28 days**, except for the following:** • **Week 48 for non-US participants ONLY: window is -28/+56 days** • **Week 72 for US participants ONLY: window is -28/+84 days (see note)**			

NOTE: The extension in the week 72 visit for US participants applies only to study participants with completed week 24/SVR visit by the date of the A5360 Version 1.0 Clarification Memo #3, dated 04/09/20.

2. In section 6.2.4, Post-Entry Evaluations, the following sentence has been added at the end of the first paragraph in the Step 2 Registration subsection:

   Refer to the Alternate Completion of Post-Entry Evaluations subsection for the instructions on completing study visits when an in-person visit cannot be safely conducted.

3. In section 6.2.4, Post-Entry Evaluations, the following subsection has been added:

   Alternate Completion of Post-Entry Evaluations

   - **Post-SVR week 48 visit:**

1) **For non-US participants: The post-SVR week 48 visit may be scheduled to occur up to and including 56 days after the week 48 ideal visit date. Complete the week 48 visit per Table 6.1-2 (Schedule of Evaluations: Step 2 - Visits Post SVR Evaluation).**

2) **For all participants: If a week 48 visit cannot be completed before the visit window closes, enter the visit as a "Participant unable to come to clinic due to COVID-19" using the instructions provided by the Data Management Center (DMC), entitled "COVID-19 DMC Updates-FINAL."**

- **Post-SVR week 72 visit:**

1) **For US participants: The post-SVR week 72 visit may be scheduled to occur up to and including 84 days after the week 72 ideal visit date. Complete the week 72 visit per Table 6.1-2 (Schedule of Evaluations: Step 2 - Visits Post SVR Evaluation).**

2) **For all participants: If a week 72 visit cannot be completed before the visit window closes, contact the A5360 core team (actg.coreA5360@fstrf.org) for further guidance.**

4. In section 6.2.5, Study Completion Evaluations, the first paragraph has been updated as follows:

   For Step 2, week 72 **(**±28-days **for non-US participants, -28/+84 days for US participants)** will be the final study visit for all participants, independent of the entry week for Step 2.

Clarification Memo #2 for:

A5360

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

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

NIAID CRMS # 30103

Clarification Memo Date: 23 September 2019

ACTG NETWORK COORDINATING CENTER
Social & Scientific Systems
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3000
Fax: 301-628-3302

CLARIFICATION MEMO

DATE: September 23, 2019

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5360 Protocol Team

SUBJECT: Clarification Memo #2 for Protocol A5360

This clarification memo (CM) does not result in a change in the protocol informed consent document. The Division of AIDS does not require you to forward it to your institutional review board (IRB); however, you must follow your IRB's policies and procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this CM with the protocol for reference.

The protocol clarifications contained in this memo should be implemented immediately.

The following are clarifications (noted in bold or strikethrough) to Protocol A5360, Version 1.0, 01/10/18, titled "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." Changes that have already been made since the previous version (either by letter of amendment or clarification memo) have been incorporated in the excerpted text shown below (and are no longer presented in bold). These clarifications will be included in the next version of the A5360 protocol if it is amended at a future date.

1. Section 4.1.7 (Inclusion Criteria [Step 1]): The laboratory requirement for non-US laboratories has been revised to read:

   For HIV co-infected participants, HIV-1 RNA obtained within 90 days prior to study entry by any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that **is VQA certified** ~~operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs~~.

2. Section 4.1.8 (Inclusion Criteria [Step 1]): The laboratory requirement for non-US laboratories has been revised to read:

   For HIV co-infected participants, CD4+ cell count obtained within 90 days prior to study entry at any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that **is Immunology Quality Assessment (IQA) certified.** ~~operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.~~

3. Section 6.1-1 (Schedule of Evaluations: Step 1- Visits up Until SVR Evaluation): Step 2 Registration has been added to the SOE to match section 6.2.3 (Step 2 Registration Evaluations) and to clarify that registration for Step 2 must occur on the same day of the last visit on Step 1.

Section 6.1-1 (Schedule of Evaluations: Step 1- Visits up Until SVR Evaluation)

Evaluation	Screening	Entry/Week 0	Weeks			SVR Evaluation Visit (*if week 24 visit is missed; can occur up to week 72*)	Unplanned Study Visits (*see section 6.2.6*)
			4	22	24		
			Window ±7 days		Window -14/+28 days		
Documentation of Active HCV Infection	X						
Documentation of HIV-1 Status	X						
Calculated FIB-4 Score	X				X	X	As needed.
MELD Score		X					
Documentation of Cirrhosis Status	X				X	X	As needed.
Calculated CTP Score (if cirrhotic by FIB-4)	X				X	X	

Evaluation	Screening	Entry/Week 0	Weeks			SVR Evaluation Visit (*if week 24 visit is missed; can occur up to week 72*)	Unplanned Study Visits (*see section 6.2.6*)
			4	22	24		
			Window ±7 days		Window -14/+28 days		
Liver Elastography (see section 6.3.7)		X			X	X	
Medical History	X	X					
Medication History	X	X					
Clinical Assessments	X	X			X	X	As needed.
Hematology	X	X			X	X	
Liver Function Tests	X	X			X	X	
Blood Chemistries	X	X			X	X	As needed.
Calculated Creatinine Clearance	X						
INR	X				X	X	As needed.
Pregnancy Testing	X	X			If pregnancy is suspected.		
HBV Panel	X						
CD4+ (if HIV+)	X				X	X	
Plasma HIV-1 RNA (if HIV+)	X				X	X	
Plasma HCV RNA	X				X	X	
Stored Plasma/PBMC/Serum		X			X	X	As needed. (*Plasma sample will be stored if blood sample obtained*.)
Adherence Assessment			X (via remote contact)		X	X	
Health Outcomes Questionnaire		X			X	X	X
Health Care Utilization Questionnaire		X			X	X	X
Substance Use Questionnaire		X			X	X	
HCV Therapy Dispensed/First Dose Observed		X					

Evaluation	Screening	Entry/Week 0	Weeks			SVR Evaluation Visit (*if week 24 visit is missed; can occur up to week 72*)	Unplanned Study Visits (*see section 6.2.6*)
			4	22	24		
			Window +7 days		Window -14/+28 days		
Adherence Education and Counseling		X					
Pregnancy Prevention Counseling	X	X					
Cirrhosis Counseling		X			X	X	
HCV Risk-reduction Counseling		X			X	X	
Step 2 Registration					**X (Registration for Step 2 must occur on the same day of the last visit on Step 1; see section 6.2.3)**		
Locator Information		X	Update information, if needed.				
Remote Contact with Participants Outside of Planned Clinic Visits			X	X (see note in section 6.2.4)			

4. Section 6.3 (Instructions for Evaluations): The following paragraph has been added as the first paragraph of this section, and the link to the Source Document Guidelines on the DAIDS website has been updated in the now second paragraph.

   Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf.

   All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document: ~~https://www.niaid.nih.gov/sites/default/files/documents/sourcedocappndx.pdf.~~ **https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf.**

5. Section 6.3.12 (Immunologic Studies [For HIV co-infected participants]): The laboratory requirements have been revised to read:

   CD4+
   Screening ~~Obtain~~ absolute CD4+ count **must be performed** within 90 days prior to **study** entry ~~from~~ **at** a laboratory that possesses a CLIA certification or equivalent **(US sites), or IQA certification (non-US sites).**

For **entry and** post-entry evaluations, all laboratories must possess a CLIA certification or equivalent **(US sites), or** ~~and must be certified for protocol testing by the DAIDS Immunology Quality Assurance (~~IQA~~) Program~~ **certification (non-US sites)**.

6. Section 6.3.13 (Virologic Studies [Plasma HIV-1 RNA (For HIV Co-infected Participants]): The laboratory requirements have been revised to read:

   Plasma HIV-1 RNA (For HIV Co-infected Participants)
   Screening HIV-1 RNA must be performed within 90 days prior to study entry ~~by~~ **at** a laboratory that possesses a CLIA certification or equivalent **(US sites) or Virology Quality Assurance (VQA) certification (non-US sites)**.

Clarification Memo #1 for:

A5360

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

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

NIAID CRMS # 30103

Clarification Memo Date: 26 March 2019

ACTG NETWORK COORDINATING CENTER
Social & Scientific Systems
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3000
Fax: 301-628-3302

CLARIFICATION MEMO

DATE: March 26, 2019

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5360 Protocol Team

SUBJECT: Clarification Memo #1 for Protocol A5360

This clarification memo (CM) does not result in a change in the protocol informed consent document. The Division of AIDS does not require you to forward it to your institutional review board (IRB); however, you must follow your IRB's policies and procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this CM with the protocol for reference.

The protocol clarifications contained in this memo should be implemented immediately.

The following are clarifications (noted in bold or strikethrough) to Protocol A5360, Version 1.0, 01/10/18, titled "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." These clarifications will be included in the next version of the A5360 protocol if it is amended at a future date.

1. Section 4.1.10 (Inclusion Criteria): The measurement unit for albumin values has been revised to read:

   - Albumin >3.0 g/**d**L

2. Section 4.1.10 (Inclusion Criteria): The measurement unit for platelet count values has been revised to coincide with the platelet count measurement unit found in section 6.3.3 (Calculated FIBROSIS-4 [FIB-4] Score):

   - Platelet count >50~~,000/mm^3~~ **x 10^9/L**

Letter of Amendment #3 for:

A5360

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

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

NIAID CRMS # 30103

Letter of Amendment Date: 11 February 2019

ACTG Network Coordinating Center
Social & Scientific Systems
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910

Telephone: 301-628-3000
Fax: 301-628-3302

LETTER OF AMENDMENT

DATE: February 11, 2019

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5360 Protocol Team

SUBJECT: Letter of Amendment #3 for Protocol A5360, Version 1.0, 01/10/18, entitled "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"

The following information impacts the A5360 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.

The following information may also impact the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory files.

This LOA is being implemented for the following reasons, per team decision:

- A laboratory report of azoospermia is no longer required to document successful vasectomy and this has been removed from the list of accepted documentation in section 4.1.14.
- Language has been updated in section 4.5.1, per recent protocol template updates, to reflect that participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify.
- Language has been updated to include replacement of study drug pills in addition to bottles in section 5.2.1.
- Language regarding HIV testing at non-US sites has been updated in section 6.3.13 to match section 4.1.7.
- Clarification was needed regarding the timing of the initial planned Study Monitoring Committee interim review and the timing of the distribution of routine safety monitoring reports in sections 7.4, and 10.5.1
- Links to the DAIDS Regulatory Support Center (RSC) website have been updated in sections 7.2, 7.3.1 and 7.3.3.
- Clarification was needed regarding the genetic testing information found in the sample informed consent (SIC) since host genetic testing is not planned for A5360.
- The team roster and study management sections have been updated to reflect recent changes to team composition.
- Per a new regulatory requirement by the Division of AIDS (DAIDS), a Protocol Signature Page (PSP) is appended for submission to DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

The following are changes (noted in bold or strikethrough) to A5360, Version 1.0, dated 01/10/18, titled " 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." These changes will be included in the next version of the A5360 protocol if it is amended at a future date. Changes that have already been made (by LOA #1 and #2) have been incorporated in the excerpted text shown below (and are no longer presented in bold or strikethrough).

TABLE OF CONTENTS

Letter of Amendment #2 for:

A5360

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

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

NIAID CRMS # 30103

Letter of Amendment Date: 08 August 2018

ACTG Network Coordinating Center
Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910

Telephone: 301-628-3000
Fax: 301-628-3302

LETTER OF AMENDMENT

DATE: August 08, 2018

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5360 Protocol Team

SUBJECT: Letter of Amendment #2 for Protocol A5360, Version 1.0, 01/10/18, entitled "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"

The following information impacts the A5360 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.

The following information may also impact the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still

required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory files.

The main reasons for this LOA are to clarify the requirement that the participant must contact the site to report taking the last pill of study drug (SOF/VEL), including adding this information to the sample informed consent; to add information on laboratory requirements for CD4+ post-entry; and to update the protocol team roster. These changes were identified by the team.

The following are changes to A5360 FINAL Version 1.0, dated 01/10/18:

1. Per a new regulatory requirement by the Division of AIDS (DAIDS), a Protocol Signature Page (PSP) is appended for submission to DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

2. Section 5.1.2, Administration and Duration: The first paragraph has been revised to read:

   Participants will take SOF/VEL orally once daily with or without food and will receive treatment for a duration of 12 weeks. Study staff will observe the first dose being taken by the participant upon completion of all entry evaluations.

   The site pharmacist should include numbering on the label of each bottle (e.g., 1 of 3, 2 of 3, and 3 of 3) as well as a line to document the study product completion date on bottle 3. Participants should be instructed to open and finish one bottle of study product at a time**, starting with bottle number 1 of 3**. When the participant takes the last pill of SOF/VEL from **the last bottle (i.e., bottle 3 of 3)** ~~each bottle,~~ he/she will be instructed to ~~contact the site to~~ **document and/or** report the completion of the **last** bottle ~~Participants will, therefore, contact a site a maximum of three times to indicate completion of bottle.~~ See A5360 MOPS for additional information on reporting ~~of~~ treatment stop date.

3. Section 6.3.10, Clinical Assessments, Study Treatment (Intervention) Modifications: This section has been updated to read as follows:

   When the participant takes the last tablet of ~~each~~ **the third** bottle of SOF/VEL, he/she will be instructed to ~~contact the site to~~ **document and/or** report the ~~treatment stop date~~ **study product completion date**. This information self-reported by the participant should be captured on the eCRF when reported outside of and during the week 24/SVR evaluation visit. See **section 5.1.2 and** A5360 MOPS for additional details.

4. Section 6.3.12, Immunologic Studies (For HIV co-infected participants): This section has been updated to read as follows:

   CD4+
   Obtain absolute CD4+ count within 90 days prior to entry from a laboratory that

possesses a CLIA certification or equivalent.

For post-entry evaluations, all laboratories must possess a CLIA certification or equivalent and must be certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program.

5. APPENDIX I, Sample Informed Consent (SIC), Section II Description of Study Visits: The fifth paragraph under Entry has been revised to read as follows:

   At this visit, you will be given your study drugs. The study staff will give you enough study drugs to last 12 weeks (3 months). Study staff will watch you take your first dose before leaving the site. You can take the study medication (SOF/VEL) with or without food. You will receive adherence education and counseling on the study drug, as described below.

   You will be given instructions on how to take the study medication and what to do if you forget to take it. **There will be instructions on the study medication bottle asking you to call the site when you finish taking the last pill of the last bottle (bottle #3), or you can write the date of when you took the last pill on the label of bottle #3 and bring the bottle with you to your week 24/SVR evaluation visit. You may also note the date you finished the last pill within your phone or write it down on a separate piece of paper, as long as you bring this date with you to your week 24/SVR evaluation visit.** You will also receive a flier with information on two types of other medications (proton pump inhibitors and H2 inhibitors [e.g., heartburn medication]) that you should not take while taking study medication. [*Sites: Please include local names of PPIs and H2 inhibitors on a flyer to give to participants at entry. Pictures should also be included on the flyer.]*

6. SIC, Section III Description of Study Evaluations: This section has been revised to read as follows:

   Study drugs distribution and storage
   You will be given a 12-week supply of study medication at entry. Study staff will watch you take your first dose, before you leave the site. You will be asked to store the study medication as instructed on the medicine bottle label**. There will be instructions on the study medication bottle asking you to write down the date of, or call the site when, you finish taking the last pill of the last bottle (bottle #3).**

7. PROTOCOL TEAM ROSTER: Update the fax numbers for Drs. Beverly Alston-Smith and Leonard Sowah.

   DAIDS Clinical Representatives
   Beverly L. Alston-Smith, MD
   Complications and Co-Infectious Research Branch
   CCRB, DAIDS, NIAID, NIH
   5601 Fishers Lane, Room 9F50, MSC #9830
   Rockville, MD 20852
   Phone: 301-435-3773
   Fax: **240-627-3107**
   Email: balston@niaid.nih.gov

Leonard Anang Sowah, MD, MPH, FACP
CCRB/TRP/DAIDS/NIAID/NIH/DHHS
Therapeutics Research Program
5601 Fishers Lane, Room 9F52B
Rockville, MD 20852
Phone: 301-761-7231
Fax: **240-627-3107**
Email: leonard.sowah@nih.gov

The information above will be incorporated into the next protocol version as necessary if the protocol is amended.

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

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

Letter of Amendment #1 for:

A5360

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

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

NIAID CRMS # 30103

Letter of Amendment Date: 15 June 2018

ACTG Network Coordinating Center

Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910

Telephone: 301-628-3000
Fax: 301-628-3302

LETTER OF AMENDMENT

DATE: June 15, 2018

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5360 Protocol Team

SUBJECT: Letter of Amendment #1 for Protocol A5360, Version 1.0, 01/10/18, entitled "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"

The following information impacts the A5360 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.

The following information may also impact the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory files.

Updates are being made to A5360 FINAL Version 1.0, dated 01/10/18, for the following reasons:

a. To comply with a new regulatory requirement of the Division of AIDS (DAIDS), a signature is being added immediately after the title page and is to be submitted with the LOA registration packet (item 9).
b. To clarify language identified by the team and sites after the protocol was distributed to sites on 02/14/18.
c. To update the protocol team roster.
d. To incorporate protocol template changes made since the protocol was distributed to the field on 02/14/18.

TABLE OF CONTENTS

Page

The specific changes that are being made via this LOA to A5360, Version 1.0, 02/14/18, are listed below. An italicized statement provides the location of the change within the identified section of the protocol. New text resulting from this LOA appears in **bold**; deleted text is shown in ~~strikethrough~~.

1. Protocol Team Roster

   The following team members have been added to the roster:

   Industry Representative
   Andrea Ocampo, CCRA
   Clinical Trial Manager
   Gilead Sciences, Inc.
   333 Lakeside Drive
   Foster City, CA 94404
   Phone: 650-358-8037
   Fax: 650-524-9872
   Email: Andrea.Ocampo@gilead.com

   Laboratory Specialist
   Allan-Michael Bills, BS
   ACTG Network Coordinating Center
   Social & Scientific Systems, Inc.
   Laboratory Science Group
   8757 Georgia Avenue, 12th Floor
   Silver Spring MD 20910
   Phone: 301-628-3273
   Fax: 301-628-3304
   Email: abills@s-3.com

   DAIDS Clinical Representative
   Leonard Anang Sowah MD, MPH, FACP
   CCRB/TRP/DAIDS/NIAID/NIH/DHHS
   Therapeutics Research Program
   5601 Fisher's Lane, Room 9F52B
   Rockville, MD 20852
   Phone: 301-761-7231
   Fax: 301-480-4522
   Email: leonard.sowah@nih.gov

2. Section 6.3.4, Model for End-Stage Liver Disease (MELD) Score

   The following note has been added after the first paragraph to read:

   The MELD score measures the mortality risk in participants with end-stage liver disease. It is used as a disease severity index to help prioritize allocation of organs for transplant. In order to calculate the MELD score, total bilirubin (mg/dl), sodium (mEg/L), INR, and serum

creatinine (mg/dl) values are needed.

NOTE: The MELD score at entry should be calculated using the INR value from screening.

3. Section 6.3.8, Medical History

The first paragraph has been updated to read:

The medical history must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within 30 days prior to entry. In addition, the following diagnoses should be reported regardless of when the diagnosis was made:

- AIDS-defining conditions (only for HIV-1 co-infected participants)
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic HCV (If available, appropriate documentation from medical records of chronic HCV-infection, defined as having a documented HCV-positive antibody serology for greater than 6 months.)
- Chronic HBV
- Substance use (injection, non-injection drugs, and alcohol) captured via the WHO ASSIST instrument
- **HIV-1 diagnosis (for HIV-1 co-infected participants)**

Any allergies to any medications and their formulations must also be documented.

4. Section 6.3.10, Clinical Assessments

The third paragraph located after Targeted Physical Exam has been updated to read:

Post entry, record the following targeted events regardless of grade:

- ~~Uterine pregnancy~~
- AIDS-defining conditions (refer to the CDC HIV Classification and the WHO Staging System for HIV Infection and Disease)
- Tuberculosis
- Chronic HBV
- Ascites
- Hepatic **e**ncephalopathy
- **Variceal bleeding**
- **Hepatocellular carcinoma**

5. Section 6.3.11, Laboratory Evaluations

The second sentence has been revised to read:

At screening and entry, all laboratory values must be recorded on the eCRF. For post-entry assessments, all laboratory values for hemoglobin, AST, ALT, blood urea nitrogen (BUN), serum creatinine, total bilirubin, sodium, INR, albumin, platelets, and **pregnancy test (**regardless of grade/**result)** must be recorded on an eCRF.

6. Section 6.3.13, Virologic Studies

   The last sentence has been revised to read:

   HCV RNA samples on study will be processed and shipped to the designated A5360 VSL for ~~real-time~~ quantitative HCV RNA analysis.

7. Section 6.3.15, Questionnaires, Substance Use Questionnaire

   The Substance Use Questionnaire paragraph has been revised to read:

   The substance use questionnaire will be administered at entry, week 24/SVR evaluation, and weeks 48 and 72 visits **to solicit participant-reported information regarding use of substances (ie, alcohol, cigarettes, drugs).** The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) survey that was developed for the WHO by an international group of researchers and clinicians as a technical tool to assist with early identification of substance use-related health risks and substance use disorders will be used. This tool has been validated globally and captures information on alcohol, smoking, and injection and non-injection drug use.

   See the A5360 MOPS for further details.

8. Section 8.3, Pregnancy

   The first paragraph has been revised to read:

   Pregnancy will result in immediate discontinuation of the study medication and initiation of counseling regarding the lack of information on safety of SOF/VEL in pregnancy. Participants who become pregnant while on study should contact the site to schedule an unplanned study visit (only up to week 22) and will be followed on study/off-treatment until study completion. A visit following the end of pregnancy will be conducted for evidence of AEs in the participant, and an outcome eCRF will be completed. Male participants whose partners become pregnant will continue treatment **and should continue to follow the study procedures** as outlined in the SOE. **No additional reporting or monitoring is required for male participants' partners who become pregnant.**

9. Section 14.2, Participant Confidentiality

   The first paragraph has been revised to remove mention of "FDA" since this is a Non-IND

study.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, ~~FDA~~, NIAID, OHRP, other local, US, and international regulatory entities as part of their duties, or the industry supporter(s) or designee.

10. Section 14.3, Study Discontinuation

    The first paragraph has been revised to remove mention of "FDA" since this is a Non-IND study.

    The study may be discontinued at any time by the ACTG, IRB/EC, ~~FDA~~, NIAID, OHRP, other country-specific government agencies as part of their duties to ensure that research participants are protected, or the industry supporter.

11. SAMPLE INFORMED CONSENT, Risks of Study Drug

    The second paragraph has been revised to read:

    SOF/VEL has limited drug interactions with HIV medications with the exception of three HIV medications- efavirenz, ~~tenofovir~~, **etravirine**, and tipranavir/ritonavir. If you are taking any of these medications, your doctor will talk to you about these interactions in detail and what symptoms to look out for. Your doctor may modify your HIV medications after discussing it with you so that you can be included in this study.

12. SAMPLE INFORMED CONSENT, WHAT ABOUT CONFIDENTIALITY?

    The second and sixth paragraphs have been revised to read:

    Your records may be reviewed by ~~the US Food and Drug Administration (FDA),~~ the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties (insert name of site) institutional review board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

    Your records may be reviewed by ~~the US FDA,~~ the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties, (insert name of site) institutional review board (IRB) or Ethics Committee (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

13. Protocol Template Changes

The following changes to the protocol template since final Version 1.0 of the protocol went to the field on 02/14/18 have also been made:

a. Section 6.3, Instructions for Evaluations

Updated link to Source Document Guidelines on the DAIDS website-
https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf.

b. Section 6.3.10, Clinical Assessments

The following sentence has been added after the list of targeted events to record regardless of grade (as found after targeted physical exam):

Post entry, see section 8.3 for collection requirements for pregnancy.

c. Section 7.4, Study Monitoring

The first sentence of the second paragraph has been revised to read:

The DAIDS clinical representative will review and assess **select** EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs as applicable.

d. Section 9.2, Premature Study Discontinuation

The third bullet has been removed:

- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- ~~Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.~~
- At the discretion of the IRB/Ethics Committee, Food and Drug Administration (FDA), NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

e. Section 13.3, Clinical Site Monitoring and Record Availability

Section 13.3.2 has been revised to read:

The site investigator will make study documents (e.g., consent forms, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, ~~the FDA,~~ the NIAID, the OHRP, the industry supporter **or designee**, and **other** local, US, and international regulatory entities for confirmation of the study data.

The information above will be incorporated into the next protocol version as necessary if the protocol is amended.

14. Signature Page

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

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

A5360

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

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:

The National Institute of Allergy and Infectious Diseases

Industry Support Provided by:

Gilead Sciences, Inc.

IND #

The ACTG Hepatitis Transformative Science Group:	**Mark Sulkowski, MD, Chair**
Protocol Chair:	**Sunil Solomon, MBBS, PhD, MPH**
Protocol Vice-Chairs:	**Mark Sulkowski, MD** **Sandra Wagner Cardoso, MD, PhD**
DAIDS Clinical Representative:	**Beverly Alston-Smith, MD**
Clinical Trials Specialists:	**Chanelle Houston, BS** **Jennifer Tiu, MPH**

FINAL Version 1.0
January 10, 2018

ACTG
AIDS CLINICAL TRIALS GROUP

A5360
FINAL Version 1.0
01/10/18

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

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

TABLE OF CONTENTS Page

CONTENTS (Cont'd) Page

SITES PARTICIPATING IN THE STUDY

A5360 is a multicenter study open to all US and non-US clinical research sites (CRSs).

PROTOCOL TEAM ROSTER

Chair
Sunil Suhas Solomon, MBBS PhD MPH
Johns Hopkins University School of Medicine
1830 E. Monument Street, Room 444
Baltimore, MD 21287
Phone: 443-287-9596
Email: sss@jhmi.edu

Vice-chairs
Mark S. Sulkowski, MD
Johns Hopkins University School of Medicine
1830 E. Monument Street, Room 445
Baltimore, MD 21287
Phone: 410-614-4172
Email: msulkowski@jhmi.edu

Sandra Wagner Cardoso, MD, PhD
National Institute of Infectious Diseases, Oswaldo Cruz Foundation (Fiocruz)
Av. Brasil 4365 Manguinhos
Rio de janeiro-RJ – 21040-360
Brazil
Phone: +55 21 38659623
Email: Sandra.wagner@ini.fiocruz.br

DAIDS Clinical Representative
Beverly L. Alston-Smith, MD
Complications and Co-Infectious Research Branch
CCRB, DAIDS, NIAID, NIH
5601 Fishers Lane, Room 9F50 MSC #9830
Rockville, MD 20852
Phone: 301-435-3773
Fax: 301-480-4522
Email: balston@niaid.nih.gov

Clinical Trials Specialists
Chanelle Houston, BS
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3367
Fax: 301-628-3302
Email: CHouston@s-3.com

Jennifer Tiu, BS, MPH
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3371
Fax: 301-628-3302
Email: JTiu@s-3.com

Statisticians
Laura Smeaton, MS
Statistical and Data Analysis Center
Harvard TH Chan School of Public Health
FXB Building, Room 511
651 Huntington Avenue
Boston, MA 02115-6017
Phone: 617-432-2525
Fax: 617-432-3163
Email: smeaton@sdac.harvard.edu

Vincent Vu, MPH
Statistical and Data Analysis Center
Harvard TH Chan School of Public Health
FXB Building, Room 508
651 Huntington Avenue
Boston, MA 02115-6017
Phone: 617-432-1352
Fax: 617-432-3163
Email: vvu@sdac.harvard.edu

Data Managers
Laura Weichmann, MPH
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900 Ext. 7281
Fax: 716-834-8675
Email: weichman@fstrf.org

Christine Scello, MA
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900 Ext. 7233
Fax: 716-834-8432
Email: scello@fstrf.org

DAIDS Pharmacist
Oladapo Alli, PharmD
Pharmaceutical Affairs Branch
DAIDS, OSCO, NIAID, NIH
5601 Fishers Lane
Room 9E16 MSC #9830
Rockville, MD 20892
Phone: 240-627-3593
Fax: 240-627-3112
Email: oladapo.alli@nih.gov

Immunologist
Donald Anthony, MD, PhD
Case CRS
Department of Medicine
Biomedical Research, Building 1028
2109 Adelbert Road
Cleveland, OH 44106
Phone: 216-368-3540
Fax: 216-368-2034
Email: dda3@case.edu

Virologist
David Wyles, MD
University of Colorado Hospital CRS
P.O. Box 6511
Aurora, CO 80045
Phone: 303-602-5148
Email: david.wyles@dhha.org

Pharmacologists
Gene Morse, PharmD
University of Rochester Adult HIV Therapeutic Strategies Network CRS
701 Ellicott Street
Buffalo, NY 14203
Phone: 716-881-7464
Email: emorse@buffalo.edu

Charles Venuto, PharmD
University of Rochester Adult HIV Therapeutic Strategies Network CRS
265 Crittenden Boulevard
Rochester NY 14642
Phone: 585-276-5622
Email: charles.venuto@chet.rochester.edu

Investigators
Anchalee Avihingsanon, MD, PhD
Thai Red Cross AIDS Research Center Treatment (TRC-ARC Treatment) CRS
104 Rajdamri Road
Patumwan, Bangkok 10330
Thailand
Phone: +66-8-68128889
Email: anchaleea2009@gmail.com

Benjamin P. Linas, MD, MPH
Boston Medical Center ACTG CRS
1 Boston Medical Center Place
Crosstown Building Room 2007
Boston, MA 02118
Phone: 617-414-5238
Email: Benjamin.Linas@bmc.org

Investigators (Cont'd)
Susanna Naggie, MD, MHS
Duke University School of Medicine
2400 Pratt St., Rm. 0311 Terrace Level
Durham, NC 27705
Phone: 919-684-2584
Email: susanna.naggie@duke.edu

Gregory Robbins, MD, MPH
Massachusetts General Hospital CRS
Infectious Disease Unit
55 Fruit Street, Cox 5
Boston, MA 02114
Phone: 617-724-0076
Fax: 617-742-4795
Email: grobbins@partners.org

Field Representative
Dimas Kliemann, MD
Hospital Nossa Senhora da Conceicao CRS
Servico de Infectologia
Av. Francisco Trein, 596
Cristo Redentor
Porto Alegre 91350-200
Rio Grande do Sul, Brazil
Phone: +55-51-33572126
Email: dimaskliemann@gmail.com

Laboratory Technologists
Christopher Lane, AAS
University of Rochester Adult HIV
Therapeutic Strategies Network CRS
Infectious Diseases Division
Department of Medicine
Box 689
601 Elmwood Avenue
Rochester NY 14642
Phone: 585-276-5574
Fax: 585-442-9328
Email:
christopher_lane@urmc.rochester.edu

Laboratory Technologists, cont'd
Sasiwimol Ubolyam, MSc
Thai Red Cross AIDS Research Center
Treatment (TRC-ARC Treatment) CRS
104 Rajdamri Road
Patumwan Bangkok 10330
Thailand
Phone: +66-2-2564648
Email: sasiwimol.u@hivnat.org

Community Scientific Subcommittee (CSS)
Representative
Angel L. Hernandez, BA
Puerto Rico AIDS Clinical Trials Unit CRS
Barrio Saltos
Road 566 Int Road 593, KM 0.2
Orocovis, PR 00720
Phone: 787-919-6145
Email: angelhdz2863@gmail.com

International Site Specialist
Carolyn Davidson, BS
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3235
Fax: 301-628-3302
Email: CDavidson@s-3.com

Industry Representatives
Betty Chiang, MD
Gilead Science, Inc.
333 Lakeside Drive
Foster City, CA 94404
Phone: 646-483-5950
Email: Betty.Chiang@gilead.com

Joe Llewellyn, PharmD
Associate Director, Hepatitis C
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Phone: 650-235-3725
Email: Joe.Llewellyn@gilead.com

Industry Representatives, Cont'd
Annie Son, BA
Sr. Medical Affairs Associate
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Phone: 650-378-2175
Email: Annie.Son@gilead.com

Laboratory Data Manager
Laura Hovind, MS
Frontier Science & Technology Research
Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 76-834-0900 Ext. 7468
Fax: 716-33-0655
Email: hovind@fstrf.org

STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.coreA5360@fstrf.org via email. The appropriate team member will respond with a "cc" to actg.coreA5360@fstrf.org. A response should generally be received within 24 hours (Monday-Friday).

Protocol Email Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5360 email group. Include the protocol number in the email subject line.

- Send an email message to actg.user.support@fstrf.org

Clinical Management
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the protocol team.

- Send an email message to actg.coreA5360@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to immunologic, virologic, or pharmacologic laboratory tests, contact the protocol immunologist, virologist, or pharmacologist.

- Send an email message to actg.coreA5360@fstrf.org (ATTN: Donald Anthony- immunologist; David Wyles- virologist; Gene Morse, Charles Venuto- pharmacologists).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), registration, and other data management issues, contact the data manager. Electronic CRFs (eCRFs) completion guidelines and participant completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact Laura Weichmann, weichman@fstrf.org, and Christine Scello, scello@fstrf.org, directly.
- For other questions, send an email message to actg.coreA5360@fstrf.org (ATTN: Laura Weichmann and Christine Scello).
- Include the protocol number, PID, and a detailed question.

Participant Registration
For participant registration questions or problems and study identification number SID lists.

- Send an email message to rando.support@fstrf.org or call the Statistical and Data Analysis Center (SDAC)/DMC Randomization Desk at 716-834-0900, extension 7301.

DMC Portal and Medidata Rave Problems
Contact DMC User Support:

- Send an email message to actg.support@fstrf.org or call 716-834-0900 x7302.

Protocol Document Questions
For questions concerning the protocol document, contact the Clinical Trials Specialists.
- Send an email message to actg.coreA5360@fstrf.org (ATTN: Chanelle Houston, CHouston@s-3.com, and Jennifer Tiu, JTiu@s-3.com).

Copies of the Protocol
To request a hard copy of the protocol, send a message to ACTGNCC@s-3.com (ATTN: Diane Delgado). Electronic copies can be downloaded from the ACTG Website (https://www.actgnetwork.org).

Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
For protocol registration questions, send an email message to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation
For questions related to protocol activation, contact the Clinical Trials Specialists (Chanelle Houston, CHouston@s-3.com, and Jennifer Tiu, JTiu@s-3.com) or ACTG Site Coordination group at actgsitecoordination@s-3.com.

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, email Oladapo Alli, protocol pharmacist, at oladapo.alli@nih.gov.

Study Drug Orders
Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741.

IND (Investigational New Drug) Number or Questions
The IND number will be available on the PSWP within 30 days of the submission to the FDA. For any questions related to the IND submission, contact the DAIDS RSC at Regulatory@tech-res.com or call 301-897-1706.

Expedited Adverse Event (EAE) Reporting/Questions
Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Phone Calls
Sites are responsible for documenting any phone calls made to A5360 team members.
- Send an email to actg.coreA5360@fstrf.org.

Protocol-Specific Web Page (PSWP)
Additional information about management of the protocol can be found on the PSWP.

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

AASLD	American Association for the Study of Liver Diseases
APRI	Aspartate Aminotransferase to Platelet Ratio Index
ARVs	Antiretrovirals
ATV	atazanavir
BIDS	Brazilian Infectious Diseases Society
CI	confidence Interval
CTP Score	Child-Turcotte-Pugh Score
CT Scan	computerized tomography scan
DCV	daclatasvir
DAA	directly acting antivirals
EASL	European Association for the Study of the Liver
EOT	end of treatment
FDC	fixed dose combination
FIB-4	Fibrosis-4
GFR	glomerular filtration rate
GT	genotype
HbA1C	hemoglobin A1C
HBcAb	hepatitis B Virus core antibody total
HBsAb	hepatitis B Virus surface antibody
HBsAg	hepatitis B Virus surface antigen
ICH	International Council for Harmonization
IDSA	Infection Diseases Society of America
IgG	immunoglobulin G
INR	international normalized ratio
IU	international units
LDV	ledipasvir
LLOQ	lower limit of quantification
LMICs	low- and middle-income countries
LTFU	lost to follow-up
MedDRA	Medical Dictionary of Regulatory Activities System Organ Class
MELD	Model for End-Stage Liver Disease
MINMON	Minimal monitoring
MRI	Magnetic Resonance Imaging
NI	non-inferiority

PEG-IFN	pegylated interferon
PCR	polymerase chain reaction
PPI	proton pump inhibitor
PR	pegylated interferon/ribavirin
PSWP	Protocol-Specific Web Page
PT	post-treatment
RAPs	resistance-associated polymorphisms
RASs	resistance-associated substitutions
RBV	ribavirin
SMV	simeprevir
SOC	standard of care
SOF	sofosbuvir
SOF/VEL	sofosbuvir/velpatasvir fixed dose combination
SVR	sustained virologic response (defined as HCV RNA <LLOQ at least 12 weeks after the EOT)
ULN	upper limit of the normal range
VEL	velpatasvir
VL	viral load
WHO	World Health Organization

SCHEMA

A5360

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

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:

- No pre-treatment HCV genotyping;
- Entire treatment course (84 tablets) given to participants at entry;
- No scheduled on-treatment laboratory monitoring or clinic visits;
- Remote contact with participants at week 4 (adherence counseling and locator update) and week 22 (scheduling of SVR visit and locator update).

Participants will receive the fixed-dose combination (FDC) of sofosbuvir/velpatasvir (SOF/VEL) for 12 weeks.

DURATION

72 weeks (see schematic diagram below)

SAMPLE SIZE

400 participants

POPULATION

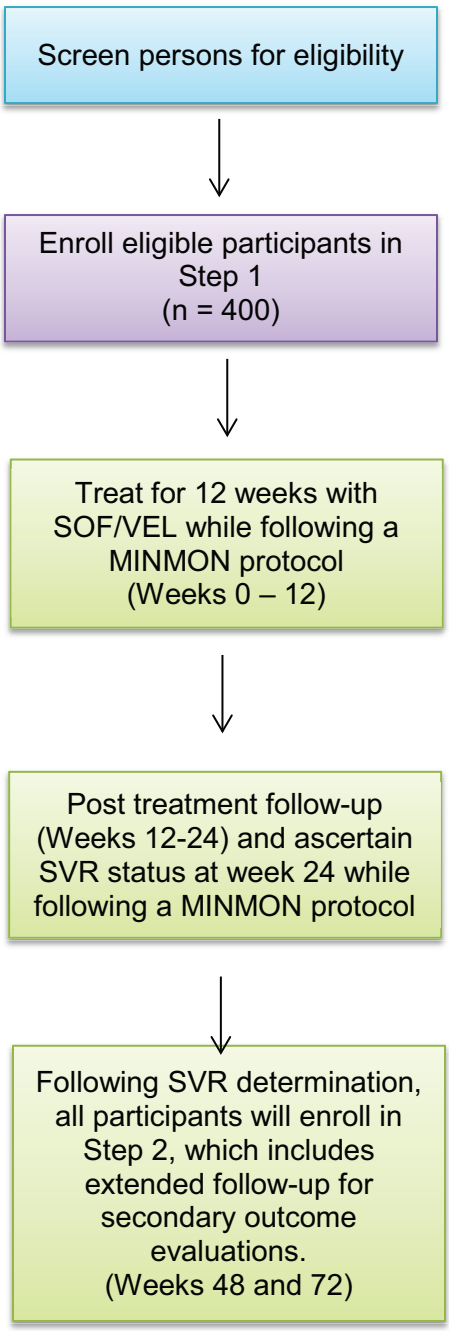
Men and women aged 18 years or older with active HCV-infection of any genotype, HCV treatment naïve, with or without HIV-1 co-infection. Persons with either compensated cirrhosis or without evidence of cirrhosis are eligible.

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.

REGIMEN Participants will receive 12 weeks of the single tablet FDC of SOF/VEL with a minimal monitoring strategy both during and after the study treatment period up to SVR evaluation.

Schema Figure 1: Minimal Monitoring of Participants with Active HCV Infection at US and Non-US Sites



1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

1.1.1 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.

1.2 Primary Objectives

1.2.1 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]).

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

1.3 Secondary Objectives

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

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

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

1.4 Exploratory Objectives

1.4.1 To estimate HCV re-infection among those who achieve SVR.

1.4.2 To examine the regression of liver disease (measured via Fibrosis-4 [FIB-4]) between study entry and final study follow-up among participants who achieve SVR.

1.4.3 To estimate the prevalence of HCV resistance-associated substitutions (RASs) among participants who do not achieve SVR.

1.4.4 To evaluate the impact of HCV treatment on participant quality of life (QoL) and disability when employing a MINMON protocol.

1.4.5 To evaluate the cost per person cured when employing a MINMON protocol among participants with active HCV-infection receiving an oral RBV-free-pan-genotypic HCV therapy according to treatment setting.

1.4.6 To explore the stability of different modes of contact information with treatment outcomes.

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

1.4.8 To explore the association of self-reported adherence to study treatment with study completion and SVR.

2.0 INTRODUCTION

2.1 Background

Global HCV Epidemiology

There are an estimated 71 million persons who are chronically infected with HCV globally [1]. Almost 90% of these persons reside in low-and-middle-income countries (LMICs). While the highest prevalence of HCV has been observed in central and East Asia, North Africa and the Middle East, the majority of the people chronically infected with HCV are believed to be residing in South and East Asia (>50 million in each; Figure 2.1-1) [2]. India alone is estimated to be home to over 20 million HCV-1 infected persons.

HCV has high genetic diversity with the most genetic diversity being seen in Africa. GT 1 is most prevalent worldwide, whereas GT 3 is found more commonly in south and southwest Asia. GT 4 and GT 5 are almost exclusively found in north-central and southern Africa, respectively. Genotype 6 is found almost exclusively in southeast Asia [3].

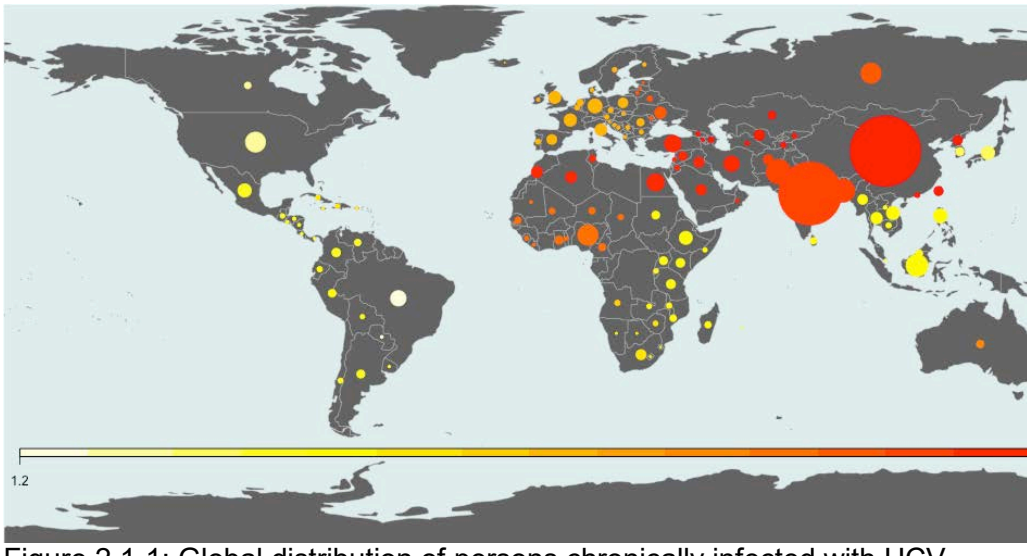


Figure 2.1-1: Global distribution of persons chronically infected with HCV
Darker red colors indicate higher prevalence and the size of the circle reflects the absolute number of people living with HCV.

HCV treatment access has been limited in most LMICs despite the advent of directly acting antivirals (DAAs) since most therapy until recently demonstrated highest efficacy rates in GT1 infection. Unlike HIV therapy, HCV therapy has varying response rates and treatment duration by genotype [4]. For example, the fixed dose combination (FDC) of SOF and ledipasvir (SOF/LDV) that is associated with cure rates of 97% in real-world cohorts of GT1 patients is not recommended for use in GT3 patients [5]. Similarly, while 12 weeks of SOF + RBV is recommended for GT1 infections, in persons infected with HCV GT3 the treatment duration recommended is 24 weeks [5, 6].

World Health Organization (WHO)/American Association for the Study of Liver Diseases (AASLD)/ Infection Diseases Society of America (IDSA)/European Association for the Study of the Liver (EASL) HCV Treatment Guidelines

AASLD/IDSA (www.hcvguidelines.org) and the EASL (www.easl.eu) guidance for monitoring of patients receiving HCV therapy are among the most commonly used in clinical practice (Table 2.1-1), given that treatment was not available outside of US and Europe until mid-2015. The 2014 WHO treatment guidelines, the first guidance on management of HCV disease released by the WHO, were based on AASLD and EASL recommendations and drug-registration literature available at that time. Preferable regimens according to the 2014 WHO guidelines are essentially interferon-based [7]. Since the WHO issued these first guidelines in 2014, several new medicines for the treatment of HCV infection have been introduced. Of these, daclatasvir (DCV), ledipasvir (LDV), and a combination of ombitasvir, paritaprevir and dasabuvir were added to the WHO Model List of Essential Medicines in 2015 [8]. Currently, the regimens recommended by WHO, and other country-specific treatment guidelines are guided by genotype and the future incorporation of these new drugs will probably need new guidance in terms of monitoring treatment.

Table 2.1-1: Monitoring schedule recommended by the various guidelines

Monitoring Evaluations	AASLD/IDSA	EASL	WHO
Baseline genotyping	X	X	X
Baseline HCV RNA	X	X	X
Baseline labs (for liver disease staging)	X	X	X
2-week HCV RNA		X	
2-week safety labs		X	
4-week HCV RNA	X	X	
4-week safety labs	X	X	X
6-week HCV RNA	X[1]		
8-week safety labs	X[2]	X	
12-week HCV RNA[2] (EOT)	X[2]	X	
12-week safety labs[2]	X[2]	X	

Monitoring Evaluations	AASLD/IDSA	EASL	WHO
16-week HCV RNA (EOT + 4)			
24 week HCV RNA (SVR 12)	X	X	X
[1]Repeat HCV RNA at 6 week if 4 week HCV RNA is detectable [2]The following tests are recommended as clinically indicated [3]Phone contact is recommended during the treatment duration to ensure optimal adherence			

Because the 2014 WHO guidelines primarily include Interferon-based regimens, the proposed monitoring process is intensive [7]. More recent monitoring guidelines can be found in the February 2016 AASLD/IDSA guidelines [9], which recommend visits or telephone contact as clinically indicated during treatment to ensure medication adherence and to monitor for adverse events and potential drug-drug interactions with newly prescribed medications. Complete blood count (CBC), creatinine level, calculated glomerular filtration rate (GFR), and hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated. Quantitative HCV viral load testing is recommended after 4 weeks of therapy and at 12 weeks following completion of therapy. If HCV RNA is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (i.e., week 6). If quantitative HCV viral load has increased by greater than 10-fold (>1 log10 international units [IU]/mL) on repeat testing at week 6 (or thereafter), then discontinuation of HCV treatment is recommended. The significance of a positive HCV RNA test result at week 4 that remains positive but lower at week 6 or week 8 is unknown. No recommendation is provided regarding whether to stop therapy or extend therapy in this rare clinical situation [1].

While the WHO in their 2016 guidelines recommend a simpler monitoring protocol when using interferon and RBV-free DAAs for the monitoring of HCV therapy [8], their recommendations have never been implemented in clinical care settings and are based on the assumption that simplification of monitoring will not adversely impact the safety and efficacy of treatment. To date, minimal monitoring has not been validated in any setting. Indeed, clinicians in LMICs have also, to date, largely followed the AASLD and EASL guidelines when delivering HCV therapy. As such, the impact of the reduced clinical contact and on-treatment monitoring remains unknown at this time.

Monitoring of HCV Therapy in Brazil

The current Brazilian guidelines for HCV and co-infections management were released on June 2015 [10]. In general, following diagnosis by the presence of HCV antibodies, HCV RNA quantification is performed to confirm the diagnosis and repeated before treatment initiation. The measurement of HCV RNA is recommended at week 4 of treatment as a futility rule if the regimen is pegylated interferon (PEG-IFN)/RBV/daclatasvir (DCV). Also, HCV RNA at the end of the treatment (i.e., week 12) and 12 weeks after the end of treatment are indicated to define SVR. HCV genotyping is performed if the participant fulfills the criteria to start treatment in order to define the genotype-specific regimen. Liver biopsy, FibroScan or Aspartate Aminotransferase to Platelet Ratio Index (APRI)/FIB-4 is mandatory to define treatment eligibility for DAAs

(DAA naïve, HCV monoinfected patients with Metavir F3 or F4, cirrhosis identified clinically or by ultrasound, cryoglobilinemia, among others). HIV co-infected patients are eligible for treatment regardless of the presence of fibrosis. The available DAAs currently distributed free of charge by the Ministry of Health are SOF, DCV and simeprevir (SMV). Distribution of DAA started in the beginning of 2016, so there has been very little experience with monitoring associated with these regimens. The Brazilian guidelines include recommendation for routine laboratory evaluation of chronic HCV, with and without cirrhosis, as well as for liver cancer screening but do not have specific recommendations in terms of treatment follow-up aside from HCV RNA. In clinical practice, standard monitoring of HCV therapy will depend on the modality of treatment and physician expertise. According to the Brazilian Infectious Diseases Society (BIDS) recommendation, treatment monitoring should include serum chemistries (i.e., AST, ALT, GGT, Alkaline phosphatase, bilirubin prothrombin and albumin), renal function (i.e., creatinine, blood urea nitrogen), CBC, glucose, sodium and potassium as minimum monitoring for safety at the end of the first month of treatment. Additional laboratory evaluations should be done according to specific patient needs, as well as repeated, if clinically necessary. In terms of viral response, the BIDS suggestion is to repeat HCV RNA PCR (polymerase chain reaction) at week 4 in order to evaluate adherence and at post-treatment weeks 12 and 24 to evaluate SVR [11].

Table 2.1-2: Standard monitoring practices currently being followed in the study settings for SOF-based DAA regimens

Standard Monitoring Evaluations	Brazil	India	Thailand	United States
Baseline genotyping	X	X	X	X
Baseline HCV RNA	X	X	X	X
Baseline labs (for liver disease staging)	X	X	X	X
4-week HCV RNA	X		X	X
4-week safety labs	X	X	X	X
6-week HCV RNA[1]				X
8-week safety labs	X	X	X	X
12-week HCV RNA (EOT)	X	X		X
12-week safety labs	X	X	X	X
16-week HCV RNA (EOT + 4)				X[2]
24 week HCV RNA (SVR 12)	X	X	X	X

[1]Six week HCV RNA recommended if HCV RNA is detectable at week 4.
[2]In some US settings, SVR_4 is performed.

Monitoring of HCV Therapy in India

Clinicians in India treating HCV-infected patients, primarily medical gastroenterologists, follow the Indian National Association for the Study of Liver guidelines [12]. There is no special training for infectious diseases such as a fellowship following residency in India and most infectious diseases are treated by internists. Until December 2015, SOF, pegylated interferons, and RBV (SOF+PEG-IFN/RBV [PR]) were the only drugs

available in India. As of December 2015, DCV and LDV have also become available. The standard practice for initiation of HCV therapy are quantification of HCV RNA following diagnosis by the presence of HCV antibodies, and HCV genotyping if HCV RNA is detected. Given the majority of patients (>75%) are GT3, the most commonly used regimen in India currently is SOF+DCV for 12 weeks with addition of RBV in cirrhotics. Hemogram and liver function tests are at 4-week intervals – additionally, if SOF+PR is selected, additional tests recommended when using interferon (e.g., thyroid stimulating hormone, alfa fetoprotein) are performed prior to initiation of therapy. HCV RNA quantification is also routinely performed at end of treatment (EOT) and if undetectable at EOT, an additional HCV RNA quantification is performed 12 weeks later to ascertain SVR status. The generic version of SOF/VEL was approved for use in India in May 2017.

Monitoring of HCV Therapy in Thailand

As of January 05, 2017, PR remains the standard of care (SOC) in national free-HCV treatment program. SOF and DCV have been registered in Thailand since October 2015 but have been inaccessible because of the price. Approximately 700,000 Thais are suffering from chronic HCV infection of which HCV GT 3 is the most prevalent genotype (40-50%), followed by GT 1 (30-40%), and GT 6 (15-20%). Previous studies showed that about 70% of Thai HCV-infected participants had significant liver fibrosis and 30% of them met the definition for cirrhosis, especially in HIV-1 co-infected individuals, but were unable to receive HCV treatment due to financial constraints.

Currently, there is no national guideline for monitoring HCV therapy in Thailand. Thai hepatologists usually treat chronic HCV based on the AASLD/IDSA guidelines. In Thailand, SOF and DCV are still expensive; therefore, HCV treatment is prioritized for patients who have an urgent medical need for HCV treatment. Diagnosis by the presence of HCV antibodies is followed by a non-invasive assessment of liver disease (FibroScan or APRI), to clarify whether the patient has an urgent need for HCV treatment. If APRI>1 or FibroScan>7.5KPa, HCV RNA quantification and HCV genotyping are performed. For 12 weeks of SOF+PR, CBC and blood chemistries are performed at 4-week intervals. Furthermore, additional safety laboratory tests such as thyroid-stimulating hormone are performed prior to initiation of therapy. For female patients, pregnancy testing is performed every 4 weeks until 6 months after completing the therapy. For interferon-free regimens (SOF+DCV for GT3 or LDV/SOF for GT 1 and GT 6), CBC and blood chemistry are done prior to treatment and at 12 weeks post-treatment. For all regimens, a HCV RNA is performed on-treatment at week 4 and post-treatment at week12 (SVR).

Monitoring of HCV Therapy in the US

As discussed above, HCV treatment guidance is provided by the AASLD/IDSA Panel and updated frequently on www.HCVguidelines.org. The US Panel recommends evaluation of the patients prior to and during HCV treatment with oral DAA regimens. Specifically, the US Panel recommends visits or telephone contact as clinically indicated during treatment to ensure medication adherence and to monitor for adverse events (AEs) and potential drug-drug interactions with newly prescribed medications. After 4 weeks of treatment, laboratory assessment including CBC, creatinine level, calculated

GFR, and hepatic function panel are recommended with additional testing as clinically indicated. Quantitative HCV viral load testing is recommended after 4 weeks of therapy and at 12 weeks following completion of therapy. If HCV RNA is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (i.e., week 6). If quantitative HCV viral-load has increased by greater than 10-fold (>1 log10 IU/mL) on repeat testing at week 6 (or thereafter), then discontinuation of HCV treatment is recommended. In the US, the standard clinical practice is to evaluate patients taking HCV DAA therapy every 4 weeks during a typical 12-week treatment course with office visits and laboratory testing. In addition, HCV DAA therapy is dispensed by commercial pharmacy and patients are required to interact with their pharmacy every 4 weeks during treatment, and HCV RNA monitoring after 4 weeks of treatment is often required to meet criteria for ongoing treatment.

Sofosbuvir/velpatasvir (SOF/VEL): A Novel Pan-genotypic FDC Regimen

SOF is an oral, nucleotide analogue inhibitor of HCV NS5B polymerase with demonstrated, potent antiviral activity in vitro and in vivo against HCV GT 1, 2, 3, 4, 5, and 6 (pan-genotypic) [13, 14, 15]. SOF was approved by the US Food and Drug Administration (FDA) in October 2013 and is widely available across the world, including as a generic agent manufactured in India which has the license to distribute SOF in 102 countries. Velpatasvir (VEL) is an oral, second generation inhibitor of HCV NS5A with demonstrated potent antiviral activity in vitro and in vivo against HCV GT 1, 2, 3, 4, 5, and 6 (pan-genotypic). VEL was evaluated with SOF as a FDC tablet (SOF 400 mg/VEL 100mg) taken by mouth once daily for 12 weeks in four clinical trials (ASTRAL-1, 2, 3, and 5), which included participants with HCV GT 1, 2, 3, 4, 5, and 6 with HIV-1 co-infection (ASTRAL-5) [16] and among HCV mono-infection (ASTRAL 1, 2, 3) [17, 18] with and without compensated cirrhosis. The regimen evaluated was interferon- and RBV-free. Of note, ASTRAL-4 tested SOF/VEL in participants with decompensated cirrhosis (Child-Turcotte-Pugh classification B, [CTP B]); patients with CTP B or C are excluded from the present study [19]. Overall, the efficacy of SOF/VEL was high with SVR observed in 95-99% of participants (Table 2.1-3). In ASTRAL 1, 2, and 3, no HCV relapse was observed between the post-treatment week 12 (SVR) and post-treatment week 24 (SVR_{24}), which is consistent with HCV eradication or cure. In the ASTRAL-1 (HCV GT 1, 2, 4, 5, 6) study, SOF/VEL was compared to placebo tablets (delayed treatment group) in a double-blind manner. Importantly, no difference in safety and tolerability was observed between SOF/VEL and placebo, with respect to the quantity and quality of reported AEs and observed laboratory abnormalities. In the ASTRAL-2 (HCV GT 2) and ASTRAL-3 (HCV GT 3) studies, SOF/VEL was compared to SOF + RBV in randomized controlled trials. SOF/VEL was superior to SOF + RBV with respect to SVR (efficacy) as well as safety and tolerability. In ASTRAL-5, two patients were incarcerated and hence did not have access to study drug while in prison, which resulted in failure to achieve SVR. In pooled analyses of data of participants from ASTRAL 1, 2 and 3, the overall efficacy was estimated to 98%. Epclusa (fixed dose single tablet regimen of SOF/VEL) was approved by the US FDA on June 28, 2016. A marketing application for SOF/VEL has also been approved by the European Medicines Agency (EMA) on July 06, 2016.

As part of the ASTRAL trials, participants were subject to an intense followup, wherein clinic visits with or without laboratory testing, and adherence counseling were performed at baseline, weeks 2, 4, 6, 8, 10 and 12. Such an intense followup schedule is difficult to implement in the real world. However, it is encouraging that the monitoring practices currently followed as listed in Table 2.1-2 (above) for the delivery of other agents such as SOF/LDV in real-world cohorts, such as the HCV TARGET [20] and TRIO [21] cohort, have resulted in SVR rates that are comparable to what were observed in the ION clinical trials of SOF/LDV. Therefore, it is likely that real-world SVR rates of SOF/VEL, with standard monitoring practices currently being used, will reflect what was observed in the ASTRAL trials.

Table 2.1-3: SVR data from ASTRAL Trials

	SVR (95% confidence interval)			
	ASTRAL-1	ASTRAL-2	ASTRAL-3	ASTRAL-5*
N	624	266	552	106
Overall	99.0 (98.0, >99.0)	99.0 (96.0, 100)	95.0 (92.0, 98.0)	95.0
Genotype				
1a	98.1 (95.2, 100)			95.0
1b	98.5 (96.5, 99.5)			92.0
2	100 (96.5, 100)	99.0 (96.0, 100)		100
3				92.0
3a			95.5 (90.9, 100)	
3b			100 (15.8, 100)	
3h				
3k			100 (2.5, 100)	
3 (no subtype confirmed)			88.9 (51.8, 99.7)	
4	100 (96.9, 100)			100
5	97.2 (85.1, 99.9)			
6	100 (91.4, 100)			
Disease				
No cirrhosis	99.0 (97.7, 99.7)		97.0 (93.5, 98.9)	94.0
Cirrhosis	99.2 (95.5, 100)		91.3 (82.8, 96.4)	100
Prior Treatment				
Naive	98.8 (97.3, 99.7)		97.1 (93.8, 98.9)	93.0
Experienced	99.5 (97.3, 99.6)		90.1 (80.7, 95.9)	97.0

*All participants were HIV-infected

Reinfection, Relapse, Cure

Optimism for the eradication of HCV has been largely driven by the ability to cure HCV infection in a relatively short duration of time using agents that are safe and well tolerated. HCV cure, in the DAA era, is defined as the absence of HCV RNA in a quantitative PCR assay 12 weeks after the completion of treatment. However, it is important to note that HCV treatment induced cure is not associated with immunity to new HCV infection following exposure in the future. There are two important caveats that need to be considered in the management of HCV namely, relapse and reinfection. A

small proportion of patients remain free of HCV at the end of treatment but exhibit HCV viremia at a time point thereafter (SVR or later)—this scenario could be attributable either to relapse or re-infection. HCV sequencing is required to distinguish one from the other. If the sequence of the virus observed is genetically identical to the sequence that was observed at baseline, the person is considered to have relapsed. However, if the sequence observed post SVR is unrelated to the sequence observed at baseline, the individual is considered to have been re-infected. In the pooled ASTRAL studies data which comprised participants from ASTRAL 1, 2, and 3 (n=1035), there were 12 relapses and 1 reinfection [16, 17, 18, 19; see summary here- http://www.gilead.com/news/press-releases/2015/9/gilead-announces-svr12-rates-from-four-phase-3-studies-evaluating-a-oncedaily-fixeddose-combination-of-sofosbuvir-sof-and-velpatasvir-vel-gs5816-for-the-treatment-of-all-six-hepatitis-c-genotypes. In recent data presented from Australia and New Zealand [22, 23], re-infection was observed in 5 out of 54 participants (Incidence of re-infection: 8.88 per 100 p-y) who had undetectable HCV RNA at EOT—active injection drug use was the strongest predictor of re-infection. Data on relapse and re-infection from settings in LMICs such as the study sites included in this study trial are lacking.

Access to and Use of Mobile Phones and Text Messaging Among Non-US Sites
Mobile phones and associated social media and messaging services are widely available in the participating countries. For example, in Brazil, WhatsApp is commonly used to contact participants and remind them of clinic visits. In India, text messaging services are used to remind participants of clinic visits.

2.2 Rationale

The MINMON strategy that is being proposed to evaluate in this study includes the following components:

a) No pre-treatment genotyping
b) Entire treatment course (84 tablets) given to participant at baseline
c) No scheduled on-treatment clinic visits
d) No scheduled on-treatment monitoring
e) Remote contact with participants at week 4 (adherence counseling and locator update) and week 22 (scheduling of SVR visit and locator update)

The rationale for each of these components are listed below:

No pre-treatment genotyping: The availability of pan-genotypic HCV treatment regimens preclude the need for HCV genotyping. Prior to SOF/DAC and SOF/VEL, genotyping was used to select treatment regimen and/or treatment duration. However, SOF/VEL has demonstrated high levels of efficacy across genotypes 1-6 and is approved by the US FDA for management of HCV disease in GT 1, 2, 3, 4, 5 or 6. The generic version of the fixed dose single-tablet regimen of SOF/VEL was recently approved for production by Indian generic manufactures for use in India and in 102 additional countries. SOF/VEL is also being utilized as the primary treatment regimen in at least two countries with ongoing robust HCV elimination programs, Iceland and Georgia.

Entire treatment course (84 tablets) given to participant at baseline and no on-treatment planned clinic visits: Most HCV treatment programs require patients to come in for refills on a 4-weekly basis and in some cases, every 2 weeks (e.g., Chennai, India). These visits could take considerable amount of time when accounting for travel and waiting time at the facility resulting in loss of wages. In the US, ensuring insurance papers are in place poses an additional burden to the patient. During these visits, patients are essentially provided with the next 2- or 4-week supply, a physician consult and a lab draw for HCV RNA monitoring and/or safety labs. Given the safety and efficacy profile of SOF/VEL, it is possible that providing patients with the entire 12-week supply of HCV treatment at initiation and not requiring any in-person follow-up could result in similar SVR rates as observed in the ASTRAL trials or real-world HCV cohorts such as TARGET and TRIO. Many HIV clinics globally provide ART for 3-6 month periods and viral suppression rates appear to be comparable to programs requiring participants to come in more frequently. More importantly, reducing the number of on-treatment clinic visits could minimize lost wages and dramatically decrease costs even in countries such as the US where manpower (physician/nurse/pharmacist) costs are significantly higher than in other settings. Further, the reduction in the number of clinic visits could potentially allow the clinic to deliver care to more patients with the same manpower. The provision of the entire 12-week supply at initiation could also improve adherence and consequently, outcomes in populations who are at risk for HCV infection and travel frequently (e.g., truck drivers).

No scheduled on-treatment monitoring: In the ASTRAL-1 trial the safety profile of SOF/VEL was comparable to that of the placebo arm—this raises the question of the necessity of on-treatment safety monitoring in a large majority of the patients. Further, given the relatively short treatment duration (12 weeks) and absence of stopping rules for futility, the role of on-treatment HCV RNA monitoring is also debatable. HCV RNA testing is currently recommended and usually ordered at on-treatment week 4 and EOT (in some settings) to assess adherence and to detect on-therapy virologic breakthrough. Virologic breakthrough is rare with SOF/VEL and has been generally linked to very poor adherence. In a pooled analysis of data from the ASTRAL trials on-treatment HCV RNA was not shown to be predictive of treatment response. Therefore, it is highly unlikely that the HCV treatment course would be modified by the results of on-treatment RNA quantification. This is an important issue in LMIC settings where access to HCV RNA quantification is limited (and expensive where available) and the reduction in the number of these tests from treatment protocols is expected to greatly improve access. Therefore, the study team proposes no planned on-treatment safety or HCV RNA monitoring. Of importance, participants with decompensated cirrhosis and chronic HBV infection (HBsAg positive) will be excluded from the study as these participants will not be eligible for a MINMON strategy; it is equally important to note that these groups probably account for <20% of persons chronically-infected with HCV globally.

Remote contact with participants at week 4 (adherence counseling and locator update) and week 22 (scheduling of SVR visit and locator update): In the real world, programs are measured by their success in objectively quantifiable outcomes. For example, in HIV, viral suppression is the gold standard to assess program effectiveness. Similarly, for HCV, proportion of patients achieving SVR is the gold standard for the assessment of

treatment programs. There are two critical components to achieving SVR: (1) Treatment persistence (taking an adequate duration of therapy) and adherence (taking daily SOF/VEL); and (2) confirmation of HCV eradication (SVR) at least 12 weeks after completing treatment. In the US, approximately 20% of patients who complete treatment do not return for SVR assessment in a timely manner. In global HCV programs, such as the free HCV program in Punjab, India, program staff are currently facing challenges bringing patients back in for the SVR assessment visit and are using different strategies to track patients.

According to the AASLD/IDSA guidelines [5, 9], the recommended approach to encourage treatment persistence/adherence and confirmation of SVR is pharmacist and/or clinicians contact with participants every 4 weeks and in most non-US settings, HCV treatment programs and treating clinicians require patients to come in for refills or safety labs at least once every 4 weeks, if not more frequently. Therefore, this study will leverage existing technology to conduct remote contacts with participants at two time points during the course of treatment and assessment of SVR. The remote contact will also be associated with minimal costs, which we will capture and factor into the cost analysis.

It is anticipated that these remote contacts will last less than 5 minutes and therefore, do not foresee this as burdensome on the staff as several programs already use similar approaches to track participants. The week 4 contact is not designed to be an intensive adherence intervention, rather a quick adherence check, clarification of the regimen, and re-enforcement of the importance of adherence early in the course of treatment. Despite detailed instructions at the time of clinical encounters, many participants may leave unsure of medical instructions. Therefore, the week 4 remote contact is in keeping with good clinical practice and will optimize outcomes in the subset of participants who may have misunderstood or have questions or concerns about the study medication. Responses will be standardized based on reasons for non-adherence: e.g., forgot, side effects, chose not to take, lost study medication, or decided to stop. Standardizing responses will ensure that participants receive the same type of support regardless of the mechanism used (i.e., phone, text, WhatsApp, etc.) This simple and inexpensive remote contact will also be helpful in assessing the success of the MINMON approach both in the trial and in the real world, as it may be possible for programs to estimate outcomes of participants who do not return for SVR assessment using week 4 adherence data. Given the advances in technology and widespread adaptation of newer informatics, remote participant contact could be pre-programmed to provide support and collect information at specific intervals, and the study team believes that these newer forms of remote contact will be increasingly used in medicine.

An additional incentive for attending the SVR visit will be included in this clinical trial. The rationale is to minimize lost-to-follow-up (LTFU) and measure SVR in as many participants as possible to validate the MINMON strategy. Any participant who does not return for the SVR visit will be considered a failure even if the true outcome was HCV cure with SOF/VEL. In light of the importance of determining the SVR outcome of the

MINMON study for the applicability of this strategy outside the trial setting, this additional measure, an incentive for attending the SVR assessment, is intended to minimize missed SVR visits. We will incorporate the value of this incentive into the cost-analysis.

If the monitoring protocol that is being proposed is found to be efficacious and comparable to what is currently being observed in clinical settings globally, it would imply that the HCV-infected persons, for the large part, could be treated from settings with minimal infrastructure. In fact, HCV care could be rolled out of primary health care centers where routine blood work is available—at baseline, one would need to perform a complete blood panel, hepatic function panel and a renal panel to stage liver disease. Point-of-care HCV antibody tests are already available. If the individual is a decompensated cirrhotic, he/she could be referred to a tertiary care center. If not, treatment could be initiated following HCV RNA quantification. The availability of the GeneXpert cartridges for quantification of HCV RNA [24] has the potential to transform any center with electricity and an individual with high-school level of education to perform HCV RNA quantification. There are approximately four to five times the number of people living with HCV globally compared to HIV—to ensure that treatment reaches them all and to truly have a shot at eradication of HCV, it is critical to improve access while reducing cost and associated treatment complexities.

However, what is being proposed is novel but high-risk and has never been piloted for the delivery of HCV care. It is possible that adherence and treatment completion rates, if the entire treatment supply is provided upfront with no health care contact thereafter for the remainder of the treatment duration, could be inferior to the SOC. This single-arm study, open to US and non-US sites, will enroll 400 participants, all of whom will be followed using the MINMON protocol only. The rationale for limiting enrollment of HIV-coinfected participants to <50% is to ensure the findings of this trial are generalizable to all HCV infected persons. Given that this trial will be recruiting from ACTG sites that are primarily HIV clinics, it is highly possible that there may be an overrepresentation of HIV-infected persons.

The rationale for limiting enrollment of cirrhotics to <20% is also to ensure that the sample is representative of all HCV-infected persons globally. Since this study seeks to evaluate a low-cost treatment delivery strategy aimed at promoting the elimination agenda, the primary target population will be the >90% of the HCV-infected persons who are unaware of their status—it is likely the >80% of these individuals will be non-cirrhotic. Cirrhotic individuals are more likely to engage in care with more frequent clinic visits and consequently, more likely to be recruited into the study.

Further, the findings from this study will inform the need for a future randomized clinical trial (RCT) that will compare the MINMON approach versus SOC. If the findings from this trial conclusively indicate that the MINMON approach achieves high SVR (>96%) that is comparable to what is observed in routine clinical settings, a RCT will not be needed as a high benchmark for SVR will be met. Conversely, if findings from this study conclusively indicate that the MINMON approach is inferior (evidence than SVR is <95%), an RCT will not be needed as a low benchmark for SVR will have been met and the characteristics of the MINMON approach will need to be reconsidered. Finally, if

neither a high nor low benchmarks is met (ie, observed SVR 93-97%), this study will inform the design and sample size of a potential future RCT comparing the MINMON approach to SOC.

Plan for Enrollment of Subpopulations

There are no exclusion criteria related to gender or race. The FDC of SOF/VEL was not associated with adverse developmental outcomes in animal studies. However, this combination has not been studied extensively in pregnant women [EPCLUSA package insert, 2016]. Therefore, we will exclude pregnant women and women of reproductive potential who are unwilling to use contraceptives while on study treatment.

3.0 STUDY DESIGN

This study will enroll 400 participants who will be followed using a MINMON protocol for a duration of 24 weeks in order to obtain primary outcome information regarding SVR status, as well as additional information for secondary objectives over the longer duration of 72 weeks. The MINMON strategy is comprised of: 1) minimal pre-treatment assessment including confirmation of viremia by HCV RNA and liver disease staging using routine clinical exam and non-invasive parameters (ALT, AST, and platelet count [and bilirubin, albumin, and INR in persons with evidence of cirrhosis by FIB-4]) and no genotyping; 2) distribution of complete HCV treatment course at study initiation (i.e., 84 days of SOF/VEL); 3) no planned on-treatment laboratory monitoring; 4) no planned clinic or pharmacy visits prior to SVR evaluation; and 5) remote contact at treatment week 4 and post-treatment at week 22 to update locator information and to facilitate attendance at the SVR evaluation visit (weeks 22 to 28). The week 4 remote contact will include adherence assessment and reinforcement which is also considered to be a part of the MINMON strategy.

All participants will be treatment-naïve, with active HCV-infection, with or without HIV-1 co-infection, and if cirrhotic, will be classified as compensated cirrhotics based on CTP score. All participants will receive study-provided treatment (FDC of SOF/VEL) for a duration of 12 weeks followed by evaluation 12 weeks later to ascertain SVR status. Upon SVR evaluation, all participants will enter Step 2 of the study and will be followed for an additional 48 weeks to examine liver disease regression post-SVR, measure the incidence of HCV re-infection, and other non-primary outcomes. Measures of disease regression after cure are important to understanding future disease burden and cost associated with liver disease. Reinfection rates are critically important for both public health planning and advocacy purposes when seeking to expand the availability of HCV treatments. In addition, cost-benefit analyses will be conducted using cost data and outcomes gathered from this study.

At entry (Step 1), all participants will receive the entire study-provided treatment supply, following study entry procedures, with the first dose being observed by study staff. The next planned study visit is the key primary outcome evaluation for SVR, scheduled at week 24. There will be no planned interim in-person study visits with participants between entry and week 24. Detailed locator information will be collected at entry (see section 6.3.21). In lieu of resource intensive in-person study visits, between entry and

the primary outcome evaluation at the week 24 visit, sites will contact participants at weeks 4 and 22, via a remote mechanism based upon the participant's choice and availability, in order to assess adherence status at week 4 and to schedule the SVR evaluation visit at week 24, as well as update the locator information. At week 4, the participant will be asked if he/she is taking the study medication and about adherence, changes in contact information, and reminders for the study visit for SVR evaluation. If participants report sub-optimal adherence or that they are not taking their HCV medication, they will be read (if a phone contact) or message (if remote contact is via email/text message/WhatsApp) a standard script highlighting the benefits of HCV therapy and the importance of adherence. They will also be asked about reasons for their non-adherence and then receive standardized encouragement and clarification about the medication and importance of adherence. There will be no further site-initiated interaction with the participant until week 22, at which time participants will be queried about any changes to their contact information and will also be reminded of their upcoming SVR visit. These contacts are designed to help keep participants engaged with the study and keep their contact information up to date in order to minimize LTFU prior to the primary outcome- evaluation of SVR. Resource utilization, including staff time (both for remote contact as well as unplanned study visits) and any associated laboratory or other tests ordered during unplanned clinic visits (e.g., Magnetic Resonance Imaging [MRI], ultrasonogram, blood tests) will be documented, translated to costs using reimbursement rates from WHO CHOICE and the U.S. Center For Medicare and Medicaid Services, and incorporated into the cost analysis.

Following the SVR evaluation visit, which is expected to be at week 24, all participants will enter Step 2 for two additional scheduled post-SVR evaluation study visits at weeks 48 and 72. At each of these Step 2 study visits, a blood sample will be drawn and liver disease will be staged in all participants using FIB-4 (and calculated CTP if cirrhotic), and where available, liver elastography, in addition to the Model for End-Stage Liver Disease (MELD) score. Participants who have SVR evaluation after week 24 will enter Step 2 at the time of SVR evaluation and the schedule of an additional post-SVR evaluation visits will be dependent on the week of Step 2 entry. Step 2 will end at week 72, from the time of study entry, independent of the time of Step 2 entry (for example, a participant who undergoes SVR evaluation at week 60 will have one remote contact visit at week 68 and a final visit at week 72).

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria (Step 1)

4.1.1 Ability and willingness of participant to provide informed consent.

4.1.2 Men and women age ≥18 years.

4.1.3 Active HCV infection confirmed by a detectable HCV RNA by PCR (HCV RNA >1000 international units (IU)/ml) within 35 days prior to study entry. HCV RNA must be obtained by any FDA-approved test for quantifying HCV RNA at any local laboratory that has a CLIA certification, its equivalent, or at any network-

approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

NOTE: HCV RNA can be obtained at screening visit (refer to section 6.3.13).

4.1.4 HCV treatment naïve defined as not having been previously treated for HCV infection with any medications approved for the treatment of HCV in any country.

4.1.5 Liver disease stage defined as non-cirrhotic or compensated cirrhotic (metric/diagnostic criteria used for fibrosis staging) within 35 days prior to study entry as listed below:

A. FIB-4 <3.25 corresponding to no cirrhosis

OR

B. FIB-4 ≥3.25 AND Child-Turcotte-Pugh (CTP) Score ≤6 indicating CTP Class A corresponding to compensated cirrhotic.

NOTE: Please refer to the A5360 PSWP for the website link to calculate the FIB-4 and CTP scores.

4.1.6 HIV-1 infection status documented as either absent or present, as defined below:

Absence of HIV-1 infection, as documented by any licensed rapid HIV test or HIV-1 enzyme or chemiluminescence immunoassay (E/CIA) test kit, within 60 days prior to entry.

OR

HIV-1 infection, documented by any licensed rapid HIV test or HIV-1 E/CIA test kit at any time prior to entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen or plasma HIV-1 RNA viral load.

NOTE: The term "licensed" refers to a US FDA-approved kit, which is recommended. For sites that are unable to obtain an FDA-approved kit, a kit that has been certified or licensed by an oversight body within the country and validated internally is acceptable.

WHO and CDC (US Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

4.1.7 For HIV co-infected participants, HIV-1 RNA obtained within 90 days prior to study entry by any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

4.1.8 For HIV co-infected participants, CD4+ cell count obtained within 90 days prior to study entry at any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

4.1.9 HIV co-infected participants must satisfy one of the two criteria listed below:

A. If a participant is HIV-infected and is taking ART then, plasma HIV RNA <400 copies/mL based on criteria listed in section 4.1.7 AND current ARV regimen does not include efavirenz (EFV) AND no exposure to EFV ≤14 days prior to study entry. Any absolute CD4+ count is acceptable if this HIV RNA criterion is met.

NOTE: Any participant on an EFV containing ART regimen during the screening period must be switched off EFV and have another regimen, excluding EFV, started at least 14 days prior to study entry.

OR

B. If a participant is HIV-infected AND not taking ART, absolute CD4+ count must be >350 cells/μl based on criteria listed in section 4.1.8.

4.1.10 The following laboratory values obtained within 35 days prior to entry by any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

- Albumin >3.0 g/L
- Hemoglobin >8.0 g/dL for women; >9.0 g/dL for men
- Platelet count >50,000/mm^3
- Calculated creatinine clearance (CrCl) using Cockcroft-Gault method >30 mL/min
- Aspartate aminotransferase (AST/SGOT) <10 times the upper limit of the normal range (ULN)
- Alanine aminotransferase (ALT/SGPT) <10 times the ULN
- Total bilirubin <1.5 times the ULN for participants not on atazanavir (ATV) and <3 times the ULN for participants on ATV

- International normalized ratio (INR) <1.5 times the ULN

NOTE: Please refer to the A5360 PSWP for the website link to calculate CrCl using the Cockcroft-Gault calculator.

4.1.11 Female participants of reproductive potential (defined as women who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or women who have not undergone surgical sterilization, specifically hysterectomy and/or bilateral oophorectomy or bilateral salpingectomy) must have a negative serum or urine pregnancy test within 48 hours prior to study entry by any laboratory or clinic that has a CLIA certificate or its equivalent, or is using a point-of-care (POC)/CLIA-waived test. The serum, urine or POC pregnancy test must have a sensitivity of at least 25 mIU/mL.

4.1.12 All participants of reproductive potential must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate, sperm donate, in vitro fertilization,) while on study treatment and for 6 weeks after stopping protocol-specified medication.

4.1.13 When participating in sexual activity that could lead to pregnancy, all participants of reproductive potential must agree to use at least one reliable form of contraceptive while receiving protocol-specified medication, and for 6 weeks after stopping the medication. Such methods include:

- Condoms (either self or require their partner to use one) with or without a spermicidal agent
- Diaphragm or cervical cap with or without spermicidal agent
- Intrauterine device (IUD)
- Hormone-based contraceptive
- Tubal ligation

NOTE: Providers and participants should be advised that not all contraceptive choices listed above can prevent HIV transmission and that some may actually increase the risk of HIV acquisition. Study participants who are sexually active with HIV-1 negative or unknown HIV-1 serostatus partners should be advised that they need to consider effective strategies for reducing the risk of HIV transmission, as well as meeting the requirement for effective contraception during their participation in the study. Study participants should discuss contraceptive choices and HIV risk reduction methods with their health care provider.

4.1.14 Participants who are not of reproductive potential (women who have been post-menopausal for at least 24 consecutive months or have undergone hysterectomy and/or bilateral oophorectomy or salpingectomy or men who have documented azoospermia or undergone vasectomy) are eligible without requiring the use of contraceptives. Acceptable documentation of sterilization and menopause is

specified below. Male participants do not need to provide information on their female partner's reproductive potential.

Written or oral documentation communicated by clinician or clinician's staff of one of the following:

- Physician report/letter
- Operative report or other source documentation in the patient record (a laboratory report of azoospermia is required to document successful vasectomy)
- Discharge summary
- Follicle stimulating hormone-release factor (FSH) measurement elevated into the menopausal range as established by the reporting laboratory.

4.1.15 Life expectancy >12 months, in the opinion of the site investigator.

4.1.16 Willingness and ability to be contacted remotely via telephone, text message, email, social media applications or any other modality.

4.2 Exclusion Criteria (Step 1)

4.2.1 Positive for the presence of hepatitis B virus (HBV) surface antigen (HBsAg).

4.2.2 For cirrhotic participants, CTP score >6 corresponding to Class B or C (Please refer to the A5360 PSWP for the website link to calculate the CTP score).

4.2.3 Breastfeeding or pregnancy.

4.2.4 Known allergy/sensitivity or any hypersensitivity to components of study drug(s) or their formulation.

4.2.5 Active drug or alcohol use or dependence and other conditions that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.6 Acute or serious illness requiring systemic treatment and/or hospitalization within 35 days prior to study entry.

4.2.7 In HIV positive participants, presence of active or acute AIDS-defining opportunistic infections within 35 days prior to study entry.

NOTE: AIDS-defining opportunistic infections as defined by the CDC found in the following document: http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm

4.2.8 Any history of hepatic decompensation including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, and/or bleeding esophageal varices prior to study entry.

4.2.9 Use of prohibited medications within the past 14 days prior to study entry (please refer to the A5360 PSWP for the list of prohibited medications).

NOTE: ART regimens must not contain prohibited medications (please refer to the A5360 PSWP for the list of prohibited medications).

4.3 Inclusion Criteria (Step 2)

4.3.1 Completion of SVR evaluation visit in Step 1.

4.4 Exclusion Criteria (Step 2)

There are no exclusion criteria for Step 2.

4.5 Study Enrollment Procedures

4.5.1 Prior to implementation of this protocol, and any subsequent full-version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for the amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. Site-specific ICF(s) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Amendment Registration Notification from the DAIDS PRO that approves the site-specific ICFs and indicates successful completion of the amendment protocol registration process. A copy of the final Amendment Registration Notification issued by the DAIDS PRO should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The participant will be asked to read and sign the approved protocol consent form.

For participants from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the Data Management Center (DMC) Participant Enrollment System.

4.5.2 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.5.3 Participant Registration

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be keyed into the database.

Participants who meet the enrollment criteria will be registered to the study according to standard ACTG DMC procedures.

4.6 Co-enrollment Guidelines

US sites are encouraged to co-enroll participants in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.” Co-enrollment in A5128 does not require permission from the A5360 protocol chairs.

Non-US sites are encouraged to co-enroll participants in A5243, “Plan for Obtaining Human Biological Samples at Non-U.S. Clinical Research Sites for Currently Unspecified Genetic Analyses.” Co-enrollment in A5243 does not require permission from the A5360 protocol chairs.

For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the protocol team via email as described in the Study Management section.

If there are concerns about exceeding volume limits for blood draws, please note that A5128 and A5243 allow participants to consent to the study without allowing a blood sample to be collected. In these cases, if a future study wants to evaluate a participant’s DNA sometime later, sites would be able to access a stored aliquot from the initial study (if there are any available). It is also possible for a participant to enroll into A5128 or A5243 and postpone the required blood draw until a later time. For more input, contact the A5128 or A5243 teams.

5.0 STUDY TREATMENT

Study treatment is defined as the once-daily oral FDC sofosbuvir/velpatasvir (SOF/VEL [Tradename: Epclusa]) containing 400 mg of SOF and 100mg of VEL. If a participant is co-infected with HIV, HIV medications will NOT be provided as part of this study.

5.1 Regimens, Administration, and Duration

5.1.1 Regimens

Participants will receive FDC SOF/VEL (400mg/100mg) orally once daily with or without food.

5.1.2 Administration and Duration

Participants will take SOF/VEL orally once daily with or without food and will receive treatment for a duration of 12 weeks. Study staff will observe the first dose being taken by the participant upon completion of all entry evaluations. Participants should be instructed to open and finish one bottle of study product at a time. When the participant takes the last pill of SOF/VEL from each bottle, he/she will be instructed to contact the site to report the completion of the bottle. Participants will, therefore, contact a site a maximum of three times to indicate completion of a bottle. See A5360 MOPS for additional information on reporting of treatment stop date.

In the scenario of lost study medication, the participant will be asked to contact the study site as soon as possible. If the participant has been off study medication less than 2 weeks (≤14 days), he/she will be eligible for a one-time replacement of study medication to complete the 12 week course. Participants who report a subsequent loss of study medication will not be eligible for replacement and will enter the follow-up phase (week 24 visit). If the participant has not taken study medication for more than 2 weeks (≥15 days), study medication will not be replaced and the participant will enter the follow-up phase (week 24 visit).

5.2 Study Product Formulation and Preparation

5.2.1 Sofosbuvir/Velpatasvir manufactured by Gilead Sciences, Inc., will be supplied as 400/100 mg film-coated tablets for oral administration. Store below 30°C (86ºF). Dispense only in original container.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

The FDC of SOF/VEL will be provided by Gilead Sciences, Inc. and will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study product(s) for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

Any study product not provided by the study must comply with the NIAID (DAIDS) policy that outlines the process for authorizing the use of study products not marketed in the US in NIAID (DAIDS)-supported and/or – sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at: https://www.niaid.nih.gov/sites/default/files/NonFDAapprovedProducts.pdf.

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. At US CRSs, all unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.* At non-US CRSs, the site pharmacist must follow the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for the destruction of unused study products.

5.4 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the ACTG Precautionary and Prohibited Medications Database located at: http://tprc.pharm.buffalo.edu/home/di_search/.

5.4.1 Prohibited Medications

Please refer to the A5360 PSWP for the list of prohibited medications.

5.4.2 Precautionary Medications

Please refer to the A5360 PSWP for the list of precautionary medications.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

6.1-1: Schedule of Evaluations: Step 1- Visits up Until SVR Evaluation

Evaluation	Screening	Entry/Week 0	Weeks			SVR Evaluation Visit (*if week 24 visit is missed; can occur up to week 72*)	Unplanned Study Visits (*see section 6.2.6*)
			4	22	24		
			Window ±7 days		Window -14/+28 days		
Documentation of Active HCV Infection	X						
Documentation of HIV-1 Status	X						
Calculated FIB-4 Score	X				X	X	As needed.
MELD Score		X					
Documentation of Cirrhosis Status	X				X	X	As needed.
Calculated CTP Score (if cirrhotic by FIB-4)	X				X	X	
Liver Elastography (see section 6.3.7)		X			X	X	
Medical History	X	X					
Medication History	X	X					
Clinical Assessments	X	X			X	X	As needed.
Hematology	X	X			X	X	
Liver Function Tests	X	X			X	X	
Blood Chemistries	X	X			X	X	As needed.

Evaluation	Screening	Entry/Week 0	Weeks			SVR Evaluation Visit (*if week 24 visit is missed; can occur up to week 72*)	Unplanned Study Visits (*see section 6.2.6*)
			4	22	24		
			Window ±7 days		Window -14/+28 days		
Calculated Creatinine Clearance	X						
INR	X				X	X	As needed.
Pregnancy Testing	X	X			If pregnancy is suspected.		
HBV Panel	X						
CD4+ (if HIV+)	X				X	X	
Plasma HIV-1 RNA (if HIV+)	X				X	X	
Plasma HCV RNA	X				X	X	
Stored Plasma/PBMC/Serum		X			X	X	As needed. (*Plasma sample will be stored if blood sample obtained*.)
Adherence Assessment			X (via remote contact)		X	X	
Health Outcomes Questionnaire		X			X	X	X
Health Care Utilization Questionnaire		X			X	X	X
Substance Use Questionnaire		X			X	X	

Evaluation	Screening	Entry/Week 0	Weeks			SVR Evaluation Visit (*if week 24 visit is missed; can occur up to week 72*)	Unplanned Study Visits (*see section 6.2.6*)
			4	22	24		
			Window ±7 days		Window -14/+28 days		
HCV Therapy Dispensed/First Dose Observed		X					
Adherence Education and Counseling		X					
Pregnancy Prevention Counseling	X	X					
Cirrhosis Counseling		X			X	X	
HCV Risk-reduction Counseling		X			X	X	
Locator Information		X	Update information, if needed.				
Remote Contact with Participants Outside of Planned Clinic Visits			X	X (see note in section 6.2.4)			

6.1-2: Schedule of Evaluations: Step 2- Visits Post SVR Evaluation

Evaluation	Weeks			
	42	48	68	72
	Window ±28 days			
Calculated FIB-4 Score		X		X
MELD Score		X		X
Calculated CTP Score (if cirrhotic by FIB-4)		X		X
Liver Elastography (see section 6.3.7)		X		X
Clinical Assessments		X		X
Hematology		X		X
Liver Function Tests		X		X
Blood Chemistries		X		X
Calculated Creatinine Clearance		X		X
INR		X		X
Plasma HCV RNA (if SVR responder)		X		X
Stored Plasma/PBMC/Serum		X		X
Health Outcomes Questionnaire		X		X
Health Care Utilization Questionnaire		X		X
Substance Use Questionnaire		X		X
Cirrhosis Counseling		X		X
HCV Risk-reduction Counseling		X		X
Remote Contact with Participants Outside of Planned Clinic Visits	X		X	

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant starting any study medications, treatments, or interventions.

Screening evaluations to determine eligibility must be completed within 35 days prior to study entry unless otherwise specified in section 4.0.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on persons who do not enroll will be captured in an eCRF and entered into the ACTG database.

6.2.2 Step 1 Entry Evaluations

Step 1 entry evaluations must occur at least 24 hours after screening evaluations, unless otherwise specified.

Participants are expected to begin treatment with SOF/VEL within 24 hours after registration and upon completion of entry evaluations. The first dose of SOF/VEL will be provided to the participant and observed by study staff.

6.2.3 Step 2 Registration Evaluations

Participants who meet criteria in section 4.3 will register to Step 2 on the same day of the last visit on Step 1 and be followed per the SOE.

6.2.4 Post-Entry Evaluations

Given the design of the MINMON strategy, there will be no on-treatment or EOT evaluations. See section 6.3.22 for post-entry site contact with participants via remote mechanism.

Post-Treatment Evaluations
Step 1: Following treatment completion at week 12, participants will undergo evaluations as outlined in the SOE 6.1-1.

NOTE: If the participant comes in for the week 24 visit during the -14 days window (i.e., week 22), then the week 22 remote call is not needed.

Week 24/SVR Evaluation Visit
The week 24 visit (visit window: week 22-28) is ideally the visit where SVR should be assessed for all participants, and subsequently they will be registered to Step 2. However, if a participant misses the visit window (>week 28), the week 24 visit will be considered a missed visit and he/she will need to be scheduled for an SVR visit prior to being registered to Step 2 of the study. The SVR visit can

take place at any time point after week 28 and up to week 72 and is mandatory for the participant to be registered to Step 2.

NOTE: Participants will be reminded of the week 24/SVR visit during the remote contact (at weeks 4 and 22), and participants only need to complete either the week 24 OR the SVR evaluation visit; they will not be required to complete both. If a participant completes week 24, his/her next visit will be at week 48 on Step 2. If a participant misses the week 24 visit and returns to the clinic for the SVR visit either at week 48 or 72, then only the SVR evaluations will be performed at that visit time point. Evaluations for weeks 48 or 72 will be performed at the next scheduled study visit. However, if a participant completes their SVR visit at week 72, this visit will be the participants' last study visit and they will not enter Step 2.

Step 2 Registration
Following completion of the SVR evaluation on Step 1 (Week 24 OR SVR visit), participants will be registered to Step 2 on that same day. Participants will undergo evaluations as outlined in the SOE 6.1-2, within the ±28-days visit window, as appropriate for the visit.

NOTE: Participants who register into Step 2 within the week 48 visit window will complete the week 48 and 72 visits. If a participant registers into Step 2 after the week 48 visit window, site staff should have the participant return to the clinic to complete week 72 (final study visit).

6.2.5 Study Completion Evaluations

For Step 2, week 72 ±28-days will be the final study visit for all participants, independent of the entry week for Step 2.

For participants who do not enter Step 2, the final study visit will be the last visit they had on Step 1, regardless of when that occurred.

6.2.6 Event-Driven Evaluations

Step 1: Unplanned Study Visits
Unplanned study visits should not occur after week 22 on Step 1.

The purpose of unplanned visits, should they occur, is to address common toxicities. Participants will be provided with a telephone number that they can call if they are having any problems (e.g., headache, fever, nausea, etc.) during the study treatment period (day 0 through week 12). Participants will be connected to the study staff who will talk to them and try to resolve the issue over the phone, whenever possible. Only if the study staff feels further investigations are required to resolve the complaint, an unplanned study visit should be scheduled within 5 days with the participant so that additional investigations, as deemed appropriate by the study staff, may be performed. It is possible no tests are ordered or tests not included in the SOE are ordered; however, while the protocol does not

require any testing to be performed at these unplanned visits, if any laboratory test is ordered (e.g., safety labs), a plasma specimen should be stored.

NOTE: If any laboratory, radiology, or other tests are ordered, they should be justified by medical need. Labs drawn for safety purposes are permitted. Any tests ordered are not meant to serve as an early indicator of a participant's HCV treatment response. The performance of HCV RNA testing at unplanned study visits is strongly discouraged and should be discussed with the core team. The purpose of these unplanned visits, should they occur, is to deal with common toxicities.

If a participant provides information about study treatment disposition, use (or change in use) of reportable concomitant medications, or gives information about reportable adverse events (e.g., AEs leading to change in study treatment regardless of severity grade) at this unplanned study visit, then this information should be captured on the appropriate eCRFs.

Participants who become pregnant while on study medications or up to week 22 should contact the site to schedule an unplanned study visit (see section 8.3 for details).

6.2.7 Discontinuation

Evaluations for Participants Who Do Not Start Study Treatment
All eCRFs must be keyed for the period up to and including the entry visit.

Premature Treatment Discontinuation
Participants who plan or who have discontinued their study medication prior to completing the full 84-day course will have been instructed to contact the site to alert them of premature discontinuation. The site staff will not be aware of any treatment discontinuations unless the participants inform the site. These participants will be encouraged, like all other participants, to return for their SVR evaluation visit at week 24 and remain on the study through study completion. No adjustments to the timing of the SVR evaluation will be made for premature treatment discontinuation. Participants will be provided a number to call or send a text message informing the site of the stop date.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document: https://www.niaid.nih.gov/sites/default/files/documents/sourcedocappndx.pdf.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the DAIDS AE Grading Table and AE reporting of AE requirements.

6.3.1 Documentation of Active HCV Infection

Positive for HCV RNA >1000 IU/mL prior to study entry.
Section 4.1.3 specifies assay requirements for HCV documentation. HCV documentation is not recorded on the eCRF.

6.3.2 Documentation of HIV-1 Status

Section 4.1.6 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the eCRF.

6.3.3 Calculated FIBROSIS-4 (FIB-4) Score

Calculated FIB-4 score is needed to determine cirrhosis status for all participants, as per the SOE, in order to evaluate other outcomes such as regression of liver disease.

This calculation requires the following data: Participant age (years), serum alanine and aspartate aminotransferase level (U/L), and platelet count (10^9/L).

Please refer to the A5360 PSWP for the website link to calculate the FIB-4 score.

6.3.4 Model for End-Stage Liver Disease (MELD) Score

The MELD score measures the mortality risk in participants with end-stage liver disease. It is used as a disease severity index to help prioritize allocation of organs for transplant. In order to calculate the MELD score, total bilirubin (mg/dl), sodium (mEg/L), INR, and serum creatinine (mg/dl) values are needed.

Please refer to the A5360 PSWP for the website link to calculate the MELD score.

6.3.5 Documentation of Cirrhosis Status

Participants with calculated FIB-4 score of <3.25 are considered to be non-cirrhotic.

Participants with calculated FIB-4 score ≥3.25 are considered to have cirrhosis and must have a calculated CTP score of ≤6 (CTP A) to be considered a compensated cirrhotic. See section 6.3.6.

6.3.6 Calculated Child-Turcotte-Pugh (CTP) Score

Calculated CTP score is needed only for participants who are considered cirrhotics as determined by the FIB-4 score (≥3.25) as per the SOE. CTP score must be ≤6 corresponding to Class A to be included in the study.

This calculation requires the following data: total bilirubin (mg/dl), albumin (g/dl), INR, evaluation for ascites (absent, slight, or moderate), evaluation for hepatic encephalopathy as per West Haven criteria (none, mild to moderate [Grade1-2], severe [Grade 3-4]).

Please refer to the A5360 PSWP for the website link to calculate the CTP score.

6.3.7 Liver Elastography

If available, liver elastography measurement will be captured at entry visit. Liver elastography data/values from the previous 3 years will be accepted. This will not be required for study entry. Where available, liver elastography will be repeated per the SOE. See A5360 MOPS for a list of liver elastography methods.

6.3.8 Medical History

The medical history must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within 30 days prior to entry. In addition, the following diagnoses should be reported regardless of when the diagnosis was made:

- AIDS-defining conditions (only for HIV-1 co-infected participants)
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic HCV (If available, appropriate documentation from medical records of chronic HCV-infection, defined as having a documented HCV-positive antibody serology for greater than 6 months.)
- Chronic HBV
- Substance use (injection, non-injection drugs, and alcohol) captured via the WHO ASSIST instrument

Any allergies to any medications and their formulations must also be documented.

6.3.9 Medication History

A medication history must be present, including start and stop dates.

Table 6.3.9-1 Required Medication History

Medication Category	Complete History or Timeframe
Antiretroviral therapy	Within 90 days before study entry
Prescription drugs for treatment of opportunistic infections	Within 35 days before study entry
Prescription drugs for prophylaxis of opportunistic infections	Within 35 days before study entry
Prescription drugs (other)	Within 35 days before study entry
Non-prescription drugs	Within 35 days before study entry
Acid suppressing medications such as proton pump inhibitors (PPIs) and/or H2 inhibitors	Within 35 days before study entry
Vaccinations	Within 35 days before study entry
Sex-hormone medications or sex-hormone analogues or antagonists*	Last 12 months except as noted below

*Includes: hormone-releasing IUDs (e.g., Mirena inserted in the last 5 years); oral, injectable, implanted, or patch contraceptives; vaginal ring, creams, or inserts; estrogen, progesterone, or testosterone therapy; leuprolide or other synthetic gonadotropin-releasing hormone; tamoxifen, raloxifene, aromatase inhibitors or any other androgen, estrogen, or progesterone analogue or antagonist therapy.

6.3.10 Clinical Assessments

Complete Physical Exam

A complete physical examination must be performed at screening and is to include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; and examination of the lower extremities for edema. The complete physical exam will also include signs and symptoms, diagnoses, and vital signs (height, weight, temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Exam

A targeted physical examination should be performed at entry, week 24/SVR evaluation visit and weeks 48 and 72, and should include vital signs (weight, temperature, pulse, respiration rate, and blood pressure), and is to be driven by any previously identified or new AE/targeted condition (as described in below bullets), that the participant has experienced within 14 days prior to study entry/since the last visit or at this visit.

Post entry, record the following targeted events regardless of grade:

- Uterine pregnancy
- AIDS-defining conditions (refer to the CDC HIV Classification and the WHO Staging System for HIV Infection and Disease)
- Tuberculosis
- Chronic HBV
- Ascites
- Hepatic Encephalopathy

Refer to section 7.2 for AE collection requirements.

Height
Height (in cm) will be collected once at study screening.

Weight
Weight (in kg) will be collected at study screening, entry, week 24/SVR evaluation visit, and weeks 48 and 72.

Concomitant Medications
At entry and at the week 24/SVR evaluation visit, new and discontinued concomitant medications should be recorded on the eCRFs. See section 5.4 for concomitant medications.

Study Treatment (Intervention) Modifications
When the participant takes the last tablet of each bottle of SOF/VEL, they will be instructed to contact the site to report the treatment stop date. This information self-reported by the participant should be captured on the eCRF when reported outside of and during the week 24/SVR evaluation visit. See A5360 MOPS for additional details.

At the week 24/SVR evaluation visit, record all study drug modifications, including participant-initiated modifications, inadvertent and deliberate interruptions of more than 7 days. Record permanent discontinuation of study treatment (see section 6.2.7).

6.3.11 Laboratory Evaluations

At screening and entry, all laboratory values must be recorded on the eCRF. For post-entry assessments, all laboratory values for hemoglobin, AST, ALT, blood urea nitrogen (BUN), serum creatinine, total bilirubin, sodium, INR, albumin, and platelets regardless of grade must be recorded on an eCRF. Additional reporting of abnormal laboratory findings should be performed as per requirements in section 7.2.

Hematology
Hemoglobin, hematocrit, red blood cells (RBC), white blood cell (WBC) count,

platelets.

Liver Function Tests
AST (SGOT), ALT (SGPT), total bilirubin and albumin.

Blood Chemistries
Serum creatinine, sodium, BUN

Creatinine Clearance (CrCl)
CrCl will be calculated throughout the study using Cockcroft-Gault method. Refer to the Cockcroft-Gault calculator located on the FSTRF web site. (Please refer to the A5360 PSWP for the website link to calculate CrCl using the Cockcroft-Gault calculator.)

International Normalized Ratio (INR)
This will be performed at a local laboratory.

Pregnancy Test
For women with reproductive potential: Serum or urine β-HCG. (Urine test must have a sensitivity of <25 mIU/mL.) Record pregnancy and pregnancy outcome per section 8.0.

HBV Panel
A HBV panel that includes hepatitis B surface antibody (HBsAb), hepatitis B core antibody total or IgG (HBcAb), and HBsAg will be performed during screening. HBV infection status must be confirmed prior to study entry. The panel must be performed at a laboratory that possesses Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent or at a DAIDS approved laboratory.

Results must be recorded on an eCRF.

NOTE: Active HBV infection is defined by the presence of hepatitis B surface antigen in serum (HBsAg+) at screening.

Table 6.3.11-1 Enrollment Eligibility Based on HBV Panel Results

HBsAg	HBsAb	HBcAb total or IgG	Status
Positive	Negative	Positive	Active HBV infection; NOT ELIGIBLE
Negative	Positive	Positive	Prior HBV infection with immunity; ELIGIBLE
Negative	Positive	Negative	Prior vaccination with immunity; ELIGIBLE
Negative	Negative	Positive	Isolated Hepatitis B core antibody. Prior HBV infection without immunity; ELIGIBLE

6.3.12 Immunologic Studies (For HIV co-infected participants)

CD4+
Obtain absolute CD4+ count within 90 days prior to entry from a laboratory that possesses a CLIA certification or equivalent.

6.3.13 Virologic Studies

Plasma HIV-1 RNA (For HIV Co-infected Participants)
Screening HIV-1 RNA must be performed within 90 days prior to study entry by a laboratory that possesses a CLIA certification or equivalent.

HCV RNA
Screening HCV RNA by PCR must be obtained by any FDA-approved test for quantifying HCV RNA at any local laboratory that has a CLIA certification or its equivalent. If no historical documentation is available, the screening HCV RNA must be obtained within 35 days prior to study entry.

All other samples will be collected per SOE. Only samples from participants who have achieved SVR will be collected at weeks 48 and 72 and tested for the presence of HCV RNA.

HCV RNA samples on study will be processed and shipped to the designated A5360 VSL for real-time quantitative HCV RNA analysis.

6.3.14 Stored Plasma/PBMCs/Serum

Stored plasma, PBMCs, and serum will be collected at the indicated visits for future HCV/HIV studies and shipped according to the A5360 Laboratory Processing Chart (LPC). Stored specimens will be used after study completion for HCV genotyping/sequencing to assess re-infection versus relapse and estimate SVR by genotype.

Further, the NS5A and NS5B regions of HCV will be sequenced for the earliest sample where HCV RNA is detected post-SVR and the corresponding entry sample will also be sequenced. Sequence data will assist in discriminating between reinfection (entry and post-SVR sequences are not related) versus relapse (entry and post-SVR sequences are identical). Incidence of reinfection will be calculated following the completion of sequencing.

Those who do not achieve SVR (SVR non-responders) will have both baseline and SVR specimens tested for HCV RASs by sequencing the NS5A and NS5B regions.

Any specimens collected during unplanned visits will be stored. See section 6.2.6.

6.3.15 Questionnaires

Adherence Assessment
Adherence will be captured at the week 4 remote contact (see section 6.3.2**2**) and week 24/SVR evaluation visit (i.e., week 22 or beyond). At both assessments, participants will be asked to estimate their adherence using Likert-type questions (all, most, half, some, or none). At the SVR visit, participants will also be asked to indicate the percentage of study medication that they actually took on a visual analog scale. At the week 4 remote contact assessment and week 24/SVR evaluation visit, participants who report less than perfect adherence will be asked about barriers to adherence.

Health Outcomes Questionnaire (EQ-5D)
The EQ-5D is a validated instrument used to collect data about quality of life (http://www.euroqol.org). The instrument asks questions and each has three possible responses (EQ5D-3L version). The instrument asks respondents to comment on their degree of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and then ask participants to record their current health-related quality of life state using a vertical visual analogue scale (0-100 range). The instrument has been translated into a variety of languages and is available as a paper form, a computer-based form, a tablet/cell phone form, or as an interview.

Responses must be recorded on an eCRF from the entry visit and week 24/SVR evaluation, and weeks 48 and 72 visits. In addition, responses must be recorded in the event of an unplanned study visit.

Health Care Utilization Questionnaire
The health care utilization questionnaire solicits participant-reported health care utilization in the past 4 weeks including: 1) nights spent in a hospital bed, 2) visits to an emergency department, and 3) visits to a doctor’s office. This questionnaire will be administered during visits at entry, week 24/SVR evaluation, and weeks 48, 72, and any unplanned visits. Responses must be recorded on an eCRF.

Substance Use Questionnaire
The substance use questionnaire will be administered at entry, week 24/SVR evaluation and weeks 48 and 72 visits. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) survey that was developed for the WHO by an international group of researchers and clinicians as a technical tool to assist with early identification of substance use-related health risks and substance use disorders will be used. This tool has been validated globally and captures information on alcohol, smoking, and injection and non-injection drug use.

6.3.16 HCV Therapy Dispensed/First Dose Observed

The entire quantity of study-provided drug (84 tablets) will be dispensed at the entry visit (week 0). Study staff will observe the first dose taken by the participant before he/she leaves the site and record this observation on an eCRF. Refer to section 5.0 for details on study product dispensation.

6.3.17 Adherence Education and Counseling

Adherence education and counseling will be conducted for all participants prior to entry. Adherence education and counseling is not recorded on the eCRF.

See the A5360 MOPS for further details.

6.3.18 Pregnancy Prevention Counseling

Pregnancy prevention counseling will be conducted for all participants at screening and entry. Pregnancy prevention counseling is not recorded on the eCRF.

6.3.19 Cirrhosis Counseling

All compensated cirrhotics will be counseled on secondary prevention and long-term surveillance of liver disease according to the SOE. Cirrhosis counseling is not recorded on the eCRF.

See the A5360 MOPS for further details.

6.3.20 HCV Risk-reduction Counseling

HCV risk-reduction counseling will be administered to all participants, per the SOE. See the A5360 MOPS for further details.

6.3.21 Locator Information

At study entry, all participants will be asked to list their primary mode of contact (e.g., telephone, email, text, or social media) and their secondary mode of contact. The site will capture these options for mode of contact (but will not record any participant locator this information on any eCRF), and use them to contact study participants without requiring them to come in to the clinic. Sites will also capture information on another person that the site can contact if the participant cannot be reached (e.g., spouse, friend, neighbor, etc.); information on the secondary contact will not be recorded on any eCRF.

6.3.22 Remote Contact with Participants Outside of Planned Clinic Visits

When contacting participants remotely, sites will have the flexibility to make adjustments to the mode of contact utilized at their discretion and at the participant's convenience – the only mode that will not be allowed is to schedule clinic visits in place of the remote contact. Sites will also be able to use different modes to contact different participants. Additionally, how the participant was contacted (i.e., mode of contact) will be collected on the eCRF.

Data that will be captured from the participant during the week 4 remote contact is whether the participant is taking study medication (i.e., adherence), in the prior 4 weeks. All participants will receive an individually tailored message, based on their adherence, which will be read or written to them in order to promote and/or encourage adherence through the end of treatment. The message will highlight the benefit of treatment for HCV and the importance of adherence and will be tailored to each participant's response as to how well he/she is adhering to the HCV treatment regimen. Additionally, at both weeks 4 and 22, locator information will be updated (if anything has changed) and participants will be reminded to return for their SVR evaluation visit. Sites will be allowed to contact and collect participant's responses on adherence and to update his/her locator information using any of the options listed above, namely phone call, text message, email, or social media (e.g., WhatsApp, Facebook Messenger, Twitter, etc.; for a complete list, please refer to the MOPS). If the participant comes in for the week 24 visit prior to the completion of the week 22 remote call, or if the participant has completed the discontinuation visit, then the week 22 remote call is not needed.

The remote contact is not designed to assess concomitant medications or AEs. At the end of each remote contact, participants will be reminded that the information that they shared will not be communicated to the study team and that if they have concerns about symptoms or study questions they should contact the site via the telephone number provided by the site. This information should be reported in a medical record then reviewed and entered into an eCRF at the week 24/SVR evaluation visit.

Since it is common for participants to lose mobile phones or change service providers in a 6-month period, it is critical to ensure that locator information is kept up-to-date to ascertain SVR status. Locator information will be maintained securely by sites and specific locator information will not be recorded onto an eCRF. However, the parts of the locator information that were updated and the mode of contact used to update this information will be recorded on an eCRF.

Participants will be provided with a telephone number to contact the study staff if they are experiencing any side effects or have any safety concerns. If the study staff contacted determines that the issue cannot be resolved over the phone, an unplanned study visit will be scheduled, as described in section 6.2.6. If participant calls but does not come in for an unplanned study visit, details related

to the call should be reported in the participant medical record and reviewed at week 24/SVR evaluation visit and entered into the eCRF.

See the A5360 MOPS for further details, including a script to be used by site staff when contacting participants.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Collection Requirements for This Protocol

Post-entry, all AEs must be recorded on the eCRFs if any of the following criteria have been met.

- All grade ≥ 3 AEs
- All AEs that led to a change in study treatment/intervention regardless of grade
- All AEs meeting SAE definition or EAE reporting requirement

NOTE: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system.

NOTE: At week 24/SVR evaluation visit, information on any AEs participants may have experienced during the prior 24 weeks (particularly while on study medication) will be collected unless this information was already obtained during an unplanned study visit.

All AEs that are reported must have their severity graded. To grade AEs, sites must refer to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

Serious Adverse Events (SAEs)

A SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or

result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual.

DAERS must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

7.3.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting are required are: Sofosbuvir/Velpatasvir (SOF/VEL) FDC
- In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are: all cancers, myopericarditis events, hepatic failures, and autoimmune diseases.

7.3.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC Web site at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is week 0 to week 24/SVR evaluation.

- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.4 Study Monitoring

The Protocol Core Team will monitor the conduct and safety of the study via regular summaries of screening, accrual, data delinquency, study and study treatment discontinuation, data and sample completeness with attention to evaluation and time of SVR evaluation, and SAEs.

The DAIDS clinical representative will review and assess EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs as applicable. Additionally, the DAIDS clinical representative will receive aggregated SAE summaries prepared quarterly by the SDAC, as part of the core team monitoring referenced above.

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 6 months after 25% of the study sample (100 participants) have completed 12 weeks on study, whichever occurs earlier. 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. See Section 10 for statistical and other considerations related to interim monitoring. Detailed plans for study monitoring will be outlined in a Study Monitoring Plan developed by the Statistical and Data Management Center (SDMC) prior to enrollment of the first participant.

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.

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

Criteria for participant management, dose interruptions, dose adjustments and discontinuation, or changes in treatment will be described only for toxicities attributable to study drugs (SOF/VEL). The grading system for drug toxicities is located in the DAIDS AE Grading Table (see section 7.2).

NOTE: The team must be notified via e-mail within 72 hours regarding toxicities that result in a change in study regimen (actg.corea5360@fstrf.org).

It is possible that some participants will experience transient or prolonged AEs during the study. However, it is important to note that, in this trial, there are no scheduled on-treatment visits and hence, participants must call the site and schedule unplanned study visits in order for AEs to be identified. AE-related unplanned study visits will be handled as listed below. However, at week 24, information on any AEs participants may have experienced during the prior 24 weeks, particularly while on study medication, will be collected.

8.2 Management of Side Effects of SOF/VEL

There are no signature abnormalities associated with SOF/VEL. If an SAE occurs, the site investigator has the option to discontinue study treatment. However, prior to the discontinuation of study drugs, the study core team should be contacted by email (actg.corea5360@fstrf.org).

Participants who meet any of the following laboratory criteria should stop treatment with SOF/VEL:

- Confirmed elevation of ALT and/or AST >5 x entry values measured while on study treatment measured at unplanned study visits.
- Confirmed direct bilirubin 3 x ULN and >2.0 mg/dL
- Any Grade 3 or greater rash associated with constitutional symptoms assessed as related to treatment with SOF/VEL.
- Any Grade 4 event assessed as related to treatment with SOF/VEL

Dose modification of SOF/VEL will not be allowed in the study. If SOF/VEL is discontinued for toxicity reasons, it should not be restarted.

NOTE: Grades 1 and 2 AEs associated with SOF/VEL require no change in study treatment.

8.3 Pregnancy

Pregnancy will result in immediate discontinuation of the study medication and initiation of counseling regarding the lack of information on safety of SOF/VEL in pregnancy. Participants who become pregnant while on study should contact the site to schedule an unplanned study visit (only up to week 22) and will be followed on study/off-treatment until study completion. A visit following the end of pregnancy will be conducted for evidence of AEs in the participant, and an outcome eCRF will be completed. Male participants whose partners become pregnant will continue treatment as outlined in the SOE.

If a female participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, site staff should request permission to contact her regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy.

Pregnancy and pregnancy outcome will be recorded on the eCRFs Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Phone: 800-258-4263; Fax: 800-800-1052. (For studies conducted at sites outside the United States: Report to The Antiretroviral Pregnancy Registry - Telephone: 910-679-1598; Fax: 44-1628-789-666 or 910-256-0637.)

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Drug-related toxicity (see section 8.1 Toxicity).
- Requirement for prohibited concomitant medications (see section 5.4).
- Pregnancy in a female participant.
- Breastfeeding.
- Completion of treatment as defined in the protocol.
- Participant request to discontinue for any reason.

  NOTE: It is important to determine whether the treatment discontinuation is primarily due to an AE, lack of efficacy, or other reason.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.

9.2 Premature Study Discontinuation

- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol so as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the IRB/Ethics Committee, Food and Drug Administration (FDA), NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

This is a single-arm study of 400 participants, to evaluate the feasibility, safety, and efficacy of a MINMON strategy of delivering interferon and RBV-free, pan-genotypic DAA therapy to qualifying persons with active HCV. The outcomes of this study may be used to inform the feasibility and utility of a future randomized controlled trial including a study arm with the MINMON strategy. Because this study includes only one arm, there is no blinding of any study intervention component.

The primary completion date (PCD) for each participant will be timed to be the date when the SVR evaluation takes place. As defined below, SVR evaluation will take place at least 22 weeks following study entry, but may take place any time up to 76 weeks following study entry (i.e., the final study visit evaluation).
Following SVR evaluation, participants will enter Step 2 for post-SVR evaluation follow-up for secondary and exploratory objectives.

10.2 Outcome Measures

10.2.1 Primary Outcome Measures

10.2.1.1 Efficacy: Sustained virologic response defined as <LLOQ of HCV RNA in plasma from the earliest sample drawn at least 22 weeks following study entry. Missing results will be treated as SVR non-responders.

10.2.1.2 Safety: SAEs as defined by International Council for Harmonization (ICH) guidelines occurring from study entry until 24 weeks following study entry.

10.2.2 Secondary Outcome Measures

10.2.2.1 Participant with at least one unplanned clinic visit prior to SVR evaluation

10.2.2.2 Reportable AEs (as per section 7.2 of the protocol) not qualifying as SAEs (see primary safety outcome above), occurring from study entry until 24 weeks following study entry.

10.2.2.3 Premature discontinuation of study treatment, as defined by self-report by study participants

10.2.3 Other Outcome Measures

10.2.3.1 HCV reinfection defined as detectable HCV RNA and HCV sequence from subsequent to evaluation of SVR response, distinct from the baseline sequence and defined only among SVR responders

10.2.3.2 Change in FIB-4 between study entry and final study evaluation, defined only among SVR responders

10.2.3.3 Treatment emergent RASs among SVR non-responders

10.2.3.4 Quality of life (health related utility) before and after HCV cure

10.2.3.5 Cost per SVR attained- both globally and stratified by country - calculated using country-specific costs and expressed in US$ 2017.

10.2.3.6 Mode of remote participant contact over time

10.2.3.7 Number and timing of unplanned visits, number of types of evaluations at unplanned visits

10.2.3.8 Adherence to study treatment as self-reported by participants

10.3 Registration and Stratification

There is no randomization to this single-arm study. Eligible participants will enroll to Step 1 and then have the following required evaluations as described in section 6. The study will use stratification factors to limit enrollment to Step 1 by certain subgroups. These stratification factors include geographic location (limited to no more than 132 participants being enrolled from US-based clinic sites), 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 geographic distribution of those participants. Step 2 enrollment occurs following SVR evaluation and is for post SVR evaluation follow-up for selected secondary and exploratory objectives.

10.4 Sample Size and Accrual

The sample size for this single-arm study is 400 participants.

This sample size was chosen for benchmark properties listed below regarding the use of efficacy data from this study to informing the utility and feasibility of future studies of the MINMON approach, and the precision (based on CI width) about SVR efficacy outcome estimates.

Table 10.4-1 below describes SVR benchmarks and their properties.

The high benchmark is defined as when the lower confidence limit of the 2-sided 95% CI about the SVR estimate is strictly greater than 96%. Observing 392 or more SVR responders out of 400 participants (i.e., ≥98% SVR responders) would meet this benchmark. Under a true SVR rate of 97%, there is only a small probability (0.15) of observing this benchmark with the study sample size of 400. However, as the true SVR rate becomes higher, the probability of observing this benchmark also increases (while holding the sample size at 400 participants). For instance, if the true SVR rate were 98.5%, then there is 0.85 probability of observing this high benchmark in the proposed study sample size of 400. If a high benchmark were observed, then a future RCT may not be needed, as the high benchmark implies that the SVR for the MINMON strategy exceeds 96%.

The 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%. Observing 371 or fewer SVR responders out of 400 participants (i.e., ≤92.8% SVR responders) would meet this benchmark. Properties of possible scenarios are given in Table 10.4-1.

If neither the high nor low benchmark is met, a future RCT of the MINMON approach versus SOC may be desired, and efficacy estimates from this study could be used to inform the design and sample size of that study.
The low and high SVR benchmarks described above and in Table 10.4-1 below were chosen to represent what is currently thought to be reasonable SVR rates based on studies presented and published, including clinical trials, as well as studies reporting use of this DAA regimen outside the context of a clinical trial.

Properties of this study's sample size regarding probability of not observing either benchmark
Table 10.4-2 below summarizes the various probabilities that neither of the benchmarks (HIGH or LOW, as described above), are observed under a range of various true rates of SVR.

Table 10.4-1. SVR benchmarks and their properties

Benchmark	Benchmark Definition *(note: CI = confidence interval)*	Observed conditions for meeting benchmarks given proposed sample size of 400 participants	Hypothesized true SVR rates	Probability of observing benchmark given hypothesized true SVR rate and proposed sample size	How observing different benchmarks could inform design of a future study
HIGH	Lower confidence limit of 2-sided 95% CI about SVR estimate is strictly greater than 96%	Number of participants with SVR ≥392 out of 400 (or conversely, 8 or fewer SVR non-responders)	96.5%	.06	A future RCT may not be needed as this benchmark implies MINMON SVR to be greater than 96%
			97%	.15	
			98%	.59	
			98.5%	.85	
LOW	Upper confidence limit of 2-sided 95% CI about the SVR estimate is strictly lower than 95%	Observed number of participants with SVR ≤371 out of 400 (or conversely, 29 or more SVR non-responders)	94%	.17	A future RCT may not be desired as this benchmark implies MINMON SVR to be lower than 95%.
			93%	.45	
			92%	.74	

Table 10.4-2. Probabilities of not observing either HIGH or LOW benchmark under sample size of 400 and various true SVR rates

Hypothesized True SVR rates	Probability of *not* observing either benchmark as defined above (i.e., observed number of SVR responders is between 372 – 391, inclusive, out of 400 participants)
90%	.023
91%	.092
92%	.264
93%	.550
94%	.829
95%	.968
96%	.978
97%	.849
98%	.407
99%	.021

Table 10.4-3 below summarizes the precision about the primary efficacy outcome of SVR (as measured by the width of the 95% CI about the SVR estimate), and location of 95% CI limits, based on various observed SVR rates and 400 individuals. The 95% confidence intervals were calculated with the binomial distribution according to the method of Wilson (Score based intervals).

Table 10.4-3. Summary of a range of observed SVR rates and their impact on the precision of the 95% CI about the observed/estimated SVR rate

Observed SVR rate among n=400	SVR 95% CI lower confidence limit	SVR 95% CI upper confidence limit	Precision of SVR estimate (95% CI width in percentages points)
90%	86.7%	92.6%	5.9
91%	87.8%	93.4%	5.6
92%	88.9%	94.3%	5.4
93%	90.1%	95.1%	5.0
94%	91.2%	95.9%	4.7
95%	92.4%	96.7%	4.3
96%	93.6%	97.5%	3.9
97%	94.8%	98.3%	3.4
98%	96.1%	99.0%	2.9
99%	97.5%	99.6%	2.2

The sample size calculation has not been adjusted for losses to study follow-up as the definition of the primary efficacy outcome includes imputing missing evaluations as SVR non-responders. The impact of missingness contributing to the (lowering of the) SVR response rate will be addressed by both enumerating what led to non-SVR responder classification such as the following: missing HCV RNA values for SVR evaluation, HCV

RNA values observed >the assay LLOQ, early stopping of study treatment (e.g., for intolerability, etc.).

Assuming uniform accrual of 25 participants per month, total accrual to the study would be completed in 16 months. If initial accrual is assumed to be slower, at rates of 10 participants per month for the first 6 months, 15 participants per month for the next 6 months, and 20 participants per month for the remaining time, the total accrual time would be about 24 months.

10.5 Data and Safety Monitoring

10.5.1 Interim Monitoring Guidelines

This study will be formally monitored at least annually by an ACTG-appointed SMC (via the standing committee for the Hepatitis TSG). The first interim review will occur no more than one year after the enrollment of the first study participant or 6 months after 25% of the study sample (100 participants) have completed 12 weeks on study, whichever occurs earlier.

A planned interim review for efficacy will be performed 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 an interim look at efficacy occur while the study is still accruing, so that if SVR rate is unacceptably low (i.e., futility), that there is still an opportunity to intervene before accrual to the study is completed.

For instance, assuming uniform accrual of 25 participants per month and SVR evaluation happening 24 weeks following study entry, the planned interim review for efficacy would occur around month 12 since study accrual commenced, with approximately 300 participants accrued, 100 participants with SVR outcome available, and 100 participants remaining to be accrued. Assuming the slower but increasing accrual rate over time and same timing of SVR evaluation, the planned interim review for efficacy would occur approximately 17 months following study opening, with approximately 265 participants accrued, 105 participants with SVR outcome, and 135 participants remaining to be accrued.

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 (i.e., 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 defined by geographical location stratification factor (ie, US versus non-US).

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. 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 below.

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 second efficacy look interim analysis sample). The same analysis plan and monitoring bounds as defined in the first look above would be applied to this second look at SVR.

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 at least 10 (as 5% was the observed upper bound of the 95% CI on number of participants with any SAE from the ASTRAL-5 trial).

Any/all SMC reviews will include administrative/trial conduct data as well as safety data according to the safety-related outcomes enumerated above.

The following routine monitoring reports are distributed to core team and are detailed in the study monitoring plan (SMP): screening, accrual, data delinquency, study status, data and sample completeness, with attention to evaluation and timing of SVR outcome. The routine safety monitoring report is distributed to the DAIDS Clinical Representative and a subset of the core team (to include the study chairs) every 3 months.

Further details about monitoring of this study are available in the SMP.

10.6 Analyses

Due to US federally mandated reporting of outcomes to clinicaltrials.gov, the timing of initiating analyses for those outcomes, are likely to occur prior to study follow-up being completed. Therefore, there will be separate primary and secondary statistical analyses reports to cover all the analyses listed below.

10.6.1 Primary Efficacy Analysis

The primary efficacy outcome (SVR) will be estimated with a point-wise estimate as well as a 95%, two-sided CI. The confidence bound will be calculated with binomial distribution according to the method of Wilson (Score based interval). The impact of missingness contributing to the (lowering of the) SVR response rate will be addressed by providing the various reasons for non-SVR (e.g., discontinued treatment early due to various reasons including intolerability, HCV RNA $\geq$ LLOQ, missing evaluation for SVR (and reasons as known), and the number of participants meeting each reason for non-SVR.

10.6.2 Primary Safety Analysis

The primary safety outcome of SAEs will be enumerated, summarized and described for all qualifying outcomes. The number and relative frequency of participants experiencing one or more SAEs will also be summarized, and a CI about the probability of experiencing a SAE will be calculated (using CI methods as described above).

10.6.3 Secondary Outcomes Analysis

Premature discontinuation of study treatment will be defined from participant self-report either via remote contact prior to SVR evaluation, or at an unplanned visit or by retrospective recall at the week 24 or SVR evaluation visit (whichever occurs first). Those participants missing information from all these mechanisms will be assumed to have prematurely discontinued. The proportion of premature study treatment discontinuation will be estimated and a CI calculated to summarize the range of plausible values using methods parallel to other dichotomous outcomes described above.

Non-serious AEs will be summarized by the Medical Dictionary of Regulatory Affairs (MeDDRA) System Organ Class by the reporting types described in section 7.2.

Those who do not achieve SVR with an observed HCV RNA $\geq$LLOQ will have both baseline and SVR specimens tested for HCV RASs. 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.

Among SVR responders, HCV RNA post SVR follow-up (i.e., Step 2) will be used to evaluate for the HCV reinfection outcome. Detectable HCV RNA, with and HCV sequence distinct from the baseline sequence will qualify for the outcome of HCV reinfection. The absolute number (and relative frequency) of participants meeting this outcome will be summarized along with a 95% CI using methods as described for other dichotomous study outcomes.

Among SVR responders, HCV disease regression will be defined by the absolute change between baseline FIB-4 value and the final study FIB-4 value. The distribution of these absolute changes will also be described using key percentiles.

Further details are outlined in the study's Statistical Analysis Plan (SAP).

11.0 PHARMACOLOGY PLAN

Not applicable.

12.0 COST-BENEFIT ANALYSIS PLAN

The cost-benefit analysis will employ the resource utilization data collected at planned/unplanned study visits until the SVR is assessed (week 24/SVR evaluation visit) as well as SVR data and utilization data to develop an estimate of cost/SVR attained.

12.1 Objective

12.1.1 To determine the cost/SVR attained using the MINMON protocol

12.2 Primary Outcome

12.2.1 Cost/SVR attained - both globally and stratified by country - calculated using country-specific costs and expressed in US$ 2017.

12.3 General Approach to Costing

The cost/SVR attained will be assessed from two perspectives.

12.3.1 The perspective of the clinic/program/site treating the participant (program perspective). These costs include the cost of staff, laboratory monitoring, and medications involved in delivering HCV treatment to a participant. These costs begin at week 0 and continue through the week 24/SVR evaluation. The program cost perspective is helpful to those who administer a clinic or treatment program who want to understand how MINMON would impact their program budget.

There are two cost components from the program perspective:

1. Cost of HCV medications
2. Cost of planned and unplanned study visit evaluations between week 0 and the week 24/SVR evaluation visit

12.3.2 The healthcare sector perspective—the health sector perspective is broader than the program perspective. It includes the costs of staff, laboratory monitoring and medications between weeks 0 and 24, the cost of healthcare

utilization outside of the study site between weeks 0 and 24, and any changes in utilization that may occur in the future as the result of the participant attaining SVR.

There are four cost components from the healthcare sector perspective:

1. Cost of HCV medications
2. Cost of planned and unplanned study visit evaluations between week 0 and the week 24/SVR evaluation visit
3. Cost of healthcare utilization outside of study sites between week 0 and the week 24/SVR evaluation visit
4. Cost saving (or additional cost) that may accrue because a person attains SVR and subsequently uses fewer (or more) healthcare resources. This cost saving (cost) is defined as the DIFFERENCE in healthcare utilization per month measured at the week 48 visit comparted to the week 0 visit. The healthcare utilization questionnaire measures utilization over a 4-week recall period. This is defined as healthcare utilization per month. The difference in healthcare utilization per month between the week 48 assessment and the week 0 assessment is the monthly savings (or cost) attributable to attaining SVR. It will be assumed that the monthly savings (cost) applies to every month between week 24 and week 72.

In addition, because this estimate of cost savings is uncertain, sensitivity analyses will be used to explore different estimates of saving attained including: 1) difference in utilization measured at the week 72 visit and the week 0 visit, 2) difference in utilization measured at week 72 and week 48 visits. In both of these sensitivity analyses, it will be assumed that the monthly savings (or cost) we estimate applies to every month between weeks 24 and 72.

Measures of utilization will be translated to cost (expressed in currency rather than units of resources consumed) using WHO CHOICE country-specific unit costs (http://www.who.int/choice/cost-effectiveness/inputs/health_service/en/).

It will be assumed that all resource utilization between weeks 0 and 24 is related to HCV medications. As a result, the cost estimate will tend to be biased toward a higher cost/SVR attained.

The primary analysis will be conducted in an intention to treat framework, whereby participants who are LTFU and do not return for the week 24/SVR evaluation visit are assumed to be treatment failures and not counted as “SVR” in the cost/SVR attained calculation. This approach will also tend to bias results to a higher cost/SVR attained. A sensitivity analysis will explore cost/SVR when it is assumed that the rate of SVR among those lost to follow-up at week 24 is similar to the SVR rate among those with week 24 confirmation of cure.

12.4 Resource Utilization Data Collection

12.4.1 Cost of HCV Medications

We will price HCV therapy by country based on the negotiated price with ministries of health. In the U.S., there is no single cost of HCV therapy. For U.S. sites, we will price SOF/VEL using the federal supply schedule. Because the cost of therapy is dynamic and changes by setting and time, we will use sensitivity analyses to explore the impact of drug prices on the cost-benefit of treatment.

12.4.2 Cost of Planned and Unplanned Study Visits

We will consider two components of the cost of a study visit: a) cost of provider time, and b) cost of labs and assessments. Cost of the healthcare visits (Doctor/physician and staff time)—we will use WHO CHOICE estimates of outpatient care delivery costs by country. We will include the week 0 visit (not the screening visit as it is a study procedure with no real-world analogue) and the visit for week 24/SVR evaluation. In addition, we will include any unplanned visits between week 0 and the week 24/SVR evaluation.

We will cost laboratory tests using the national fee schedule for public sector healthcare payers in each country. For example, we will use the Center for Medicare and Medicaid Services (CMS) reimbursement schedule for laboratory test costs in the U.S. and the National Health Laboratory Service schedule for sites in South Africa.

12.4.3 Cost of Healthcare Utilization

To collect healthcare utilization data a questionnaire similar to the ACTG Instrument named “ACTG A5265 Resource Utilization Interview” will be used following minor adaptation for A5360.

Staff will administer this instrument at the entry visit, the week 24/SVR evaluation visit, at the weeks 48 and 72 planned study visits, and at any unplanned study visit.

To translate utilization to cost, we will use WHO CHOICE estimates of the cost of health care delivery (clinic visits, hospital nights, casualty ward visits) by country.

12.5 Assessing SVR Status

See section 10.2.1 for primary outcome measures. Sensitivity analyses will explore cases where non-SVR inferred due to LTFU.

12.6 Estimation of Cost/SVR Outcome

12.6.1 Program perspective. We will estimate the mean cost per participant including:
- Cost of medications
- Cost of all planned and unplanned study visits between weeks 0 and 24/SVR evaluation including staff time and laboratory tests

12.6.2 Healthcare sector perspective
- Cost of medications
- Cost of all planned and unplanned study visits between weeks 0 and 24/SVR evaluation including staff time and laboratory tests
- Cost of healthcare utilization between weeks 0 and 24/SVR evaluation
- The DIFFERENCE in healthcare utilization as measured at weeks 0 and 48

Cost/SVR attained in each country will be calculated, as well as for the entire study population. Cost/SVR both in local currency and in international dollars will be stated. The cost/participant who does NOT attain SVR will also be estimated. Sensitivity analyses will demonstrate the impact of HCV therapy costs on the cost-benefit of MINMON.

In addition, although there is no control arm to which we can compare the cost/SVR attained in MINMON, we will estimate the cost/SVR attained for the standard of care treatment protocol based on the cost of laboratory tests and medications and the planned schedule of events for a standard of care treatment course.

13.0 DATA COLLECTION AND MONITORING

13.1 Records to Be Kept

eCRFs will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon registration.

13.2 Role of Data Management

13.2.1 Instructions concerning entering study data on eCRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

13.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

13.3 Clinical Site Monitoring and Record Availability

13.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, eCRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and the accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

13.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, the NIAID, the OHRP, the industry supporter and local, US, and international regulatory entities for confirmation of the study data.

14.0 PARTICIPANTS

14.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix **I**) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the participant (or legal guardian, or person with power of attorney for participants who cannot consent for themselves. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, or legal guardian and this fact will be documented in the participant's record.

14.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, other local, US, and international regulatory entities as part of their duties, or the industry supporter(s) or designee.

14.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, other country-specific government agencies as part of their duties to ensure that research participants are protected, or the industry supporter.

15.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

16.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood, and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

17.0 REFERENCES

1. Blach S, Zeuzem S, Manns M, et al. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2(3):161-76. doi: 10.1016/S2468-1253(16)30181-9. Epub 2016 Dec 16.
2. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013;57(4):1333-42. doi: 10.1002/hep.26141. Epub 2013 Feb 4.
3. Ray SC, Bailey JR, Thomas DL. Hepatitis C virus. In: Knipe DM, Howley PM, editors. Fields Virology. 6th ed. Philadelphia PA: Lippincott Williams & Wilkins; 2013. p.795-824.
4. Zoulim F, Liang TJ, Gerbes AL, et al. Hepatitis C virus treatment in the real world: optimising treatment and access to therapies. Gut 2015;64(11):1824-33. PMID: 26449729.
5. AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015;62(3):932-54.
6. European Association for the Study of the Liver. Guidelines. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol 2017;66:153-94. PMID: 27667367.
7. World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. April 2014. Available from: http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/.
8. World Health Organization. New recommendations in the updated WHO guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Policy brief. February 2016. Available from: http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-policy/en/.
9. AASLD-IDSA. HCV Guidance. Recommendations for testing, managing, and treating adults infected with hepatitis C. www.hcvguidelines.org; Accessed July 11, 2017.
10. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de DST. Aids e Hepatites Virais. Protocolo Clínico e Diretrizes Terapêuticas para Hepatite C e Coinfecções. Brasília, Brazil: MS; 2015.
11. Consensus of Hepatitis C Carried Out by Sociedade Brasileira de Infectologia, Brazilian Society of Infectious Diseases, SBI BJID 2007; 11 Suplemento 1 (October).
12. Puri P, Saraswat VA, Radha K, et al. Indian National Association for Study of the Liver (INASL) Guidance for Antiviral Therapy Against HCV Infection: Update 2016. J Clin Exp Hepatol 2016;6:119–45.
13. Foster GR, Pianko S, Brown A, et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. Gastroenterology 2015;149(6):1462-70. PMID: 26248087.

14. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368(20):1878-87. PMID: 23607594.
15. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013;368(20):1867-77. PMID: 23607593.
16. Wyles D, Brau N, Kottilil S, et al. Sofosbuvir/Velpatasvir for 12 weeks in patients coinfected with HCV and HIV-1: The ASTRAL-5 Study. [Abstract 32]. Presented at the International Liver Congress; 13-17 April 2016; Barcelona, Spain.
17. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 infection. N Engl J Med 2015;373(27):2599-607. PMID: 26571066.
18. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med 2015;373(27):2608-17. PMID: 26575258.
19. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373(27):2618-28. PMID 26569658.
20. Terrault NA, Zeuzem S, Di Bisceglie AM, et al. Effectiveness of ledipasvir-sofosbuvir combination in patients with hepatitis C virus infection and factors associated with sustained virologic response. Gastroenterology 2016;151(6):1131-40.e5. PMID: 27565882.
21. Curry MP, Bacon B, Dieterich D, et al. Effectiveness of 8 or 12 week LDV/SOF in treatment-naïve patients with non-cirrhotic, genotype 1 hepatitis C: real-world experience from the Trio network. Presented at: 66th Annual Meeting of the American Association for the Study of Liver Diseases; November 13-17, 2015; San Francisco, CA.
22. Pol S, Bourliere M, Lucier S, et al. Safety and efficacy of the combination daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients from the French observational cohort ANRS co22 hepather. [Abstract 44]. Presented at the 50th Annual Meeting of the European Association for the Study of the Liver; 22-26 April 2015; Vienna, Austria.
23. Martinello M, Petoumenos K, Grebely J, et al. Incidence of HCV reinfection among treated individuals with recently acquired infection. J Hepatol 2016;64(Suppl):S620-S621.
24. McHugh M, Wu A, Pawlotsky J-M, Chevaliez S, Hallin M, Templeton K. Evaluation of the Cepheid Xpert® HCV Viral Load Assay. J Clin Virol 2015;70(Suppl 1):S84.

APPENDIX I: SAMPLE INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
For protocol: A5360

FINAL Version 1.0, 01/10/18: 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

SHORT TITLE FOR THE STUDY: A5360 FINAL Version 1.0, 01/10/18, Monitoring SOF/VEL in Treatment Naïve, HCV Participants with Active Infection

INTRODUCTION

You are being asked to take part in this research study because you have been infected with hepatitis C virus (HCV, a virus that affects the liver), and have not been treated before for HCV. You may also be infected with human immunodeficiency virus (HIV, the virus that causes AIDS). You may have compensated liver cirrhosis, which means that the liver is damaged, but is still working. This study is sponsored by the National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Currently, people who are infected with HCV are often closely monitored by medical staff. This requires patients to come to the clinic at least five times for visits, medication refills, and blood tests over a 12-week course of treatment. These guidelines are based on older HCV medications that had more side effects and were less successful at curing HCV than the medications used in this study. New HCV medications can cure 95 out of 100 infected persons who receive treatment. The medication that is provided in this study is approved by the US FDA for use in persons infected with HCV and coinfected with HCV/HIV. In large clinical trials, the side effects reported by study participants were comparable to a placebo (no medicine).

This study is being done to see if a minimal monitoring approach is effective and safe when providing HCV treatment. The minimal monitoring approach will require fewer study visits and lab tests with no medication refills. This study is trying to see whether taking an HCV treatment with fewer clinic visits and laboratory tests can cure just as many people as the standard approach that uses more visits and laboratory tests. We will compare the results of this study with what we have observed in other studies using a standard approach.

People are considered cured of HCV if the HCV virus cannot be detected in the blood 12 weeks after they have completed HCV treatment. This is called a sustained virologic response (SVR).

This study will measure the amount of HCV virus in your blood at entry, week 24, week 48, and week 72. The study staff will share these results with you. If the HCV virus is detectable in your blood at week 24 or after, the study staff will let you know, and help you find a health care provider who can discuss your future treatment options. You can become re-infected with HCV after you are cured. The study staff will discuss with you how to remain HCV free after your treatment is completed.

The study will also examine the convenience to you and the cost to cure a person of HCV using this minimal approach.

HOW MANY PEOPLE WILL BE IN THIS STUDY?

About 400 people (men and women age 18 years and older) will take part in this study.

WHERE IS THIS STUDY BEING DONE?

This study will take place across the world and will include participants from the US and non-US sites.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for up to 72 weeks.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

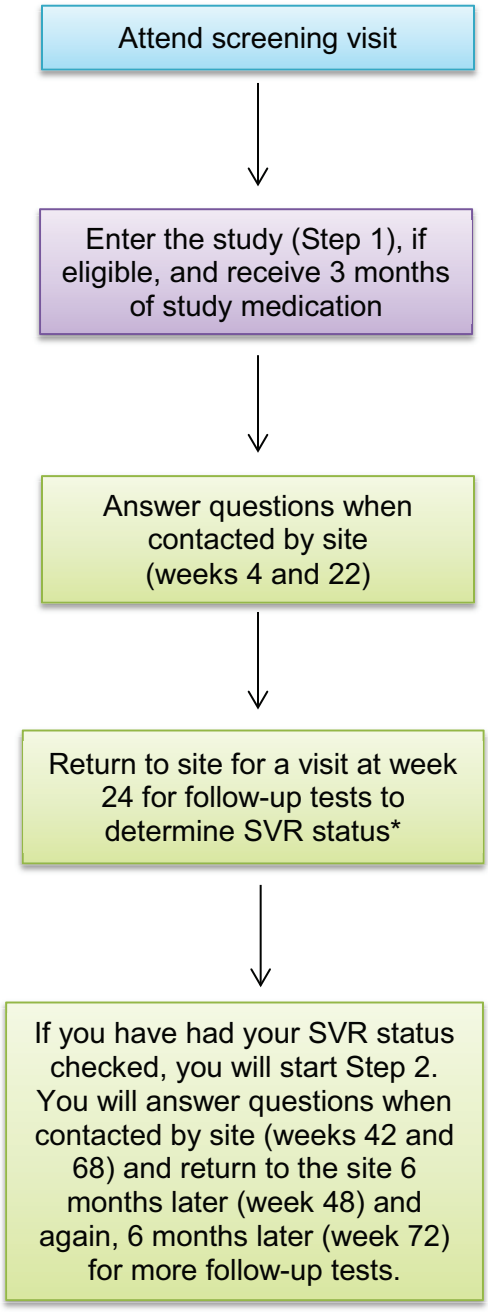
If you decide to join this study and meet the study requirements after the screening visit, you will be enrolled into the study, unless enrollment has been closed to the subgroup(s) as described below.

Individuals with HIV infection and/or have compensated cirrhosis (liver is damaged but it is still working) are also eligible for the study. Enrollment, however, of HIV-infected individuals or those with compensated cirrhosis will be limited in the study (i.e., only a certain number of persons will be included in the HIV-infected subgroup and compensated cirrhosis subgroup). The study staff will let you know if this limit has been reached for either subgroup, and what this means for you.

At the entry visit, you will be given your study medication for all 3 months to take home. You will need to store the medication in a safe place at room temperature (below 30°C [86ºF]) and take one tablet a day for the 3-month period.

If you are also infected with HIV, you will continue taking your current anti-HIV drugs if you are receiving them. If you are not currently on HIV medications and your provider does not think you will need HIV medications for the next 3 months, this is also acceptable. If your HIV medications include efavirenz (EFV), you will be switched to another HIV medication. EFV should not be taken with the HCV study medications.

A diagram of the study follows.



*After a person has successfully completed treatment for HCV, there is a period when HCV viral load in the blood is so low that even the most sensitive test cannot detect the virus. If this period of “undetectability” lasts for 12 weeks in a row after the end of treatment, it is called SVR (sustained virologic response).

Everyone who enters the study will take a fixed-dose combination of sofosbuvir/velpatasvir (SOF/VEL), which will be provided by the study. Anti-HIV drugs will not be provided by the study.

While you are in this study, you will need to be seen in the clinic about 5 times. The longest visit, which will be your enrollment visit, could take up to 2 hours. Study staff will tell you about how long each visit will be. You may need to come to the clinic more often if you have side effects. More information about the study tests is given below. During the study, you will get the results from any routine tests that are done during the study and relevant to your care when they are available.

If you do not enroll into the study
If you decide not to take part in this study or if you do not qualify to take part in this study, we will still use some of your information. As part of the screening visit, some demographic (for example, age, sex, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4+ T-cell count, HCV and HIV viral load) information is being collected from you so that ACTG researchers may see if there are patterns or common reasons why people do not join a study.

Required Blood Tests
Your blood will be drawn from a vein in your arm and used to measure your HCV viral load (the amount of HCV virus in your blood), to measure levels of certain hormones (chemical messengers in your blood), to see if the hepatitis B virus (HBV; another virus that affects your liver) is in your body, and for routine safety tests and metabolic tests (to test how your body uses the food that you eat). If you are a woman able to become pregnant, you will have a pregnancy test at the screening and entry visits and at later study visits if you think you might be pregnant. If you are infected with HIV, you will have blood drawn to measure your HIV viral load (the amount of HIV virus in your blood) and your CD4+ cell counts (these are cells in your blood that fight infection). You will be told the results of these tests when they become available.

Some of your blood will also be stored (with no information that will identify you) and used for HCV genotyping (a test to see the genetic makeup of the HCV virus) and sequencing (a test to check for the pattern/code of the genetic makeup of the HCV virus) for this study. HCV genotyping and sequencing are used to see which genotype of HCV you are infected with. Since these stored samples will be tested in the future, the results will not be available to you.

Blood will also be collected and stored for future testing at the end of the study. Some of your blood samples may be shipped and/or stored outside of the country from which they are collected.

Genetic (the message in your DNA) testing
If you agree, your blood will be drawn and used to examine different genes (pieces of your DNA). Results of testing done on these samples may not be given to you because they will be done in the future. If you do not agree to have genetic testing done, then the amount of blood drawn for future testing will be less (up to 20 mL less).

Please initial below if you agree to have any of your blood used for ACTG-approved future unspecified genetic testing. You may change your mind at any time and your samples will be destroyed.

_____ YES _____ NO

Optional Tests
If you agree, any blood left over after all required study testing is done may be stored (with no information that will identify you) and used for future ACTG-approved research. These blood samples may be stored for an unknown period of time. Results of testing done on these samples may not be given to you because they will be done in the future.

Please initial below if you agree to have any of your leftover blood used for future ACTG-approved research. You may change your mind at any time and reasonable efforts will be made to destroy your samples, though this may not always be possible.

_____ YES _____ NO

A5360 Study Visits

The study staff can answer any questions you have about individual study visits, the evaluations that will occur, or how long each visit will be. The table below can be used as a quick reference for you, along with the explanations that follow.

I. Appendix Table 1: Study Schedule

Evaluation or test	Screening	Entry	Post-Entry Visits							Unplanned Visits (Entry-Week 24)
			Week 4	Week 22	Week 24/SVR Evaluation	Week 42	Week 48	Week 68	Week 72	
Consent & Contact Information Collected	✓									
Documentation of HCV, HIV, & Cirrhosis Status	✓									
Liver Elastography (if available)		✓			✓		✓		✓	

Evaluation or test	Screening	Entry	Post-Entry Visits							Unplanned Visits (Entry-Week 24)
			Week 4	Week 22	Week 24/SVR Evaluation	Week 42	Week 48	Week 68	Week 72	
Physical Exam	✓	✓			✓		✓		✓	✓(if indicated)
Medical & Medication History	✓	✓								
Blood Samples Collected (for laboratory testing)	✓	✓			✓		✓		✓	✓(if indicated)
Blood Samples Stored (for later testing)		✓			✓		✓		✓	✓(if indicated)
Pregnancy Test	✓	✓			✓(if suspected)					✓(if suspected)
Pregnancy Prevention Counseling	✓	✓								
Cirrhosis Counseling		✓			✓		✓		✓	
HCV Risk-reduction Counseling		✓			✓		✓		✓	
Adherence Counseling		✓								
Questionnaires		✓	✓(via remote contact)		✓		✓		✓	✓
Study Drugs Distribution		✓								
Locator Information		✓	✓	✓						
Remote Contact With Participants Outside of Study Visits			✓	✓		✓		✓		

II. Description of Study Visits

Screening
After you have read and signed the consent form, you will be asked questions about your health, medical history, and medication history. You will have a complete physical exam to check your vitals (temperature, pulse, respiration rate, and blood pressure) and several tests, including blood tests, to make sure that you qualify to join the study. You will have your height and weight recorded.

Up to 42 mL of blood will be drawn during this visit. You will have blood drawn for HCV RNA testing. Some of the blood taken will be shipped to a testing lab and some of the blood will be stored for future testing. Your HCV infection and how long you have been infected will be confirmed. Your HIV infection and cirrhosis status will also be evaluated.

If you are a woman able to become pregnant, you will have a blood draw or urine collected for pregnancy testing. You may not continue with the screening process if your pregnancy test is positive. If you are able to become pregnant or to impregnate a partner, you will receive pregnancy prevention counseling.

Entry
If all of the results from your screening tests show that you are eligible, you will be enrolled in the study. You will be asked about your health and the medications you are taking. You will also have a brief physical exam to check your vitals (temperature, pulse, respiration rate, and blood pressure). You will have your weight recorded.

Up to 51 mL of blood will be drawn during this visit. You will also have additional samples collected and stored for later testing. If you are a woman able to become pregnant, you will be asked to provide a blood or urine sample for pregnancy testing. You may not enroll in the study if your pregnancy test result is positive.

If available at the site, liver elastography (scan of your liver) will be performed. This is described below in more detail. If you had a liver elastography done as part of standard care, this measurement will be recorded but it is not required for enrollment into the study.

You will be asked for your primary preferred contact information as well as a second contact (spouse, friend, neighbor, etc.) in order for the study staff to reach you throughout the study. This is known as locator information. If you are not able to be reached through the primary contact information, then the study staff will try to reach you through the second contact you provide.

At this visit, you will be given your study drugs. The study staff will give you enough study drugs to last 12 weeks (3 months). Study staff will watch you take your first dose before leaving the site. You can take the study medication (SOF/VEL) with or without food. You will receive adherence education and counseling on the study drug, as described below. You will be given instructions on how to take the study medication and what to do if you forget to take it. You will also receive a flier with information on two

types of other medications (proton pump inhibitors and H2 inhibitors [e.g., heartburn medication]) that you should not take while taking study medication. [*Sites: Please include local names of PPIs and H2 inhibitors on a flyer to give to participants at entry. Pictures should also be included on the flyer.]*

You will be asked to complete questionnaires that asks how you are doing and feeling, if you went to the hospital within the past 4 weeks, and if you use any substances such as alcohol, cigarettes, and other drugs. If you have compensated cirrhosis, you will also receive counseling for your cirrhosis, as described below. If you are able to become pregnant or to impregnate a partner, you will receive pregnancy prevention counseling. You will also receive HCV risk-reduction counseling and adherence counseling, as described below.

Post-entry visits

Since you will be given enough study drugs to last you for 12 weeks of the treatment period, you will not need to come back to the clinic until week 24 (3 months later). Study staff will contact you by the preferred contact at weeks 4 and 22 to update your contact (locator) information and at week 4, to collect information about whether you are taking your study medication. If study staff are unable to reach you after two tries, they will try to reach you via your second contact. While you are taking the study drug, if you are not feeling well or have any questions about the study medication, you should contact the study site directly at (*Site to insert site contact information: Name- Number-*).

All participants will be seen post-treatment at week 24. If you miss the week 24 visit, you may come back to the site to have your SVR status checked any time after week 24, up until week 72. Following your SVR status check, you will be followed through week 72. You will need to make two more visits to the site -- one at week 48 and one at week 72, which is Part 2 of the study. These visits will last about 1-1½ hours each.

At the week 4 remote contact, you will be asked how you are doing with taking your study medication. At the week 24/SVR evaluation visit, you will be asked how you did with taking your study medication.

At weeks 24, 48, and 72, you will have blood samples collected for routine safety tests and for a few required blood tests (HCV RNA). Up to 76 mL of blood will be drawn during each of these visits. You will also have additional samples collected and stored for later testing. You will be asked about your health and any changes in your medicines since your last visit. You will have your weight recorded. You will be asked to complete questionnaires that asks how you are doing and feeling, if you went to the hospital within the past 4 weeks, and if you use any substances such as alcohol, cigarettes, and other drugs.

Based on other tests done, the study staff will calculate different scores that will measure liver and kidney function and cirrhosis status. If you have compensated cirrhosis, you will also receive counseling for your cirrhosis, as described below.

If available at the study site where you were enrolled, you will have a liver elastography done at weeks 24, 48, and 72.

You will receive HCV risk-reduction counseling, as described below. If you have compensated cirrhosis, you will also receive counseling for your cirrhosis, as described below.

Unplanned visits
If you have any side effects during the treatment period, you must contact the study site. The study staff may require you to come in to the study site for an in-person evaluation. It is possible samples are collected for routine safety laboratory tests, or stored for future testing. If suspected, pregnancy testing and counseling will be done up to week 22. Up to 52 mL of blood could be drawn during this visit.

If you come to the study site for an unplanned visit, you will be asked to complete questionnaires that asks how you are doing and feeling, and if you went to the hospital within the past 4 weeks.

Early discontinuation
There are two types of discontinuation (stopping study treatment or leaving the study early). If at any point in the study, you want to discontinue study treatment or discontinue the study, you must contact the site immediately.

1. Stop study treatment early

   You or your doctor may decide to stop the study medication that you began at entry.

   If you must stop taking the study medication early, the study doctor may ask you to stay in the study and come in for the scheduled visits and tests.

2. Leave study early

   You or your doctor decides that you will no longer stay in the study or you are notified the study is stopped early.

III. Description of Study Evaluations

Consent and contact information collected
After you read the consent form and have had a chance to ask questions about the study, you will sign the consent form if you want to continue the screening process.

Documentation of HCV, HIV, and cirrhosis status
Study staff will check your medical records for the availability of test results for HCV, HIV, and cirrhosis. If these results are not available, then you will have these tests done as part of the screening visit.

Liver Elastography
At entry, a liver elastography measurement (if available) will be recorded. A liver elastography is an easy, simple, and safe ultrasound procedure that measures the stiffness of the liver by placing a small probe over the area of the liver while you lie on your back.

Clinical Assessments
You will have the following clinical evaluations in this study:

Physical examination
You will have a physical exam. At screening, the study staff will check the different areas of your body such as head, neck, eyes, ears, nose, throat, mouth and tongue, chest (excluding breasts), heart, abdomen, skin, hair, nails, and muscles and joints. The study staff will also check your vital signs such as temperature, pulse, blood pressure, and respiratory rate. Your height and weight will be recorded. After screening, the physical exam will be more limited and based on symptoms or problems that you are experiencing. Your weight will be recorded.

Medical and medication history
You will be asked questions about your health and about any medicines you have taken or are taking now. At week 24/SVR evaluation visit, you will be asked about any signs or symptoms that you are experiencing and any changes in other medications that you have had since your last visit.

Sample collections and laboratory testing
You will have the following samples collected and tested in this study:

Blood collected
Blood will be taken from a vein in your arm for various tests during the study.

Stored blood
Additional blood will also be collected from you and stored for testing at the end of the study.

Pregnancy test
If you are a woman who is able to become pregnant, you will have blood or urine taken for pregnancy testing at screening and entry. After you enter the study, you will have blood drawn or urine collected for pregnancy testing, if pregnancy is suspected up to week 22.

Pregnancy prevention counseling
All participants in the sexually reproductive age group will be counseled on family planning options for the duration of treatment (12 weeks). There is limited data on the safety of this medication during pregnancy and risk to the baby. Female participants who become pregnant during the course of treatment will be required to contact the site immediately and come in for a study visit as soon as possible.

Cirrhosis Counseling
If you have compensated cirrhosis, you will be counseled by study staff on managing your cirrhosis. Even though you may be cured of HCV, you will still have cirrhosis.

HCV Risk-reduction Counseling
You will be counseled by study staff on how HCV can be passed onto others and how to reduce your risk for HCV reinfection. HCV risk-reduction counseling will be done at entry, and weeks 24/SVR evaluation, 48, and 72. Study staff will talk with you about how you could become reinfected with HCV after being cured and ways to decrease risk of re-infection.

Adherence Counseling
You will get some adherence counseling from the study staff. The study staff will explain to you in detail how to take your study medication and help you find ways to take the medication correctly.

Questionnaires
You will be asked to complete a questionnaire that will ask how you are feeling and how you are doing with your daily activities. If you had stayed at a hospital or been to an emergency room, you will be asked to complete a questionnaire when you come in for your visits at entry, weeks 24/SVR evaluation, 48, 72, and unplanned visits (if any). You will also be asked about substance use such as alcohol, cigarettes, and other drugs at your entry and weeks 24/SVR evaluation, 48, and 72 visits.

See remote contact section below for information on what questions will be asked during the week 4 and 22 remote contacts.

Study drugs distribution and storage
You will be given a 12-week supply of study medication at entry. Study staff will watch you take your first dose, before you leave the site. You will be asked to store the study medication as instructed on the medicine bottle label.

If you lose your study medication, you will be able to return to the site and receive replacement medication (one-time replacement only).

Locator Information
Study staff will ask you about the best way to reach you when they need to contact you remotely at weeks 4, 22, 42, and 68. They will also ask you for a second way to contact you (for example, through a spouse or friend) if they are unable to reach you.

Remote contact with participants outside of study visits
Study staff will contact you using your preferred method at week 4 to ask questions about adherence information (if you are taking your study drug), to update your contact information, and to remind you to return to the site to have your SVR status checked at week 24.

During Part 1 of the study while you are taking the study (HCV) medication, you will be asked at week 4 if you are currently taking your study medication.

At week 22, study staff will contact you to schedule your week 24 visit to have your SVR status checked and to update your contact information.

During Part 2 of the study, after the week 24 visit, you will be contacted using your preferred remote method at weeks 42 and 68 to update contact information, if needed, and remind you of your upcoming study visits at weeks 48 and 72.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- The study is cancelled.
- Your doctor thinks the study is no longer in your best interest.
- The site investigator thinks that you are at significant risk of failing to comply with the requirements of the protocol.

The study doctor may also need to take you off the study drugs without your permission if:

- You become pregnant.
- You are breastfeeding.
- Continuing the study drugs may be harmful to you.
- You need a treatment that you may not take while on the study.

If I have to permanently stop taking study drugs through the study, or once I leave the study, how can I get study drugs?

If you must permanently stop taking SOF/VEL before the study is over, the study staff will talk with you about other options.

After you have finished the study, you will not be able to get SOF/VEL through the study.

WHAT ARE THE RISKS OF THE STUDY?

Risks of Social Harm
Although the study site will make every effort to protect your privacy and confidentiality, it is possible that others could find out that you are participating in this study and that social harm may result (because you could become labeled as being infected with HCV and/or HIV). For example, you could be treated unfairly or discriminated against by family members, friends, and/or the community.

Risks of Drawing Blood
Drawing blood may cause some discomfort, lightheadedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases, fainting, or infection.

Risks of Study Drug
The study drug (SOF/VEL) is relatively safe and in controlled clinical trials it was found to have a safety profile similar to a placebo (no medicine). The most common side effects you may experience are headache, nausea, vomiting, fatigue and diarrhea.

SOF/VEL has limited drug interactions with HIV medications with the exception of three HIV medications- efavirenz, tenofovir, and tipranavir/ritonavir. If you are taking any of these medications, your doctor will talk to you about these interactions in detail and what symptoms to look out for. Your doctor may modify your HIV medications after discussing it with you so that you can be included in this study.

SOF/VEL also has some interactions with other types of medications. There is risk of slow heartbeat if you also take amiodarone (a medication to help control heart rate). While you are on the study, you will be instructed not to take any of the prohibited medications (for example, heartburn medication mentioned earlier). The study staff will explain the prohibited and precautionary medications and discuss alternative options if you must take any of these concomitant medications.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Other Risks
There is a risk that your stored samples may be misused. There are laws against this kind of misuse, but they may not fully protect you. The chance that this will happen is considered small because of the security taken with your samples.

Your genetic information is unique to you. There is a risk in genetic research that someone using your samples may identify you. However, this risk is very small, but may increase with the progress of science. Researchers will inform you of any newly identified risks.

If you are cured of your HCV, you could still become infected again with HCV. You can get HCV from coming in contact with blood and/or sexual fluid that is infected with HCV.

ARE THERE RISKS RELATED TO DELAYING HIV THERAPY?

You are not required to be on HIV medications to enter this study. If you are not on HIV medications at the time of your HCV infection and you and your doctor do not think you need to start HIV medications, we will not exclude you from the study. We also do not recommend delaying HIV medications for entry into the study if your doctor feels they are medically

necessary. Although the dosing period of the HCV medication is short (84 days), a delay in necessary HIV medications could allow for progression of HIV disease, which can increase your risk of opportunistic infections and long-term after effects of HIV infection. If you have any concerns about these risks, we suggest that you discuss them with your medical provider.

ARE THERE RISKS RELATED TO PREGNANCY?

The drugs or drug combinations in this study have not been studied extensively in pregnancy. If you are having sex that could lead to pregnancy, you must agree not to become pregnant or to impregnate your partner while you are taking the study medication and for 6 weeks after stopping study medication. Note that if you become pregnant, study drug will be stopped and you will be asked to remain on the study. If you think you may be pregnant at any time during the study, tell your study staff right away. Pregnancies occurring on study will be reported to the Antiretroviral Pregnancy Registry, and study staff will request permission from you to obtain additional information after the baby is born.

Because of the risk involved, you must use at least one method of birth control that you discuss with the study staff. You must continue to use at least one method as long as you are taking study medication and for 6 weeks after stopping study medication. You must agree to one or more of the birth control methods listed below:

- A condom (male or female) with or without a spermicide
- Diaphragm or cervical cap with or without spermicide
- An intrauterine device (IUD)
- Tubal ligation
- Hormone-based contraceptives

Male and female participants not of reproductive potential are not required to use contraceptives.

Some of the methods listed above may not prevent the spread of HIV to other people. If you are also infected with HIV, you should discuss your contraceptive choices with your health care provider to choose the best way for you to both prevent pregnancy as required by this study and to prevent the spread of HIV to your partner.

Male participants should not donate sperm while on study treatment and for six weeks after stopping study medication.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you. The study is designed to treat your HCV infection with an approved study medication and you may be cured of your HCV. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HCV and/or HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study, you have the choice of:
- treatment with prescription drugs currently available to you
- treatment with other experimental drugs, if you qualify
- no treatment

Please talk to your doctor about these and other treatment choices available to you and the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

For Sites in the US

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties (insert name of site) institutional review board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

For Sites outside the US

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the US FDA, the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties, (insert name of site) institutional review board (IRB) or Ethics Committee (a committee

that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for the study drugs, the study visits, physical examinations, laboratory tests or other tests required by the study. You or your insurance company, or your health care system will be responsible for the costs of your regular medical care as well as for the costs of drugs not given by the study.

WILL I RECEIVE ANY PAYMENT?

[*Sites: Please indicate whether you will provide payment to participants. If so, please describe the amount to be paid or reimbursed, the payment schedule, and any prorated schedule should the participant decide to withdraw or is withdrawn early by the investigator*. *Please also include a value to be used as an incentive (as justified by your IRB) for attending the SVR visit, as determined appropriate according to site location.]*

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of taking part in this study, you will be given treatment right away for your injuries and be referred for further treatment, if necessary. However, you or your insurance company may have to pay for this care. There is no program for compensation, either through this institution or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. The care that you would normally receive will not be affected if you decide not to take part. Your decision will not affect other studies done by NIH in which you may be taking part, and will not lead to any penalty or loss of benefits that you have the right to expect.

We will tell you about new information from this or other studies that may affect your health, welfare, or decision to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research participant, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE ACTG Study A5360

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)	Participant's Signature and Date
Participant's Legal Representative's Name (print) (As appropriate)	Legal Representative's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date