ACTG

Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections

A5380

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

A Multicenter Trial of Advancing Clinical Therapeutics Globally (ACTG)

NIAID CRMS # 38553

This file contains the current ACTG A5380 protocol, which includes the following document:

- Clarification Memo #3, dated 12 Apr 2022
- Letter of Amendment #4, dated 13 Oct 2020
- Letter of Amendment #3, dated 09 Sep 2020
- Letter of Amendment #2, dated 14 Aug 2020
- Clarification Memo #2, dated 20 Apr 2020
- Letter of Amendment #1, dated 18 Dec 2019
- Clarification Memo #1, dated 15 Oct 2019
- Protocol Version 1.0, dated 07 June 2019

Clarification Memo #3 for:

A5380

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

A Multicenter Trial of Advancing Clinical Therapeutics Globally (ACTG)

NIAID CRMS # 38553

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

CLARIFICATION MEMO

DATE: April 12, 2022

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

FROM: A5380 Protocol Team

SUBJECT: Clarification Memo #3 for Protocol A5380

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 clarification(s) contained in this memo should be implemented immediately.

The following are clarifications (noted in bold and strikethrough) to Protocol A5380, Version 1.0, 06/07/19, titled, "A Phase II Trial of Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection (PURGE-C)."

Section 6.3.10 (Virologic Studies): The first paragraph of the fourth subsection has been revised to read:

Plasma HCV Genotype

At Step 1 screening, the HCV genotype **sample** ~~result~~ will be **collected, and the result will be** obtained locally (real-time) from any laboratory that has a CLIA certification or its equivalent. ONLY IF IT IS NOT AVAILABLE LOCALLY should it be done (real-time) at the designated testing laboratory (see A5380 LPC). **The participant may be enrolled with the HCV genotype result pending.**

Letter of Amendment #4 for:

A5380

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

A Multicenter Trial of Advancing Clinical Therapeutics Globally (ACTG)

NIAID CRMS # 38553

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LETTER OF AMENDMENT

DATE: October 13, 2020

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

FROM: A5380 Protocol Team

SUBJECT: Letter of Amendment #4 for Protocol A5380

The following information affects the A5380 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 site 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 extend the upper window for Step 2 entry to 270 days to allow for a more flexible timeline for sites and participants, given the ongoing COVID-19 pandemic.

The following are changes (noted in bold or strikethrough) to A5380, Version 1.0, 06/07/19, titled, "A Phase II Trial of Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection (PURGE-C)." These changes will be included in the next version of the A5380 protocol if it is amended at a future date. Changes that have already been made via LOA #3, dated 09/09/20, have been incorporated in the excerpted text shown below (and are no longer presented in bold or strikethrough).

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

2. Section 4.3 (Step 2 Inclusion Criteria): The following revisions have been made:

   4.3.3 Detectable HCV RNA from the confirmatory sample (see section 6.2.4) collected within ~~112~~ **270** days of Step 2 entry.

   4.3.5 The following laboratory values obtained within ~~112~~ **270** days prior to Step 2 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 GCLP and participates in appropriate external quality assurance programs.
   - INR <1.5
     NOTE: INR ≥1.5 is acceptable in participants with known hemophilia or stable on an anticoagulant regimen affecting INR at the discretion of the site PI.
   - Albumin ≥3.0 g/dL
     NOTE: For INR and albumin values, values from the virologic failure/recurrence results in Step 1 can be used and there is no need to draw additional samples.
   - For participants receiving RBV, hemoglobin ≥12 g/dL for male, ≥11 g/dL for female.

3. Section 6.2.1 (Screening Evaluations): The third paragraph has been revised to read:

   For Step 1, screening evaluations to determine eligibility must be completed within 28 days prior to entry unless otherwise specified. For Step 2, participants can enter Step 2 up to ~~112~~ **270** days after the confirmatory HCV RNA sample date completed as part of Step 1.

4. Section 6.2.4 (Event-Driven Evaluations): The second paragraph of the <u>HCV Viral Recurrence/Virologic Failure</u> subsection has been revised to read:

   <u>HCV Viral Recurrence/Virologic Failure</u>

   In Step 1, all cases of confirmed HCV recurrence/virologic failure occurring before or at the week 16/SVR12 visit will undergo evaluation for preliminary determination of suspected relapse versus re-infection (see Table 6.1-1, A5380 MOPS, and A5380 LPC. Viral recurrence is defined as confirmed HCV RNA value >LLOQ after achieving HCV RNA <LLOQ (TD or TND). Virologic failure is defined as failure to achieve HCV RNA

<LLOQ (TD or TND) and confirmed increase in HCV RNA >1 log10 from nadir. These participants will enter Step 2. This confirmatory sample should be collected within ~~112~~ **270** days prior to Step 2 entry.

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

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 #3 for:

A5380

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

A Multicenter Trial of Advancing Clinical Therapeutics Globally (ACTG)

NIAID CRMS # 38553

ACTG NETWORK COORDINATING CENTER
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LETTER OF AMENDMENT

DATE: September 09, 2020

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

FROM: A5380 Protocol Team

SUBJECT: Letter of Amendment #3 for Protocol A5380

The following information affects the A5380 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 site 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 #2 (CM #2), dated 04/20/20, as US and non-US sites begin to open to research visits in the presence of the ongoing COVID-19 pandemic. A Study Monitoring Committee (SMC) review occurred on 08/17/20 for the first 10 enrolled participants who were enrolled prior to the temporary closure in March 2020 due to the COVID-19 pandemic. The outcome of the SMC review was that the study may proceed as planned. However, enrollment into the study (i.e., Step 1 entry) will remain paused until approval of this LOA #3, dated 08/26/20.

Follow-up for these 10 enrolled participants remains ongoing with modifications to allow for a mix of virtual and in-person visits. Registration for Step 2 for those already enrolled in Step 1 will resume upon approval of LOA #2, dated 08/14/20.

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

- The contact information for the Clinical Trials Specialist (CTS) needed to be updated in the roster, and the replacement of one of the statisticians. In response, the following section has been updated: cover page, roster, and study management section.
- Per DAIDS directive, changes made via CM #1, dated 10/15/19, and CM #2 (with additional revisions to reflect the current situation with the COVID-19 pandemic) have been incorporated and remain in bold/strikethrough. In response, the following sections have been updated: 4.1.5, 4.1.7, 4.1.8b, 6.2.3, 6.2.4, 6.3, 6.3.8, 6.3.9, 6.3.10.
- The upper window for Step 2 entry has been extended to 112 days from the confirmation sample. In response, the following sections have been updated: 4.3 (4.3.3, 4.3.5), 6.2.1, and 6.2.4.
- Remote consent for Step 1 and Step 2 is permitted, per local IRB guidance. In response, the following sections have been updated: 6.2.1 and the Sample Informed Consent (SIC).
- The upper window for the Step 1 week 16/SVR12 in-person follow-up visit will remain extended when the study reopens to accrual, per the COVID-19-related CM #2, dated 04/20/20 (extended upper window = +42 days). This visit remains critical for the primary outcome of the study; thus blood sample collection is required within the study window. In response, the following section has been updated: 6.2.3.
- For the Step 1 week 16/SVR12 visit, a virtual visit can be scheduled to conduct all other evaluations with a brief in-person lab visit for blood sample collection. In response, the following sections have been updated: 6.2.3, 6.3.21, and the SIC.
- For the Step 2 SVR12 visit (R+20, R+24, or R+28), the virtual visit should also be paired with a brief in-person lab visit for blood sample collection. In response, the following sections have been updated: 6.2.3, 6.3.21, and the SIC.
- In the event of possible HCV recurrence/virologic failure in Step 1, participants should return to the site within 2 weeks for collection of the HCV recurrence/virologic failure evaluations. All samples should be collected per Table 6.1-1 and stored at the site. In addition, due to COVID-19, for this visit, Liver Function Tests (LFTs), HCV RNA, HCV genotype, and HCV RAS testing, and should be drawn locally for immediate testing. In response, the following sections have been updated: 6.2.4 and the SIC.
- If at any point shipment of study samples is paused due to COVID-19, for the Step 1 week 16/SVR12 visit and for the Step 2 SVR12 visit, all samples should be drawn per protocol Table 6.1-1 or Table 6.1-2, respectively, and stored at the site. In addition, due to COVID-19, for this visit, an HCV RNA should also be drawn locally for immediate testing. In

response, the following section has been updated: 6.3.8.

- If hematology, chemistries, or LFTs are drawn within 7 days prior to entry (i.e., as a part of standard of care), these labs do not need to be repeated at entry. In response, the following section has been updated: 6.3.8.
- Testing required for Step 2 entry can be done at the site lab or a local commercial lab. In response, the following section has been updated: 6.3.8.
- Substance use testing has been changed to optional since this is not a clinical test and does not affect study integrity. Sites would be able to conduct the respective visit without collecting urine, given potential logistical challenges sites may face amidst the COVID-19 pandemic. In response, the following sections have been updated: 6.3.8 and the SIC.
- The methods for substance use urine testing was revised to reflect the use of either CLIA-waived point of care assays or laboratory-based methods. In response, the following section has been updated: 6.3.8.
- HCV RAS testing could be done locally. In response, the following section has been updated: 6.3.10.
- Virtual visits can be utilized for all follow-up visits (i.e., non-SVR12 visits for Step 1 and Step 2), due to COVID-19 and the participant's inability to come in for an in-person visit, or their preference not to come to the site for this visit. In response, the following sections have been updated: 6.3.21 and SIC.
- For participants on ribavirin (RBV), virtual visits for Step 2 should also be paired with a brief in-person lab visit for blood sample collection and for women, pregnancy testing. In response, the following sections have been updated: 6.3.21 and the SIC.
- Per recent template updates, a section on *Information Collected at Screening* has been added. The following section has been updated: SIC.
- Per ACTG requirements, a separate consent form has been added for storage of samples. In response, the following section has been added: Appendix III.

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The following are changes (noted in bold or strikethrough) to A5380, Version 1.0, 06/07/19, titled "A Phase II Trial of Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection (PURGE-C)." These changes will be included in the next version of the A5380 protocol if it is amended at a future date. Changes that have already been made via Letter of Amendment #1, dated 12/18/19, have been incorporated in the excerpted text shown below (and are no longer presented in bold or strikethrough). Note: LOA#2, dated 08/14/20, did not have any specific protocol changes, and only provided Step 2 registration guidance.

1. 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.

2. Protocol: Cover Page, Roster, and Study Management Section

   The last name and email address of the Clinical Trials Specialist has been changed within the following areas of the protocol: cover page, roster, and study management section, along with a change in the ACTG's Network Coordinating Center's parent company name; and Vincent Vu has been removed from the roster, and Trinh Umbleja added to the roster.

   - Clinical Trials Specialist
     Chanelle ~~Houston~~ **Wimbish**, BS
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3. Section 4.1.5 (Step 1 Inclusion Criteria)

   The laboratory requirements have been revised to read:

   HCV genotype obtained within 24 weeks prior to entry by any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, or at any network-approved non-US laboratory that **is Virology Quality Assurance (VQA) certified.** ~~operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.~~

4. Section 4.1.7 (Step 1 Inclusion Criteria)

   The laboratory requirements have been revised to read:

   For HIV-1 co-infected participants on ART, screening HIV-1 RNA must be <50 copies/mL or <LLOQ of local assay if LLOQ is >50 copies/mL **obtained** within 28 days prior to **study** entry ~~as measured~~ 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 GCLP and participates in appropriate external quality assurance programs~~.

5. Section 4.1.8b (Step 1 Inclusion Criteria)

   The laboratory requirements have been revised to read:

   For HIV-1 co-infected participants, HIV-1 ART should meet one of the following criteria:

   a) ART untreated due to (1) lack of indication per provider (CD4+ T-cell count ≥500 cells/mm^3) or (2) decision by provider and participant to defer ART during the G/P dosing period (4 weeks).

   OR

   b) On a stable, protocol-defined compatible ART regimen (per sections 2.2 [Rationale for Inclusion of Concomitant ART Regimens] and 5.4.1) for >2 weeks prior to starting G/P with a CD4+ T-cell count >100 cells/mm^3 **obtained** within 180 days prior to the screening visit~~. Laboratory testing can be done by~~ **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 GCLP and participates in appropriate external quality assurance programs.~~

6. Section 4.3 (Step 2 Inclusion Criteria)

   The following revisions have been made:

   4.3.3 Detectable HCV RNA from the confirmatory sample (see section 6.2.4) collected within ~~56~~ **112** days of Step 2 entry.

   4.3.5 The following laboratory values obtained within ~~56~~ **112** days prior to Step 2 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 GCLP and participates in appropriate external quality assurance programs.

- INR <1.5
  NOTE: INR ≥1.5 is acceptable in participants with known hemophilia or stable on an anticoagulant regimen affecting INR at the discretion of the site PI.
- Albumin ≥3.0 g/dL
  NOTE: For INR and albumin values, values from the virologic failure/recurrence results in Step 1 can be used and there is no need to draw additional samples.
- For participants receiving RBV, hemoglobin ≥12 g/dL for male, ≥11 g/dL for female.

7. Section 6.2.1 (Screening Evaluations)

   This section has been revised to read:

   Remote consent for Step 1 entry and Step 2 registration is permitted, according to IRB-approved site guidelines.

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

   For Step 1, screening evaluations to determine eligibility must be completed within 28 days prior to entry unless otherwise specified. For Step 2, participants can enter Step 2 up to ~~56~~ **112** days after the confirmatory HCV RNA sample date completed as part of Step 1.

   In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

8. Section 6.2.3 (Post-Entry Evaluations)

   This section has been revised to read:

   All post-entry evaluations occur in reference to the start of study therapy.

   All Step 1 study visits for the 10 participants enrolled on or before March 18, 2020 can occur remotely (via telephone), except for the Step 1 week 16/SVR12 visit, which must remain an in-person visit, if this visit can be conducted safely. For this visit, there is potential for a hybrid visit in which a virtual visit can be scheduled to conduct all other evaluations with a brief in-person lab visit for blood sample collection.

   For the Step 2 SVR12 visit (R+20, R+24, or R+28), which must remain an in-person visit, if this visit can be conducted safely. For this visit, there is potential for a hybrid visit in which a virtual visit can be scheduled to conduct all other evaluations with a brief in-person lab visit for blood sample collection, and conduct pregnancy testing if the participant is a woman of child-bearing potential and is taking RBV.

   The safety of participants and study staff must be taken into account when scheduling ~~this~~ visits and any remote contact prior to ~~this~~ in-person visits, with the consideration of delaying visits if needed. If there is a need to limit in-person interactions at the site, the in-person component can be restricted to the blood draw, and the remaining visit evaluations can be completed via telephone.

If the blood draw at this visit is limited, then prioritize sample use as follows:

- **Local testing for safety**
- **HCV RNA**
- **HIV-1 RNA**
- **CD4+ (for participants living with HIV-1 infection)**
- **Storage**

Until further notice, store samples for central testing (e.g., HCV RNA and HIV-1 RNA) in accordance with the guidance distributed by the ACTG Lab Center on 03/17/2020. The team will provide further guidance on these samples as needed.

On-Treatment Evaluations

Study visits must be scheduled on the weeks indicated in Tables 6.1-1 and 6.1-2, within the visit windows described below, as appropriate for the visit.

~~**NOTE: Step 2 entry may be deferred until further notice.**~~

Step 1 (**remote, via telephone, permitted**):

- Weeks 1 and 2 have a window of ±3 days.
- Week 4 has a window of -7 days and +14 days.

Step 2 ~~**(deferred until further notice)**~~:

- Week R+2 has a window of ±3 days.
- Weeks R+4, R+8, R+12, and R+16 have a window of -7 days and +14 days.

Treatment Completion Evaluations

Clinical assessment and laboratory evaluation, as outlined in section 6.1, will be performed at treatment completion (Step 1: week 4, Step 2: week R+8, R+12, or R+16).

~~**NOTE: Step 2 entry may be deferred until further notice.**~~

Post-Treatment Evaluations

Following treatment completion, participants will undergo evaluations as outlined in Tables 6.1-1 and 6.1-2, within the study windows, as indicated below.

~~**NOTE: Step 2 entry may be deferred until further notice.**~~

After the last dose of study drugs, the post-treatment study visits have the following windows:

Step 1 (**remote [via telephone] permitted, EXCEPT week 16**):

- Study weeks 8 and 12~~, and 16~~: -5 days and +21 days
- **Study week 16: -5 days and +42 days**
- Study week 28: -7 days and +28 days

NOTE: In the midst of the COVID-19 pandemic, for study week 28, all evaluations ~~should~~ may be conducted remotely, and the week 28 specimen can be collected at a future date, prior to study closure, up until 36 weeks post treatment completion, as

long as the week 16/SVR12 visit was conducted in person. ~~Participants should only have the week 28 visit in person if the week 16/SVR12 visit and sample were missed.~~

~~If a participant has successfully attended the week 16/SVR12 visit and the blood sample has been collected, then that participant does not need to have an in-person visit at week 28.~~

Step 2 **~~(deferred until further notice)~~**:

- Study week R+20, R+24, or R+28 (12 weeks after re-treatment completion for those not receiving RBV depends on Step 2 treatment duration): -5 days and +28 days
- Study week R+32, R+36, or R+40 completion (for those receiving RBV): -14 days and + 28 days

9. Section 6.2.4 (Event-Driven Evaluations)

- The following revisions have been made to HCV Viral Recurrence/Virologic Failure subsection to include a newly added first paragraph and revisions to the second paragraph:

  HCV Viral Recurrence/Virologic Failure
  In the event of possible HCV recurrence/virologic failure, participants should return to the site within 2 weeks for collection of the HCV recurrence/virologic failure evaluations (per Table 6.1-1, A5380 MOPS, and A5380 Laboratory Processing Chart [LPC]), and stored at the site. In addition, due to COVID-19, for this visit, Liver Function Tests (LFTs), HCV RNA, HCV genotype, and HCV RAS testing should be drawn for immediate local testing (i.e., at the local site lab or a commercial lab).

  In Step 1, all cases of confirmed HCV recurrence/virologic failure occurring before or at the week 16/SVR12 visit will undergo evaluation for preliminary determination of suspected relapse versus re-infection (see Table 6.1-1, A5380 MOPS, and A5380 ~~Laboratory Processing Chart [~~LPC~~]~~). Viral recurrence is defined as confirmed HCV RNA value >LLOQ after achieving HCV RNA <LLOQ (TD or TND). Virologic failure is defined as failure to achieve HCV RNA <LLOQ (TD or TND) and confirmed increase in HCV RNA >1 log10 from nadir. These participants will enter Step 2. This confirmatory sample should be collected within ~~56~~ **112** days ~~of~~ **prior to** Step 2 entry.

- The third paragraph in the HIV-1 Virologic Breakthrough subsection has been revised to read:

  The increase in plasma HIV-1 RNA should be confirmed with repeat central ~~or local~~ testing as soon as possible (not to exceed 4 weeks); see HIV-1 Virologic Breakthrough Confirmation in Tables 6.1-1 and 6.1-2. For participants with confirmed HIV-1 viral breakthrough (≥200 copies/mL), a plasma specimen should be sent for HIV genotyping ~~and sent~~ to the designated A5380 VSL for evidence of HIV-1 drug resistance. Results will be reported back to sites in real-time from the designated A5380 VSL. See section 6.3.10, Stored Serum and Plasma for HIV-1/HCV Studies.

10. Section 6.3 (Instructions for Evaluations)

The following paragraph has been added as the first paragraph of this section.

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

11. Section 6.3.8 (Laboratory Evaluations)

The following notes have been added after the first paragraph (before the hematology subsection):

NOTE A: **If the following labs are drawn within 7 days prior to Step 1 entry (i.e., as a part of standard of care), these labs do not need to be repeated at entry: hematology, chemistries, and liver function tests.**

NOTE B: **Testing for Step 2 entry can be done at the site lab or a local commercial lab, and not sent to the central testing lab.**

NOTE C: **If at any point shipment of study samples is paused due to COVID-19, for the Step 1 week 16/SVR12 visit, or the Step 2 SVR12 visit, all samples should be drawn per protocol Table 6.1-1 and 6.1-2, respectively, and stored at the site. In addition, due to COVID-19, for these visits, an HCV RNA should also be drawn locally for immediate testing.**

The following changes have been made to Urine Sample for Substance Use Screen subsection:

Urine Sample for Substance Use Screen
Urine substance use screening **to be performed for** ~~must be done using a CLIA-waived urine drug use screening tool with~~ these common drugs of abuse: amphetamines, buprenorphine, benzodiazepines, cocaine, ecstasy, methadone, methamphetamine, barbiturates, marijuana, opiates, oxycodone, and phencyclidine. The screening will be assessed by urine test and must include the following ancillary testing, pH and creatinine to help in confirmation of sample against adulterants. **The methods used may be either CLIA-waived point of care assays or laboratory-based methods.** The following results would be used as confirmation of an unadulterated human urine sample; pH of 4.5 – 8.0 and urine creatinine ≥20 mg/dL. Urine fentanyl testing will be done using a test ~~which~~ **that** is not currently FDA approved or CLIA-waived.

Testing will be done per Table 6.1-1 on each scheduled study visit**,** and participants with positive screens will be counseled before and/or at the next scheduled visit with regard to potential impact on medication adherence, health-related risks, as well as in accordance with prevailing local laws.

NOTE: Collection of urine for substance use testing is optional given the potential logistical challenges sites may face amidst the COVID-19 pandemic. Sites may proceed with all other evaluations for the respective study visit, per Table 6.1-1, except for collection of urine for substance use testing.

The HCV Ab subsection has been revised to read:

HCV Ab must be obtained by any FDA-approved test at any local laboratory that has a CLIA certification or its equivalent **(US sites) or VQA certification (non-US sites)**. HCV Ab is only to be sent at screening and at a subsequent visit if the result is negative on the preceding visit. Once a single positive Ab is recorded, no further HCV antibody testing is required.

12. Section 6.3.9 (Immunologic Studies)

The CD4+/CD8+ requirement at screening has been revised to read:

CD4+/CD8+ (For participants with HIV-1 infection only)
Screening ~~Obtain~~ absolute CD4+/CD8+ count and percentages **must be performed** within 28 days prior to **study** entry ~~from~~ **at** a laboratory that possesses a CLIA certification or equivalent (US sites) or IQA certification (non-US sites).

13. Section 6.3.10 (Virologic Studies)

The first subsection has been revised to read:

Plasma HCV RNA (screening)
The screening HCV RNA result must be obtained by any FDA-approved test for quantifying HCV RNA at any local laboratory that has a CLIA certification or its equivalent **(US sites) or VQA certification (non-US sites)**. Screening HCV RNA must be obtained within 28 days prior to study entry.

The second subsection has been revised to read:

Plasma HCV RNA (real-time, on-study evaluations)
At the entry and post-entry visits, HCV RNA quantification will be performed as follows:

Plasma HCV RNA real-time testing will be collected, processed, and shipped to the designated testing laboratory (see A5380 LPC for directions). These results will be reported within 2 weeks after specimen receipt for both Steps 1 and 2.

NOTE A: For Step 1, HCV RNA should only be done at the week 16/SVR12 visit for the 10 participants enrolled on or before 03/18/20.

NOTE **B** For Step 2, an increase in plasma HCV RNA at any time point meeting HCV virologic response-based treatment stopping criteria must be confirmed with repeat testing within 2 weeks of receipt of results. For more information please see section 6.2.4.

The third subsection has been revised to read:

Plasma HCV RNA (real-time)
After the treatment is completed in Step 1, for participants entering Step 2 (Viral Recurrence [Reinfection/Suspected Relapse/Undefined Post-Treatment Viremia] or

virologic failure): a detectable HCV RNA after the end of treatment after achieving HCV RNA <LLOQ is virologic evidence of recurrence which will require confirmation and should be performed in real-time at the designated testing lab as soon as possible ~~but no later than 2 weeks~~.

The first paragraph of the fourth subsection has been revised to read:

Plasma HCV Genotype
At Step 1 screening, the HCV genotype result will be obtained locally (real-time) from any laboratory that has a CLIA certification or its equivalent **(US sites) or VQA certification (non-US sites)**. ONLY IF IT IS NOT AVAILABLE LOCALLY should it be done (real-time) at the designated testing laboratory (see A5380 LPC).

The first paragraph in the fifth subsection has been revised to read:

Plasma HIV-1 RNA
For participants with documented HIV-1 infection, a documented plasma HIV-1 RNA level must be noted within 28 days prior to Step 1 study entry from any laboratory that has a CLIA certification or its equivalent **(US sites) or VQA certification (non-US sites)**. On-study HIV-1 RNA is only required for HIV-1-infected participants and should be performed at the ACTG central laboratory. See the A5380 LPC for processing, shipping, and storage information.

The eighth subsection has been revised to read:

HCV RAS testing
Using stored samples for HIV-1/HCV studies above, resistance genotype near-time sequencing will be carried out for NS3 and NS5A genes on participants experiencing confirmed virologic failure or recurrence. Sequencing will be performed on baseline and post-treatment recurrence samples with HCV RNA >1,000 IU/mL. **RAS testing related to the virologic failure visit described in section 6.2.4 can be done locally.**

14. Section 6.3.21 (Virtual Visits during the COVID-19 Pandemic)

The following section has been added to allow for virtual visits in the scope of COVID-19:

6.3.21 Virtual Visits during the COVID-19 Pandemic

Virtual visits by telephone or video conference will be permitted for Step 1 and Step 2, in the scope of COVID-19, if the participant is unable/prefers not to come to the site for an in-person visit due to COVID-19. In this instance, it is permitted that safety labs can be completed at a local commercial lab. The other non-safety/research labs will be completed when the participant is able to come back to the site for an in-person visit. See section 6.3.8.

NOTE A: For participants on RBV, virtual visits for Step 2 should also be paired with a brief in-person lab visit for blood sample collection and for women of child bearing potential, pregnancy testing.

NOTE B: For the Step 2 SVR12 visit (R+20, R+24, or R+28), the virtual visit

should also be paired with a brief in-person lab visit for blood sample collection.

These visits should be recorded as "virtual visit due to COVID-19."

15. Appendix I: Step 1 SAMPLE INFORMED CONSENT, PART 1 SUMMARY

The first bullet under the *Blood and urine collections* subsection of Required Activities has been revised as follows:

At most visits, some blood will be collected from a vein in your arm. At a few visits, ~~you will be asked to provide a urine sample.~~ **some of your urine will be collected, if you choose.**

16. APPENDIX I: STEP 1 SAMPLE INFORMED CONSENT, "WHAT DO I HAVE TO DO IF I AM IN STEP 1 OF THIS STUDY?"

The following have been added as the 1st and 2nd paragraphs:

Information Collected at Screening
There is some information that we collect on everyone who is screened for an ACTG study. As part of your screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count, viral load) information will be collected from you. We also collect information on whether you use (or have used) IV drugs.

We will collect this information even if you do not enroll in this study. This information is collected so that ACTG researchers may determine whether there are patterns and/or common reasons why people do not join a study.

The following has been added as the 8th paragraph:

If the COVID-19 pandemic is still going on when you enroll into Part 1 of this study, you will be allowed to have some virtual visits (by telephone or video call), if you are unable to come to the site, or if you prefer not to come to the site for an in-person visit due to COVID-19. In this instance, you will be allowed to get your blood drawn for the safety evaluations at a lab outside of the site. The other non-safety/research labs will be completed when you are able to come back to the site for an in-person visit. Site staff will discuss the details of this option with you.

17. APPENDIX I: STEP 1 SAMPLE INFORMED CONSENT, Appendix I Table 1: Part 1 Study Schedule

The following revisions have been made to the Blood Collection & Laboratory Testing row at Entry, and the Urine Sample for Substance/Drug Use Test row:

Evaluation or Test	Screening	Entry	Post-Entry Visits			Unplanned Visits	HCV Virologic Failure Confirmation	HIV Virologic Failure (Breakthrough) Confirmation	Early Discontinuation
			Weeks 1 and 2	Week 4	Weeks 8, 12, 14, 16, 28				
Blood Collection & Laboratory Testing	✓	✓ **(see note in 4th bullet of Part 1 Entry subsection)**	✓	✓	✓	✓	✓	✓	✓
Optional Urine Sample for Substance/Drug Use Test		✓	✓	✓	✓	✓	✓		✓

18. APPENDIX I: STEP 1 SAMPLE INFORMED CONSENT, Description of Part 1 Study Visits

The 3rd and 4th bullets in the Part 1 Entry subsection of APPENDIX I: STEP 1 SAMPLE INFORMED CONSENT, Description of Part 1 Study Visits, has been revised to read:

- You ~~will~~ **may** provide a urine sample to look for the use of drugs.
- You will have blood drawn for routine lab tests for safety, virologic, immunologic (to test how your body fights infection), and pharmacokinetic studies (to look at your body's response to the study medication). If you are living with HIV, blood will be drawn to measure the amount of HIV in your blood, and to measure your CD4+ and CD8+ cell counts. Some of the blood you provide will be stored for future protocol-required testing. **There are some safety blood tests that will not need to be done again at entry if they were done within the last 7 days (as part of a recent doctor's visit).**

The 5th bullet in the During Most Study Visits for Part 1 subsection of APPENDIX I: STEP 1 SAMPLE INFORMED CONSENT, Description of Part 1 Study Visits, has been revised to read:

You ~~will~~ **may** provide a urine sample to look for the use of drugs.

The beginning of the HCV Virologic Failure Confirmation subsection of APPENDIX I: STEP 1 SAMPLE INFORMED CONSENT, Description of Part 1 Study Visits, has been revised to read:

HCV Virologic Failure Confirmation
If laboratory tests show there is evidence of virologic failure (the amount of HCV in your blood is still detectable when tested), you will be asked to return to the clinic **within 2 weeks** to confirm your lab results.

The third bullet of the HCV Virologic Failure Confirmation subsection of APPENDIX I: STEP 1 SAMPLE INFORMED CONSENT, Description of Part 1 Study Visits, has been revised to read:

A urine sample ~~will~~ **may** be taken for the substance use screen.

19. APPENDIX I: STEP 1 SAMPLE INFORMED CONSENT, Description of Part 1 Study Evaluations

    The following has been added to the Consent subsection of APPENDIX I: STEP 1 SAMPLE INFORMED CONSENT, Description of Part 1 Study Evaluations:

    Consent
    Remote consent (via email/video call) will be allowed if you are unable to come to the site due to the COVID-19 pandemic [*Note to sites- if allowed by IRB.*]. After you read this consent form and have had a chance to ask questions about the study, you will sign this consent form if you want to continue to be tested to see if you qualify for the study.

    The following has been added to the Sample collections and laboratory testing subsection of APPENDIX I: STEP 1 SAMPLE INFORMED CONSENT, Description of Part 1 Study Evaluations, under *Urine Sample for Substance/Drug Use:*

    Urine Sample for Substance/Drug Use
    Urine sample for substance use screening ~~will~~ **may** be done at study entry, and at every Part 1 study visit, HCV virologic failure confirmation, and early discontinuation visits.

20. APPENDIX I: STEP 1 SAMPLE INFORMED CONSENT, "CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?"

    The following revisions have been made to this whole section:

    Some of your blood will be stored and used for study-required pharmacologic, immunologic, and virologic testing.

    Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

    The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.

    Please refer to APPENDIX III to consent for use of your samples in other studies.

    ~~For non-US locations, biological specimens will be shipped and/or stored outside of the country from which they are collected.~~

    ~~Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.~~

    ~~The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.~~

Some blood that is collected from you during the study may be left over after all required study testing is done. This blood will be stored and, if you give your consent below, may be used for ACTG-approved research. This means that researchers who are not part of the protocol team may use your samples without asking you again for your consent. As noted above, none of your samples will have any private information about you on their labels.

You may decide whether this "extra" blood may be stored and, if so, whether additional testing may be performed on it. None of this testing will be used for commercial profit.

At this time, we do not know whether any of the research will include testing of your genes or your DNA (your own genetic information). We do not know whether a type of testing called whole genome sequencing, or WGS, might be done. In WGS, researchers look at all of your genes and at almost all of your DNA. In "standard" genetic testing, researchers look at specific genes or subsets of genes, but not at all genes. Some possible genetic testing is described below.

For each of the questions below, choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selections.

Research Without Human Genetic Testing – OPTIONAL (Research on leftover blood; no human genetic testing)

If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my blood.

OR

____ (initials) I understand but I do not agree to this storage or possible use of my blood.

Research With Human Genetic Testing – OPTIONAL (Human genetic research on leftover blood)

If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that includes human genetic testing, and may include whole genome sequencing (WGS).

____ (initials) I understand and I agree to this storage and possible use of my blood.

OR

____ (initials) I understand but I do not agree to this storage or possible use of my blood.

~~Sharing Genetic Data - OPTIONAL~~

~~Genetic Research Databases: If you agreed to possible genetic testing of your blood above, researchers may want to share genetic information (with protection of your identity) with other researchers around the world, so that they can learn more about the causes and treatment of diseases. They may store this information in dbGaP, a genetic database maintained by the National Institutes of Health, as well as in other protected databases.~~

~~____ (initials) I understand and I agree to this possible sharing of my genetic data.~~

~~*OR*~~

~~____ (initials) I understand but I do not agree to this possible sharing of my genetic data.~~

21. APPENDIX II: STEP 2 SAMPLE INFORMED CONSENT, "WHAT DO I HAVE TO DO IF I AM IN STEP 2 OF THIS STUDY?"

    The following has been added as the 7th paragraph:

    If the COVID-19 pandemic is still going on when you enter into Part 2 of this study, you will be allowed to have some virtual visits (by telephone or video call), if you are unable to come to the site, or if you prefer to not to come to the site for an in-person visit due to COVID-19. In this instance, you will be allowed to get your blood drawn for the safety evaluations at a lab outside of the site. The other non-safety/research labs will be completed when you are able to come back to the site for an in-person visit. Site staff will discuss the details of this option with you.

22. APPENDIX II: STEP 2 SAMPLE INFORMED CONSENT, Description of Part 2 Study Visits

    The following has been added as the last bullet in the <u>During Most Study Visits for Part 2</u> subsection of APPENDIX II: STEP 2 SAMPLE INFORMED CONSENT, Description of Part 2 Study Visits has been revised to read:

    If you are also taking RBV as a part of your retreatment for HCV, virtual visits for Step 2 will be paired with a short in-person visit to have a blood sample collected for safety tests. If you are a woman and able to get pregnant, some of your blood or urine will be tested for pregnancy.

    The <u>HCV Virologic Failure Confirmation</u> subsection of APPENDIX I, SAMPLE INFORMED CONSENT, Description of Part 2 Study Visits, has been revised to read:

    <u>HCV Virologic Failure Confirmation</u>
    If laboratory tests show there is evidence of virologic failure (the amount of HCV in your blood is still detectable when tested), you will be asked to return to the clinic **within 2 weeks** to confirm your lab results.

23. APPENDIX II: STEP 2 SAMPLE INFORMED CONSENT, Description of Part 2 Study Evaluations

    The following new subsection has been added as the first subsection to APPENDIX II, SAMPLE INFORMED CONSENT, Description of Part 2 Study Evaluations:

Consent

Remote consent (via email/video call) will be allowed if you are unable to come to the site due to the COVID-19 pandemic [*Note to sites- if allowed by IRB.*]. After you read this consent form and have had a chance to ask questions about the study, you will sign this consent form if you want to continue to be tested to see if you qualify for Step 2 of the study.

24. APPENDIX II: STEP 2 SAMPLE INFORMED CONSENT, "CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?"

The following revisions have been made to this whole section:

Some of your blood will be stored and used for study-required pharmacologic, immunologic, and virologic testing.

~~For non-US locations, biological specimens will be shipped and/or stored outside of the country from which they are collected.~~

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.

Please refer to APPENDIX III to consent for use of your samples in other studies.

~~Some blood that is collected from you during the study may be left over after all required study testing is done. This blood will be stored and, if you give your consent below, may be used for ACTG-approved research. This means that researchers who are not part of the protocol team may use your samples without asking you again for your consent. As noted above, none of your samples will have any private information about you on their labels.~~

~~You may decide whether this "extra" blood may be stored and, if so, whether additional testing may be performed on it. None of this testing will be used for commercial profit.~~

~~At this time, we do not know whether any of the research will include testing of your genes or your DNA (your own genetic information). We do not know whether a type of testing called whole genome sequencing, or WGS, might be done. In WGS, researchers look at all of your genes and at almost all of your DNA. In "standard" genetic testing, researchers look at specific genes or subsets of genes, but not at all genes. Some possible genetic testing is described below.~~

~~For each of the questions below, choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selections.~~

~~Research Without Human Genetic Testing – OPTIONAL (Research on leftover blood; no human genetic testing)~~

~~If you agree, some of your blood that is left over after all required study testing is done may~~

~~be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that does not include human genetic testing.~~

~~____ (initials) I understand and I agree to this storage and possible use of my blood.~~

~~*OR*~~

~~____ (initials) I understand but I do not agree to this storage or possible use of my blood.~~

~~Research With Human Genetic Testing – OPTIONAL (Human genetic research on leftover blood)~~

~~If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that includes human genetic testing, and may include whole genome sequencing (WGS).~~

~~____ (initials) I understand and I agree to this storage and possible use of my blood.~~

~~*OR*~~

~~____ (initials) I understand but I do not agree to this storage or possible use of my blood.~~

~~Sharing Genetic Data - OPTIONAL~~

~~Genetic Research Databases: If you agreed to possible genetic testing of your blood above, researchers may want to share genetic information (with protection of your identity) with other researchers around the world, so that they can learn more about the causes and treatment of diseases. They may store this information in dbGaP, a genetic database maintained by the National Institutes of Health, as well as in other protected databases.~~

~~____ (initials) I understand and I agree to this possible sharing of my genetic data.~~

~~*OR*~~

~~____ (initials) I understand but I do not agree to this possible sharing of my genetic data.~~

25. APPENDIX III: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES

A new appendix has been added for the consent to use samples in other ACTG studies.

APPENDIX III: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES

When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called "extra samples." The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will know that the samples or information came from you.

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the ACTG repository located in the United States.

There is no limit on how long your extra samples will be stored. [Site: Revise the previous sentence to insert limits if your regulatory authority imposes them.]

When a researcher wants to use your samples and information, their research plan must be approved by the ACTG. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. [Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.] IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher's location. This means that researchers who are not part of the protocol team may use your samples without asking you again for your consent.

You will not be paid for your samples. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you.

You may withdraw your consent for research on your extra samples at any time, and the specimens will be discarded.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selection.

<u>Research without Human Genetic Testing</u>
If you agree, your extra samples may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that does not include human genetic testing.

<u>Step 1:</u>

____ (initials) I understand and I agree to this storage and possible use of my samples

OR

____ (initials) I understand but I do not agree to this storage and possible use of my samples

Step 2, *if applicable:*

____ (initials) I understand and I agree to this storage and possible use of my samples

OR
____ (initials) I understand but I do not agree to this storage and possible use of my samples

Research with Human Genetic Testing
Your extra samples will not be used for human genetic testing unless you sign a consent form for A5128 or A5243.

The ACTG has two different studies that collect samples for genetic testing.

If you live in the US, this study is called ACTG A5128, Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.

If you live outside of the US, this study is called ACTG A5243, Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.

Your site might ask you if you would like to participate in one of these studies if it is being done where you live. If you would like to participate, you will sign a separate consent form.

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

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 #2 for:

A5380

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

A Multicenter Trial of Advancing Clinical Therapeutics Globally (ACTG)

NIAID CRMS # 38553

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

LETTER OF AMENDMENT

DATE: August 14, 2020

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

FROM: A5380 Protocol Team

SUBJECT: Letter of Amendment #2 for Protocol A5380

The following information affects the A5380 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 site 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 on Step 2 registration, in follow-up to the COVID-19-related Clarification Memo #2 (CM #2), dated 04/20/20, as US and non-US sites begin to open to research visits in the presence of the ongoing COVID-19 pandemic. However, enrollment into the study (i.e., Step 1 entry) will remain paused until a Study Monitoring Review occurs on 08/17/20, per the protocol, for the first 10 participants who were enrolled prior to the temporary closure in March 2020 due to the COVID-19 pandemic. Follow-up for these 10 enrolled participants remains ongoing with modifications to allow for a mix of virtual and in-person visits.

At this time, any of the 10 participants who are currently in Step 1 of the study, and who qualify for Step 2, may now register to Step 2. The Data Management Center will open the Step 2 registration screens upon release of this LOA. Sites should follow Final Protocol Version 1.0, and subsequent CMs #1 and #2, and LOA #1 for the Step 2 registration procedures.

For sites who have any of the 10 participants on Step 1, in-person visits are permitted at this time for these participants if the site is able to conduct in-person visits. The COVID-related CM #2, dated 04/20/20, was written in a way to allow flexibility for remote visits with the only stipulation being that the week 16/SVR12 visit occur in person.

Additional guidance is forthcoming from the team to allow for further flexibility in light of uncertainties in regards to the COVID-19 pandemic.

The following is a change to A5380, Version 1.0, 06/07/19, titled "A Phase II Trial of Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection (PURGE-C)." This change will be included in the next version of the A5380 protocol if it is amended at a future date.

1. Step 2 registration may proceed.

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

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

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 #2 for:

A5380

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

A Multicenter Trial of Advancing Clinical Therapeutics Globally (ACTG)

NIAID CRMS # 38553

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 20, 2020

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

FROM: A5380 Protocol Team

SUBJECT: Clarification Memo #2 for Protocol A5380- Impact of 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 local institutional review board (IRB) approval prior to implementing this CM.

DAIDS does not require you to forward this CM to your IRB; however, you must follow your IRB's policies and procedures. If IRB review of CMs 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 following are clarifications (noted in bold or strikethrough) to Protocol A5380, Version 1.0, 06/07/19, titled "A Phase II Trial of Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection (PURGE-C)," in response to the COVID-19 pandemic.

As of March 18, 2020, 10 participants have enrolled into the study and all subsequent

enrollment has been put on hold during the ongoing COVID-19 pandemic. Therefore, this CM is only pertinent for these 10 participants, and is follow up to the memo sent to sites on March 18, 2020.

1. Section 6.2.3 (Post-Entry Evaluations): This section has been revised to read:

   All post-entry evaluations occur in reference to the start of study therapy.

   All Step 1 study visits for the 10 participants enrolled on or before March 18, 2020 can occur remotely (via telephone), except for the Step 1 week 16/SVR12 visit, which must remain an in-person visit, if this visit can be conducted safely.

   The safety of participants and study staff must be taken into account when scheduling this visit and any remote contact prior to this visit, with the consideration of delaying visits if needed. If there is a need to limit in-person interactions at the site, the in-person component can be restricted to the blood draw, and the remaining visit evaluations can be completed via telephone.

   If the blood draw at this visit is limited, then prioritize sample use as follows:
   - **local testing for safety**
   - **HCV RNA**
   - **HIV-1 RNA**
   - **CD4+ (for participants living with HIV-1 infection)**
   - **storage**

   Until further notice, store samples for central testing (e.g., HCV RNA and HIV-1 RNA) in accordance with the guidance distributed by the ACTG Lab Center on 3/17/2020.

   On-Treatment Evaluations
   Study visits must be scheduled on the weeks indicated in Tables 6.1-1 and 6.1-2, within the visit windows described below, as appropriate for the visit.

   NOTE: Step 2 entry may be deferred until further notice.

   Step 1 (**remote, via telephone**):
   - Weeks 1 and 2 have a window of ±3 days.
   - Week 4 has a window of -7 days and +14 days.

   Step 2 (**deferred until further notice**):
   - Week R+2 has a window of ±3 days.
   - Weeks R+4, R+8, R+12, and R+16 have a window of -7 days and +14 days.

   Treatment Completion Evaluations
   Clinical assessment and laboratory evaluation, as outlined in section 6.1, will be performed at treatment completion (Step 1: week 4, Step 2: week R+8, R+12, or R+16).

   NOTE: Step 2 entry may be deferred until further notice.

   Post-Treatment Evaluations

Following treatment completion, participants will undergo evaluations as outlined in Tables 6.1-1 and 6.1-2, within the study windows, as indicated below.

NOTE: Step 2 entry may be deferred until further notice.

After the last dose of study drugs, the post-treatment study visits have the following windows:

Step 1 (**remote, via telephone, EXCEPT week 16**):
- Study weeks 8 **and** 12~~, and 16~~: -5 days and +21 days
- **Study week 16: -14 days and +42 days**
- Study week 28: -7 days and +28 days

NOTE: In the midst of the COVID-19 pandemic, for study week 28, all evaluations should be conducted remotely, and the week 28 specimen can be collected at a future date, prior to study closure, up until 36 weeks post treatment completion, as long as the week 16/SVR12 visit was conducted in-person. Participants should only have the week 28 visit in person if the week 16/SVR12 visit and sample were missed.

If a participant has successfully attended the week 16/SVR12 visit and the blood sample has been collected, then that participant does not need to have an in-person visit at week 28.

Step 2 (**deferred until further notice**):
- Study week R+20, R+24, or R+28 (12 weeks after re-treatment completion for those not receiving RBV depends on Step 2 treatment duration): -5 days and +28 days
- Study week R+32, R+36, or R+40 completion (for those receiving RBV): -14 days and + 28 days

2. Section 6.3.10 (Virologic Studies): The second subsection has been revised to read:

Plasma HCV RNA (real-time, on-study evaluations)
At the entry and post-entry visits, HCV RNA quantification will be performed as follows:

Plasma HCV RNA real-time testing will be collected, processed, and shipped to the designated testing laboratory (see A5380 LPC for directions). These results will be reported within 2 weeks after specimen receipt for both Steps 1 and 2.

NOTE A: For Step 1, HCV RNA should only be done at the week 16/SVR12 visit for the 10 participants enrolled on or before March 18, 2020.

NOTE **B**: For Step 2, an increase in plasma HCV RNA at any time point meeting HCV virologic response-based treatment stopping criteria must be confirmed with repeat testing within 2 weeks of receipt of results. For more information please see section 6.2.4.

Letter of Amendment #1 for:

A5380

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

A Multicenter Trial of Advancing Clinical Therapeutics Globally (ACTG)

NIAID CRMS # 38553

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

DATE: December 18, 2019

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

FROM: A5380 Protocol Team

SUBJECT: Letter of Amendment #1 for Protocol A5380 (Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection [PURGE-C])

The following information affects the A5380 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 affect 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

file.

This LOA is being implemented for the following reasons:

- A team decision has been made to clarify the meaning of active, serious infection prior to study entry. In response, the following sections have been updated: 4.2.7 and 4.4.5.
- A team decision has been made to create separate rows for “Less than 30 mL/min” and “Hemodialysis” creatinine clearance categories for RBV dose. In response, the following table has been updated: 5.1.1-2.
- A team decision has been made to clarify the requirements for fentanyl testing. In response, the following section has been updated: 6.3.8.

The following are changes (noted in bold or strikethrough) to A5380, Version 1.0, 06/07/19, titled "Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection (PURGE-C)." These changes will be included in the next version of the A5380 protocol if it is amended at a future date. Changes that have already been made (either by Letter of Amendment or by Clarification Memo) have been incorporated in the excerpted text shown below (and are no longer presented in bold or strikethrough).

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

2. Section 4.2 (Step 1 Exclusion Criteria), exclusion criterion 4.2.7: This exclusion criterion has been revised to read:

   Active, serious infection (other than HIV-1 or HCV) ~~-~~requiring parenteral antibiotics, antivirals, or antifungals**)** ~~within 30 days prior to~~ **at the time of** study entry.

   NOTE: Entry may occur when the infection is considered inactive, defined by:
   - **Minimum duration of antibiotic, antiviral, or antifungal treatment of 72 hours, AND**
   - **Improved and stable clinical status as determined by a site investigator.**

3. Section 4.4 (Step 2 Exclusion Criteria), exclusion criterion 4.4.5: This exclusion criterion has been revised to read:

   Active, serious infection (other than HIV-1 or HCV) ~~-~~requiring parenteral antibiotics, antivirals, or antifungals**)** ~~within 28 days prior to study~~ **at the time of** Step 2 entry.

   NOTE: Entry may occur when the infection is considered inactive, defined by:
   - **Minimum duration of antibiotic, antiviral, or antifungal treatment of 72 hours, AND**
   - **Improved and stable clinical status as determined by a site investigator.**

4. Table 5.1.1-2 (Renal Dosing for RBV): The “less than 30 mL/min” and “hemodialysis” creatinine clearance categories have been separated for clarity as shown below:

Table 5.1.1-2: Renal Dosing for RBV

Creatinine Clearance	RBV Dose
30-50 mL/min	Alternating doses, 200 mg (1 tablet) ~~daily alternating with~~ **and** 400 mg (2 tablets) **every other day** ~~daily~~
Less than 30 mL/min ~~and Hemodialysis~~	200 mg (1 tablet) daily
Hemodialysis	**200 mg (1 tablet) daily**

5. Section 6.3.8 (Laboratory Evaluations): The first paragraph within the Urine Sample for Substance Use Screen subsection has been revised to read:

   Urine Sample for Substance Use Screen
   Urine substance use screening must be done using a CLIA-waived urine drug use screening tool with these common drugs of abuse: amphetamines, buprenorphine, benzodiazepines, cocaine, ecstasy, methadone, methamphetamine, barbiturates, marijuana, opiates, oxycodone, ~~fentanyl,~~ and phencyclidine. The screening will be assessed by urine test and must include the following ancillary testing, pH and creatinine to help in confirmation of sample against adulterants. The following results would be used as confirmation of an unadulterated human urine sample; pH of 4.5 – 8.0 and urine creatinine ≥20 mg/dL. **Urine fentanyl testing will be done using a test which is not currently FDA approved or CLIA-waived.**

Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection (PURGE-C)

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 #1 for:

A5380

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

A Multicenter Trial of Advancing Clinical Therapeutics Globally (ACTG)

NIAID CRMS # 38553

ACTG NETWORK COORDINATING CENTER
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CLARIFICATION MEMO

DATE: October 15, 2019

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

FROM: A5380 Protocol Team

SUBJECT: Clarification Memo #1 for Protocol A5380

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 A5380, Version 1.0, 06/07/19, titled "A Phase II Trial of Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection (PURGE-C)." These clarifications will be included in the next version of the A5380 protocol if it is amended at a future date.

1. Section 4.1.5 (Inclusion Criteria [Step 1]): The laboratory requirements have been revised to read:

   HCV genotype obtained within 24 weeks prior to entry by any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, or at any network-approved non-US laboratory that **is Virology Quality Assurance (VQA) certified.** ~~operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.~~

2. Section 4.1.7 (Inclusion Criteria [Step 1]): The laboratory requirements have been revised to read:

   For HIV-1 co-infected participants on ART, screening HIV-1 RNA must be <50 copies/mL or <LLOQ of local assay if LLOQ is >50 copies/mL **obtained** within 28 days prior to **study** entry ~~as measured~~ 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 GCLP and participates in appropriate external quality assurance programs~~.

3. Section 4.1.8b (Inclusion Criteria [Step 1]): The laboratory requirements have been revised to read:

   For HIV-1 co-infected participants, HIV-1 ART should meet one of the following criteria:

   a) ART untreated due to (1) lack of indication per provider (CD4+ T-cell count ≥500 cells/mm^3) or (2) decision by provider and participant to defer ART during the G/P dosing period (4 weeks).

   OR

   b) On a stable, protocol-defined compatible ART regimen (per sections 2.2 [Rationale for Inclusion of Concomitant ART Regimens] and 5.4.1) for >2 weeks prior to starting G/P with a CD4+ T-cell count >100 cells/mm^3 **obtained** within 180 days prior to the screening visit~~. Laboratory testing can be done by~~ **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 GCLP and participates in appropriate external quality assurance programs.~~

4. Section 6.2.4 (Event-Driven Evaluations- HIV-1 Virologic Breakthrough): The third paragraph in the <u>HIV-1 Virologic Breakthrough</u> subsection has been revised to read:

   The increase in plasma HIV-1 RNA should be confirmed with repeat central ~~or local~~ testing as soon as possible (not to exceed 4 weeks); see HIV-1 Virologic Breakthrough Confirmation in Tables 6.1-1 and 6.1-2. For participants with confirmed HIV-1 viral breakthrough (≥200 copies/mL), a plasma specimen should be sent for HIV genotyping and sent to the designated A5380 VSL for evidence of HIV-1 drug resistance. Results will be reported back to sites in real-time from the designated A5380 VSL. See section 6.3.10, Stored Serum and Plasma for HIV-1/HCV Studies.

5. Section 6.3 (Instructions for Evaluations): The following paragraph has been added as the first paragraph of this section.

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

6. Section 6.3.8 (Laboratory Evaluations): The last paragraph has been revised to read:

   HCV Ab HCV Ab must be obtained by any FDA-approved test at any local laboratory that has a CLIA certification or its equivalent **(US sites) or VQA certification (non-US sites)**. HCV Ab is only to be sent at screening and at a subsequent visit if the result is negative on the preceding visit. Once a single positive Ab is recorded, no further HCV antibody testing is required.

7. Section 6.3.9 (Immunologic Studies): The CD4+/CD8+ requirement at screening have been revised to read:

   CD4+/CD8+ (For participants with HIV-1 infection only)
   Screening ~~Obtain~~ absolute CD4+/CD8+ count and percentages **must be performed** within 28 days prior to **study** entry ~~from~~ **at** a laboratory that possesses a CLIA certification or equivalent (US sites) or IQA certification (non-US sites).

8. Section 6.3.10 (Virologic Studies): The laboratory requirements in the first paragraphs of the Plasma HCV RNA (screening), Plasma HCV Genotype, and Plasma HIV-1 RNA subsections have been revised to read:

   Plasma HCV RNA (screening)
   The screening HCV RNA result must be obtained by any FDA-approved test for quantifying HCV RNA at any local laboratory that has a CLIA certification or its equivalent **(US sites) or VQA certification (non-US sites)**. Screening HCV RNA must be obtained within 28 days prior to study entry.

   Plasma HCV Genotype
   At Step 1 screening, the HCV genotype result will be obtained locally (real-time) from any laboratory that has a CLIA certification or its equivalent **(US sites) or VQA certification (non-US sites)**. ONLY IF IT IS NOT AVAILABLE LOCALLY should it be done (real-time) at the designated testing laboratory (see A5380 LPC).

   Plasma HIV-1 RNA
   For participants with documented HIV-1 infection, a documented plasma HIV-1 RNA level must be noted within 28 days prior to Step 1 study entry from any laboratory that has a CLIA certification or its equivalent **(US sites) or VQA certification (non-US sites)**. On-study HIV-1 RNA is only required for HIV-1-infected participants and should be performed at the ACTG central laboratory. See the A5380 LPC for processing, shipping, and storage information.

A5380

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

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

Sponsored by:

National Institute of Allergy and Infectious Diseases

Industry Support Provided by:

AbbVie

IND #

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FINAL Version 1.0
June 07, 2019

ACTG
AIDS CLINICAL TRIALS GROUP

A5380

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

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

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SITES PARTICIPATING IN THE STUDY

A5380 is a multicenter study open to all US clinical research sites (CRSs) and limited to select non-US CRSs. The non-US sites that are eligible for participation in the study can be found on the A5380 protocol-specific web page (PSWP).

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STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5380@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5380@fstrf.org. A response should generally be received within 24 hours (Monday through Friday).

Protocol E-mail 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.protA5380 e-mail group. Include the protocol number in the e-mail subject line.

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

Clinical Management:
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the Clinical Management committee (CMC).

- Send an e-mail message to actg.cmcA5380@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 e-mail message to actg.teamA5380@fstrf.org (ATTENTION: Georg Lauer – immunologist; Raymond Chung - virologist; Jennifer Kiser - pharmacologist).

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. Completion guidelines for eCRFs 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 Apsara Nair (nair@fstrf.org) directly.
- For other questions, send an e-mail message to actg.teamA5380@fstrf.org (ATTENTION: Apsara Nair).
- Include the protocol number, PID, and a detailed question.

DMC Portal and Medidata Rave Problems
Contact DMC User Support.

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

Protocol Document Questions
For questions concerning the protocol document, contact the Clinical Trials Specialist.

- Send an e-mail message to actg.teamA5380@fstrf.org (ATTENTION: Chanelle Houston).

Copies of the Protocol
To request a hard copy of the protocol, send an e-mail message to ACTGNCC@s-3.com. Electronic copies can be downloaded from the ACTG website at 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 e-mail message to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation
For questions related to protocol activation at US sites, contact the clinical trials specialist.
- Send an e-mail message to actg.teamA5380@fstrf.org (ATTENTION: Chanelle Houston, CHouston@s-3.com)

For questions related to protocol activation at non-US sites contact the ACTG Site Coordination Group.
- Send an email message to actgsitecoordination@s-3.com

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call Cynthia Parker and Katherine Shin, Protocol Pharmacists, at 301-496-8213.

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 protocol-specific web page (PSWP) within 30 days of the submission to the Food and Drug Administration (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.

Telephone Calls
Sites are responsible for documenting telephone calls made to A5380 team members.
- Send an e-mail message to actg.teamA5380@fstrf.org.

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

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
ARV(s)	antiretroviral(s)
ART	antiretroviral therapy
CLIA	Clinical Laboratory Improvement Amendments
CMC	Clinical Management Committee
CSA	colony stimulating agents
DAA	direct-acting antiviral
DBS	dried blood spot
DOT	directly observed therapy
E/CIA	enzyme or chemiluminescence immunoassay
FACS	fluorescence-activated cell sorting
FDC	fixed dose combination
FSH	follicle stimulating hormone-release factor
GCLP	Good Clinical Laboratory Practices
G/P	glecaprevir/pibrentasvir
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HLA	human leukocyte antigen
HVR1	hypervariable region 1
IFN	interferon
IEG	interferon effector gene
ISG	interferon-stimulated gene
IgM	immunoglobulin M
INR	international normalized ratio
LDV/SOF	ledipasvir/sofosbuvir
LFT	liver function test
LLOQ	lower limit of quantification
mITT	modified intention to treat
MOPS	Manual of Procedures

MSM	men who have sex with men
pegIFN	pegylated interferon
PTT	partial thromboplastin time
PI	Principal Investigator
PPI	proton-pump inhibitor
PSWP	protocol specific web page
PT	prothrombin time
PWID	people who inject drugs
PYFU	person-years of follow-up
QOL	quality of life
RASs	resistance-associated substitutions
RBV	ribavirin
RTV	ritonavir
SNP	single nucleotide polymorphism
SOF	sofosbuvir
SVR	sustained virologic response
TD	target detected
TND	target not detected
ULN	upper limit of the normal range
WB	weight-based

SCHEMA

A5380

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

DESIGN

This is a phase II single-arm, open-label study to assess the efficacy of a fixed dose combination (FDC) of glecaprevir/pibrentasvir (G/P) given for 4 weeks in acute hepatitis C (HCV)-infected participants, with and without HIV-1 coinfection.

The study has two steps:

Step 1: Four weeks of treatment for acute HCV infection and up to 24 weeks of follow-up. Post-treatment follow-up visits in Step 1 will occur at 4, 8, 12, and 24 weeks after the end of study treatment (G/P). Participants with HCV recurrence (reinfection, suspected relapse or undefined post-treatment viremia) or HCV virologic failure before or at the week 16/SVR12 (sustained virologic response 12 weeks post-treatment) visit during Step 1 will be eligible for re-treatment (Step 2).

Step 2: Re-treatment will be with G/P with or without ribavirin (RBV) for up to 16 weeks. Post-treatment follow-up for Step 2 will include visits for SVR12 determination.

DURATION

Up to 28 weeks in Step 1: 4 weeks on treatment and 24 weeks of post-treatment follow-up.

Up to 40 weeks in Step 2: up to 16 weeks of re-treatment and up to 24 weeks of post-treatment follow-up.

SAMPLE SIZE

Minimum of 44 participants, including at least 10 participants living with HIV-1 co-infection. If a participant discontinues early for reasons unrelated to study treatment and is not evaluable for SVR12 while registration is ongoing, then an additional participant may be enrolled as determined by the study team to attain an adequate number for key supporting analysis on SVR12. Additional enrollment may occur more than once, up to maximum enrollment of 50 participants.

POPULATION

Men and women age $\geq$18 years with acute HCV-infection (may be first HCV infection or re-infection) of any genotype, living with or without HIV-1 co-infection.

REGIMEN

Participants will receive a FDC of G/P administered orally once daily for 4 weeks. A subset of participants who have HCV recurrence (reinfection, suspected relapse, or undefined post-treatment viremia) or HCV virologic failure after receipt of G/P for 4 weeks will receive re-treatment with FDC of G/P administered orally once daily with or without weight-based RBV for up to 16 weeks.

NOTE: Alterations in the re-treatment regimen for suspected relapses and virologic failures are permitted based on local standard of care at the discretion of the site Principal Investigator (PI) upon discussion with A5380 Clinical Management Committee (CMC; actg.cmcA5380@fstrf.org). Acceptable alternate regimens are found in section 5.1.1 and in the A5380 Manual of Procedures (MOPS).

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

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

1.2 Primary Objectives

1.2.1 To evaluate acute HCV treatment response to G/P given for 4 weeks as assessed by sustained virologic response 12 weeks post-treatment (SVR12, defined as HCV RNA <lower limit of quantification [LLOQ], either target detected [TD] or target not detected [TND]).

1.2.2 To evaluate the safety and tolerability of combination oral antiviral therapy with G/P given for 4 weeks in persons with acute HCV-infection, regardless of genotype and HIV status.

1.3 Secondary Objectives

1.3.1 To evaluate the antiviral efficacy of G/P given for 4 weeks for the treatment of acute HCV infection, as measured by the proportion of participants with HCV RNA <LLOQ (TD or TND) at study weeks 1, 2, 4, 8 (SVR4), 12 (SVR8), and 28 (SVR24).

1.3.2 To evaluate evidence of virologic failure, defined as failure to achieve HCV RNA <LLOQ (TD or TND at end of treatment) and confirmed increase in HCV RNA >1 $\log_{10}$ from on-treatment nadir.

1.3.3 To evaluate the antiviral efficacy of G/P given for 4 weeks by HIV status.

1.4 Exploratory Objectives

1.4.1 To estimate incidence of relapse, defined as HCV RNA <LLOQ (TD or TND) at end of treatment or during follow-up and confirmed HCV RNA >LLOQ during follow-up with phylogenetics excluding a new HCV viral infection.

1.4.2 To estimate incidence of re-infection, defined as HCV RNA <LLOQ (TD or TND) at end of treatment or during follow-up and confirmed HCV RNA >LLOQ during follow-up with phylogenetics consistent with a new HCV viral infection.

1.4.3 To assess the emergence of viral resistance to glecaprevir and/or pibrentasvir in participants with relapse or virologic failure, when 4 weeks of G/P is administered for acute HCV infection.

1.4.4 To evaluate re-treatment strategies for study participants with post-treatment viremia.

1.4.5 To characterize active substance use in the study population.

1.4.6 To assess the pharmacokinetic-dynamic associations for G/P.

1.4.7 To evaluate potential drug interactions between common drugs of abuse, antiretrovirals (ARVs), and G/P.

1.4.8 To evaluate participants' adherence by using several tools, including self-report, pill count, and drug concentrations.

1.4.9 To evaluate novel serologic and virologic biomarkers of acute immunologic host response in early HCV infection.

1.4.10 To evaluate whether successful direct-acting antiviral (DAA)-based therapy during acute HCV infection induces more profound T-cell recovery than treatment during chronic infection and alleviates type I interferon (IFN)-induced immune dysfunction during acute HCV infection.

1.4.11 To evaluate the long-term clinical impact and cost-effectiveness of 4 weeks of G/P treatment for acute HCV infection compared with the standard of care, that is, wait for 6 months and treat only those who develop chronic HCV infection (referred to as "treat chronic HCV" strategy).

2.0 INTRODUCTION

2.1 Background

Rationale for identifying and treating of acute HCV

Hepatitis C virus infection affects more than 4 million persons and causes at least 20,000 deaths annually in the United States, exceeding the mortality burden due to HIV [1, 2]. Recently, incidence of acute HCV has been rising [3], with the Centers for Disease Control and Prevention (CDC) estimating that there are about 30,000 new cases of acute HCV per year, with a range of 24,200-104,200 cases [4]. The two groups at highest risk for acute HCV infection are people who inject drugs (PWID) and HIV positive men who have sex with men (MSM). For a variety of reasons, only a fraction of persons with acute HCV are reported to public health authorities [5]. Those with recent infection, if unaware of their status, are at high-risk for transmission to others. Early identification of acute HCV infection is essential to provide preventive counseling and, if necessary, curative treatment to clear virus and prevent onward transmission. Models suggest that clearance of HCV among high-risk individuals may reduce overall prevalence and incidence, despite risks for re-infection [6].

During the era of IFN-based treatments, early identification and treatment of HCV during the acute phase has resulted in significantly higher response rates with less intensive and shorter durations of therapy, in both HCV mono-infected and HIV/HCV co-infected individuals [7-10]. A meta-analysis of IFN-treated HCV mono-infected individuals with acute HCV infection (N=602) reported an overall sustained virologic response rate (SVR) of 78%, significantly higher than those individuals not receiving any therapy (55%, OR=3.08; 95% CI 1.8-4.8) [9]. A majority of individuals were treated with pegylated interferon (pegIFN) mono-therapy with an average duration of therapy of 19.7 weeks. The above meta-analysis also reported that those individuals initiated on treatment within the first 12 weeks of diagnosis had the highest SVR rates [9]. The first approved protease inhibitors, boceprevir and telaprevir, were also used for the treatment of acute HCV in combination with pegIFN and ribavirin (RBV); these also suggested that the duration of overall therapy could be shortened to as low as 12 weeks with enhanced efficacy compared to those receiving treatment in the chronic phase [11,12]. Moreover, a randomized controlled trial of immediate versus delayed treatment found improved SVR rates in the immediate treatment group, in part due to lack of follow-up for those assigned to the delayed arm [13]. In sum, these studies suggested that the timing of IFN-based therapy matters in determining efficacy and improving follow-up when utilizing shortened IFN-based treatment courses.

For the DAA era, current guidance provided at http://hcvguidelines.org recommends that treatment for acute HCV in many cases can be delayed for at least 12 weeks [12]. This recommendation is based on (1) the extraordinarily low frequency of fulmination during acute HCV infection; (2) the possibility of spontaneous clearance which is maximal in that timeframe, especially if female or jaundiced [14, 15]; and (3) the availability of safe and effective antiviral treatments in the chronic phase of infection. This strategy avoids overtreatment, especially for those who would have spontaneously cleared. However, the guidance also states that benefits of early treatment may outweigh the cost-savings of waiting for HCV clearance, especially for those at highest risk for onwards transmission. As HCV is increasing in incidence in the United States, a “test and treat” approach similar to many communicable diseases may be appropriate to combat this epidemic. Recent data from the Netherlands, where large scale roll out of DAA therapy has been achieved, have shown a dramatic decrease in incident HCV infections among HIV positive MSM [16, 17].

However, it is equally important to note the high incidence of re-infection of HCV among individuals with elevated risk for acquisition. A meta-analysis showed that for HCV monoinfected "high-risk" participants (n = 771), the pooled recurrence rate was 22.32/1000 person-years of follow-up (PYFU), leading to a summary 5-year risk of 10.67%. For the 4 studies of HIV/HCV coinfected participants, the pooled recurrence rate was 32.02/1000 PYFU leading to a summary 5-year risk of 15.02% [18]. These individuals are monitored routinely for re-infection and will be an optimal population where shorter duration of treatment could play a key role in reducing costs. Additionally, curing these infections earlier (as these individuals are more likely to engage in high-risk behaviors) will help further the HCV elimination agenda.

As chronic HCV infection is associated with dysregulation of innate and adaptive immune responses, earlier treatment may also prevent dysregulation that may interfere with protective immunity for future infections [19-22].

Antiviral treatment in the acute phase with regimens of shorter duration than those used in the chronic phase with similar SVR rates may mitigate concerns regarding costs associated with overtreatment, with potential societal cost saving due to both shorter duration of treatment and reduced risk of transmission [23]. As in the IFN-era, shorter duration regimens are also compelling for patient acceptability and adherence.

Thus far, clinical trials using novel DAAs to cure acute HCV have produced mixed results. Initial attempts at using sofosbuvir (SOF) plus RBV for genotype 1 infection with much abbreviated duration compared to courses used in the chronic phase have resulted in suboptimal SVR rates. The DARE-C II trial treated 19 participants with 6 weeks of SOF plus RBV and only achieved 32% SVR [24]. ACTG A5327 titled, "Sofosbuvir-Containing Regimens without Interferon for Treatment of Acute HCV in HIV-1 Infected Individuals (SWIFT-C)," Cohort 1 included 17 participants treated with 12 weeks of SOF plus RBV and only achieved 59% SVR [25]. A smaller study suggested a higher SVR rate with this regimen [26]. The more potent regimen of ledipasvir/sofosbuvir (LDV/SOF) has been applied for 6-8 weeks for acute HCV with genotypes 1 or 4. For HIV positive MSM, 6 weeks of LDV/SOF achieved more robust cure rates for 22 out of 26 individuals (85% SVR); of note, the four relapses all had high HCV RNA levels >9,000,000 IU/mL at the time of treatment initiation [27]. More encouragingly, a recent trial in 20 HIV negative individuals with symptomatic acute HCV showed a 100% SVR rate with 6 weeks of LDV/SOF; HCV RNA at time of initiation was lower than the above trials [28]. The ACTG A5327 SWIFT-C Cohort 2 achieved SVR in all 27 participants with 8 weeks of LDV/SOF [26]. Other DAA regimens are also currently being studied including 8 weeks of elbasvir/grazoprevir (EBR/GZR), although like LDV/SOF, will be limited to genotypes 1 and 4. In sum, these data suggest that more potent regimens may achieve acceptable cure rates, with shorter durations compared to the 8-12 weeks necessary to cure chronic infection. As shown in Table 2.1-1, studies of DAAs during acute HCV have tended to focus on persons with HIV and those infected with either genotypes 1 or 4 infection.

Table 2.1-1: Clinical Trials of Acute HCV with DAAs, IFN-sparing [24-29]

Study	Location/N	HIV included?	GT	Design/ Regimen	Status	SVR
DARE-C II	Australia N=19	Both mono and co	All	SOF/RBV x 6 weeks	Completed	32% (6/19)
NYAHCSN-1	NYC N=12	All HIV	1	SOF/RBV x 12 weeks	Completed	92% (11/12)
SWIFT-C Group 1	US (ACTG) N-17	All HIV	All	SOF/RBV x 12 weeks	Completed	59% (10/17)
SOL	Europe, multi-center	All HIV	1,4	LDV/SOF x 6 weeks	Completed	85% (22/26)

Study	Location/N	HIV included?	GT	Design/ Regimen	Status	SVR
	N=26					
HepNet Acute HCV IV	Europe, multi-center N=20	No	1	LDV/SOF x 6 weeks	Completed	100% (20/20)
SWIFT-C Group 2 [29]	US (ACTG) N=27	All HIV	1,4	LDV/SOF x 8 weeks	Completed	100% (27/27)
NYAHCSN-2 [30]	US (NYC) N=25	All HIV	1,4	LDV/SOF x 8 weeks	Completed	100% (25/25)
Target 3D [31]	Europe, Australia N=30	Both mono and co	1	PrOD + RBV x 8 weeks	Completed	96% (29/30)
DAHHS-2 [32]	Netherlands Belgium N=80	All HIV	1,4	EBR/GZR x 8 weeks	Active, not recruiting	98% (62/63)*
SAHIV	France N=50	All HIV	1,4	EBV/GZR x 8 weeks	Recruiting	
REACT	Europe, North America, Australia N=250	Both mono and co	All	RCT SOF/VEL 6 vs 12 weeks	Recruiting	

*Boerekamps et al. [32] presented interim results from 63 of 80 enrolled participants.
LDV/SOF = ledipasvir/sofosbuvir, PrOD = paritaprevir/ritonavir/ombitasvir + dasabuvir, EBR/GZR = elbasvir/grazoprevir, SOF/VEL = sofosbuvir/velpatasvir

Efficacy and safety of glecaprevir/pibrentasvir

Glecaprevir (GLE), an NS3/4A protease inhibitor, and pibrentasvir (PIB), an NS5A inhibitor were approved together as a pangenotypic FDC for the treatment of chronic HCV infection in August 2017. Administered as three 100 mg/40 mg FDC pills, clinical trials have shown proven efficacy and is recommended for all major 6 genotypes. Eight weeks is recommended for most individuals without cirrhosis, whereas a longer course of 12 weeks is recommended for those with cirrhosis. Treatment extension to 12-16 weeks is also recommended for those with previous exposure to either HCV protease or NS5A inhibitors (but not recommended for dual class failures). Neither GLE nor PIB are significantly metabolized nor eliminated by the kidneys, allowing use in chronic kidney disease, including patients on dialysis. The safety profile of G/P is favorable, with an overall proportion of participants receiving 8-16 weeks in clinical trials permanently discontinuing treatment due to adverse reactions of 0.1%. The most common adverse reactions including all grades in greater or equal to 5% of participants were headache (13%), fatigue (11%), and nausea (8%), with 80% of all adverse reactions classified as mild in severity. [Mavyret USPI; AbbVie Inc., North Chicago, IL; August 2018]

For HIV-1/HCV co-infected individuals, the safety and efficacy of glecaprevir and pibrentasvir were evaluated in the phase III, multicenter EXPEDITION-2 study [33]. This study evaluated 8 weeks of the daily FDC of glecaprevir (G) 300 mg/pibrentasvir (P) 120 mg administered as three 100 mg/40 mg FDC pills in 137 HIV/HCV-co-infected

participants without cirrhosis and 12 weeks of G/P in 16 HIV/HCV-co-infected participants with compensated cirrhosis. Treatment-naïve and treatment-experienced participants with genotype 1, 2, 3, 4, or 6 infection were enrolled. Participants were either antiretroviral (ARV)-naïve with a CD4 cell count ≥500/mm^3, or on a stable antiretroviral therapy (ART) regimen for at least 8 weeks with a CD4 cell count ≥200/mm^3. Overall SVR12 was 100% (136/136) among those without cirrhosis on the 8-week regimen, and 93% (14/15) in those with compensated cirrhosis on the 12-week regimen. Four serious adverse events (AEs) were reported, none of which were DAA-related. One of these led to treatment discontinuation (cerebral hemorrhage) [31].

2.2 Rationale

The combination regimen of G/P is an ideal candidate for the treatment of acute infection. This regimen has broad efficacy across HCV genotypes, is dosed once daily, avoids RBV, and is associated with minimal side effects. Together, these medications have an extremely high barrier to development of resistance and are potent against NS3 and NS5 resistance-associated substitutions (RASs). In contrast to other DAA regimens studied in acute HCV infection, 8 weeks of therapy with G/P is highly effective across a wide variety of populations with chronic HCV infection and specifically addresses genotype 3, which represents a significant proportion of new cases in the U.S. In phase III trials of participants without cirrhosis, the 8-week regimen had high SVR rates, ~95-100%, for all genotypes and regardless of baseline HCV RNA level [34, 35]. In addition, the pharmacokinetics (PK) of this nucleotide-sparing regimen result in rapid steady state exposure in the liver tissue, providing biologic plausibility for the potential to shorten length of therapy in acute HCV. The efficacy and appropriate duration of G/P in the acute phase is unknown but we hypothesize that SVR rates with a shorter duration of the highly potent G/P regimen for 4 weeks may supersede 90% based on the above reported studies.

The study is designed to conclude with reasonable evidence that the true SVR12 proportion is greater than 80% in the study population. The 80% SVR threshold was chosen as an adjusted average rate from three studies that similarly used half of the treatment regimen recommended at that time for chronic HCV: LDV/SOF x 6 weeks [25] and two studies examining SOF/RBV x 12 weeks [25, 26].

Based on the success of the LDV/SOF arm of the two-arm study A5327, which examined shortened courses of SOF-based regimens, we propose a phase II trial of G/P FDC treatment for acute HCV infection (PURGE-C), an open-label study in which participants receive 4 weeks of G/P FDC.

<u>Rationale for Inclusion of HIV Negative Participants and Minimum Number of HIV-1 Positive Participants</u>

Unlike A5327, those uninfected with HIV-1 will be included in this trial. As the majority of those with HIV and acute HCV are men, this broader inclusion criteria would be expected to enhance enrollment of women and those with injection drug use as a

primary risk factor. However, given the mission and emphasis of the ACTG, a minimum of 10 participants with HIV-1 will be enrolled. There is no maximum limit to the enrollment of HIV-1-infected participants.

Rationale for Inclusion of Concomitant ART Regimens

Formal drug-drug interaction studies in HIV/HCV seronegative individuals have been performed with G/P and the following antiretroviral agents:

- abacavir/lamivudine/dolutegravir
- atazanavir/ritonavir
- darunavir/ritonavir
- lopinavir/ritonavir
- raltegravir
- rilpivirine
- tenofovir alafenamide/emtricitabine/elvitegravir/cobicistat
- tenofovir disoproxil fumarate/emtricitabine/efavirenz

No clinically significant interactions were observed with abacavir, lamivudine, dolutegravir, raltegravir, rilpivirine, tenofovir alafenamide, tenofovir disoproxil fumarate or emtricitabine. Interactions were observed and/or are expected with atazanavir, efavirenz, and etravirine and ritonavir and cobicistat-based regimens [Mavyret USPI]. A description of the potential for clinically significant interactions follows.

Co-administration of efavirenz with G/P did not affect efavirenz levels but glecaprevir and pibrentasvir exposures were significantly lower compared to historical data. Etravirine has similar potential for drug interactions and while not formally studied to date, is not recommended for coadministration with G/P. In contrast, coadministration with rilpivirine resulted in similar glecaprevir and pibrentasvir levels to controls and while rilpivirine levels were increased (Cmax by 105%, AUC by 84%), no safety issues were identified [36, 37].

Ritonavir-boosted protease inhibitors increase glecaprevir exposures. When G/P was co-administered with atazanavir and ritonavir, glecaprevir Cmax and AUC were increased 4-fold and 6.5-fold, respectively and asymptomatic (Grades 1 and 2) ALT elevations were observed. When G/P was co-administered with darunavir and ritonavir, glecaprevir Cmax and AUC were increased to 3.1 and 5.0-fold, respectively compared to controls, but no ALT elevations were observed [Mavyret USPI]. Given this study will enroll non-cirrhotic individuals and the duration of co-administration is limited to 4 weeks, we will allow participants on ritonavir-boosted darunavir. LFTs will be monitored at Weeks 1 and 2 of G/P therapy. Ritonavir-boosted atazanavir will not be allowed.

The pharmacologic booster cobicistat when administered as part of a combination (tenofovir alafenamide, emtricitabine, cobicistat, elvitegravir) resulted in increases of Cmax and AUC for both glecaprevir (150 to 205%) and pibrentasvir (24-57%), while elvitegravir and cobicistat levels were increased by 29-47%. No attributable AEs were reported [38]. Cobicistat-boosted darunavir will be allowed.

The EXPEDITION-2 trial included HIV/HCV co-infected participants on abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, rilpivirine, tenofovir alafenamide, and tenofovir disoproxil fumarate. One patient received elvitegravir/cobicistat [33].

To summarize, drug-drug interaction studies and trial data support the concomitant use of raltegravir, dolutegravir, rilpivirine, tenofovir disoproxil fumarate, tenofovir alafenamide, abacavir, emtricitabine, and lamivudine. Bictegravir is expected to have similar properties as dolutegravir and will be allowed. Cobicistat with elvitegravir, cobicistat with darunavir and ritonavir-boosted darunavir will be allowed as the exposure of G/P is only 4 weeks and participants are non-cirrhotic.

Neither glecaprevir nor pibrentasvir have any activity against HIV-1 in vitro; their use in participants infected with HIV-1 who meet criteria for being off therapy is therefore considered safe from a virologic standpoint.

Rationale for Retreatment Approaches
This study will re-treat participants with viral recurrence or virologic failure.

Viral relapse rates are very low after 8-16 weeks of G/P treatment in NS5A-inhibitor naïve populations with chronic infection (0-1%). However, for the small percentage of individuals that do experience viral relapse, RASs in NS3 and/or NS5A are present in the majority (89%) [39]. Given that the use of ultra-short duration of treatment for acute HCV infection could be associated with increased viral relapse rates and there are no data to inform the risk of RAS selection with 4 weeks of G/P treatment, a retreatment strategy within the study is desirable. When G/P alone was assessed as a retreatment strategy for individuals who had failed prior DAA-containing therapy with multiple drug class exposure, the presence of concurrent NS3 and NS5A RASs adversely impacted outcomes. In part 1 of the MAGELLAN-1 study, a small number of participants with prior DAA treatment were retreated with G/P plus RBV (n=22) or G/P alone (n=22) for 12 weeks [40]. The modified intention to treat (mITT) SVR12 was the same in both groups, 95%. In the subset with prior exposure to both NS3 and NS5A inhibitors, 5/6 (83%) and 8/9 (89%) treated with 12 weeks plus RBV and 12 weeks without RBV, respectively achieved SVR12. In part 2 of the MAGELLAN-1 study, SVR12 was 100% for those without RASs or only NS3 RASs, 89% NS5A RASs and 56% for those with both NS3 and NS5A RASs [39]. The duration of G/P retreatment (12 vs 16 weeks) had no clear impact on responses in those with dual class (NS3 and NS5A) exposure with 79% (CI: 52-92%) treated for 12 weeks (n=14) achieving SVR and 81% (CI: 57-93%) in those treated for 16 weeks. While supporting the potential impact of RASs on retreatment with G/P after DAA failure, none of the participants in this study had prior exposure to G/P limiting the applicability to the current study and retreatment approaches. However, in the Magellan 3 study retreatment of 23 prior GT1, 2, and 3 G/P treatment failures with 16 weeks of G/P plus SOF plus RBV was highly efficacious with an SVR rate of 96% (22/23) [41].

In the DAA era, re-treatment with longer durations using the same agent(s) has been attempted with success. For instance, 9 HIV-1/HCV co-infected individuals experienced relapse after 12 weeks of LDV/SOF and 8 of 9 achieved sustained virologic response

with 24 weeks of LDV/SOF plus RBV [42]. In an HCV-mono-infected cohort, participants failing 8 weeks of sofosbuvir/velpatasvir/voxilaprevir were retreated with 12 weeks of the same regimen with 100% (17/17) SVR12 [43]. In addition preliminary data suggest that Sof/Vel/Vox may be also be a suitable retreatment regimen for G/P treatment failures with 13/14 G/P treatment failures achieving SVR12 following 12 weeks of Sof/Vel/Vox retreatment [44].

In sum, the limited data remain inconclusive on the benefits of adding RBV or extending duration when using G/P to retreat individuals previously exposed to both NS3 and NS5A DAAs. Extrapolation of data from other re-treatment studies does suggest some benefit of treatment extension and/or the addition of RBV. Given the ultra-short duration of treatment in the current study and that participants are not yet in the chronic phase and will not have cirrhosis, 16 weeks of G/P plus RBV could be an effective treatment strategy for recurrence and virologic failures. However, acknowledging the more robust data on the use of SOF-based triple DAA regimens for re-treatment of DAA failures, site investigators will have discretion to use a SOF-based triple DAA treatment regimen for re-treatment of participants. SOF-based treatments will not be provided by this study and may require insurance approval.

For viral recurrence that is clearly re-infection (defined by new genotype/subtype), the participant will receive the standard regimen used for chronic HCV (8 weeks of G/P) during Step 2. In such circumstances, despite diagnosis of a new acute re-infection, the participant may not be “re-enrolled” into Step 1.

Rationale for IL28-B and Human Leukocyte Antigen (HLA) Testing

IL28-B is a gene polymorphism associated with natural clearance of HCV infection and of innate IFN stimulation. IL28-B polymorphism and HLA typing determination will be important for interpretation of immunologic studies. IL28-B genotyping is also important in acute HCV infection studies to characterize the study population’s innate potential for natural clearance.

Rationale for Rapid Treatment of Acute HCV

Guidelines have suggested a waiting period to assess for spontaneous clearance before treatment of acute HCV. Reported rates of spontaneous clearance of HCV among HIV-1-infected individuals are highly variable due to small sample sizes and significant variance across study populations. On average it is reported that 5-15% of HIV-1 infected individuals acutely infected with HCV will spontaneously clear the infection [38, 45-49]. Multiple baseline factors have been reported as predictive of clearance including female sex, host genetic factors including the IL28-B favorable genotype, and early favorable HCV-RNA kinetics [14, 50, 51]. There are studies assessing viral kinetics in the early infection period and report ranges from 6%-48% of participants having detectable HCV RNA 12 weeks after first clinical evidence of infection and go on to spontaneously clear the infection [52-54]. Indeed on rare occasions participants have been reported to spontaneously clear the infection after 12-13 months or even longer [41, 55]. Many of these are very small, single center studies; however, the bulk of studies suggest that the majority of participants with acute HCV infection will develop chronic infection. Recent data from Europe indicate that the minimal rate of spontaneous

clearance among HIV positive MSM was only 11.9%; as the majority of the remainder received relatively early antiviral treatment, the true rate of clearance may be somewhat higher [55, 56]. Ultimately, if antivirals are offered for acute HCV it is a minority (6-10%) of participants who may receive treatment unnecessarily. Moreover, these data must be balanced with the evidence that suggests a delay in initiation of therapy for acute HCV decreases the chance of achieving a SVR. A meta-analysis of early treatment in 417 HCV mono-infected participants reported that those participants who delayed therapy >12 weeks) from diagnosis had lower SVR (67%) than those treated at or within 12 weeks of diagnosis (83%) [9]. Delayed therapy was also associated with decreased SVR in a large pooled cohort of injection drug users [57]. In ACTG A5327 Cohort 1, those with a “less active” immunologic profile had a lower rate of SVR. Preliminary data also indicate that earlier treatment may preserve multi-specific HCV-specific T-cell responses, which are thought to be critical to the ability to prevent HCV viral persistence [Lauer et al., unpublished data]. Especially for those with HIV, where spontaneous clearance rates are as low as 11.9%, a “test and treat” strategy similar to other infectious diseases is justified, especially if the cost-saving strategy of shortened DAA courses is validated [23].

2.3 Overall Risk/Benefit Assessment

No clinical safety issues specifically related to G/P have been identified to date in HCV mono-infected or HIV-1/HCV co-infected participants without cirrhosis or with compensated cirrhosis.

The expected benefits to participants being treated with G/P is a rapid and durable eradication of HCV virus and a shortened treatment period. Potential risks include unforeseen safety issues and unknown implications of virologic failure due to the emergence of resistant virus.

For the population of HIV-1/HCV co-infected participants, the potential benefit of achieving SVR with 4 weeks of an IFN-free regimen outweighs the risks associated with the possible development of previously unidentified safety issues or the emergence of quasi-species resistant to glecaprevir or pibrentasvir [58]. Furthermore, the benefits of limiting the potential for onward transmission carries significant societal benefit and cost savings. For participants who experience recurrence or virologic failure after 4 weeks of treatment, a re-treatment regimen will be offered, minimizing risk of participating in this study.

If high rates of SVR can be obtained with a shortened, IFN-free regimen, without frequent emergence of resistant HCV, the anticipated improvements in safety and tolerability would offer a favorable risk-benefit determination for individuals with acute HCV infection.

Other risks of the study are outlined below including risks associated with blood draws, risks of study drugs, risks of changing ART or other medications in order to qualify for the study, and the small risk of HBV reactivation.

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

Risks of Study Drugs
The drugs used in this study may have side effects, such as headaches, fatigue, diarrhea, nausea, asthenia, pruritic skin, and abnormal liver function tests. There is a risk of serious and/or life-threatening side effects when certain non-study medications are taken with the study drugs.

Drug interactions may increase the chances of side effects, may affect the levels of ARVs or other medications and/or cause changes in liver enzymes and other abnormal blood tests. Certain HIV medications may be changed to reduce this risk. For certain HMG-CoA reductase inhibitors (statins), others may require dose adjustment or careful monitoring. For digoxin, the dose should be reduced and closely monitored while on G/P. Drug interactions that lower the levels of glecaprevir or pibrentasvir may decrease the participant's chances for a cure of hepatitis C and/or select for drug resistance. Certain drugs known to cause lower levels of glecaprevir or pibrentasvir will be avoided.

Some people with HCV and HBV coinfection receiving DAA therapy for HCV, have experienced reactivation of HBV. Some of these cases have led to severe hepatitis, liver failure and death. This has been reported mostly in individuals who are positive for HBsAg and extremely rarely in those who appear to have resolved HBV infection by lab tests. Those with HBsAg will be excluded, while those with resolved HBV infection will be monitored.

Ribavirin may be used in Step 2 for those with detection of viremia after 4 weeks of glecaprevir/pibrentasvir in Step 1. The most common AE of RBV therapy is anemia due to hemolysis. Anemia typically occurs within 1 to 2 weeks of initiating RBV therapy and usually resolves within 4 to 8 weeks of drug discontinuation or dose reduction. Indirect bilirubin elevation is commonly seen in those participants with anemia secondary to RBV-induced hemolysis.

Another major side effect of RBV is its teratogenicity. It is therefore strongly recommended that pregnant women or breastfeeding women and men with pregnant sexual partners not receive RBV. Women who become pregnant on study and men on study whose partners become pregnant must discontinue study treatment and complete the discontinuation evaluations as indicated in section 8.2.

Risks of Delaying HIV Therapy
While participants with HIV are not required to be on ARVs to enter the study and, although the HCV treatment period is 4 weeks for Step 1, a delay in necessary HIV medications could allow for progression of HIV disease, which can increase the risk of opportunistic infections and long-term after effects for participants living with HIV.

2.4 Adherence Measures

The efficacy of G/P for the treatment of acute HCV may be influenced by participants' adherence to the study medications. There is no perfect measure of adherence, but tools include pill counts, pharmacy refill records, self-report, directly observed therapy (DOT), measurement of drug concentrations, and electronic monitoring (video DOT). This study will use some of these measures (see section 6.3.14).

2.5 Cost-effectiveness Analysis

The cost of treating chronic HCV infection has been a major concern since the beginning of the DAA era. While treatments have been extremely successful, this has come at major cost to the health care system [23]. The potential for treating acute infection with a 4-week course has the potential to not only improve outcomes, but also to provide cost savings or extremely good value for the resources spent. A questionnaire on self-report resource use and quality of life (QOL) will be used to assess the number of outpatient visits, hospital days (if any), and quality of life associated with G/P treatment, and a microsimulation model [23] for assessment of the cost-effectiveness of the strategy (see section 6.3.16).

Using the microsimulation model, the life expectancy, quality-adjusted life years, total costs, and reduction in HCV transmission for the following two strategies: (1) 4-week G/P treatment of acute HCV; and (2) wait for 6 months and treat only those who develop chronic HCV infection (referred to as "treat chronic HCV" strategy) will be estimated. In both strategies, simulated patients that get re-infected may get re-treatment. The incremental cost-effectiveness ratio of "treat acute HCV" compared to "treat chronic HCV" strategy will be estimated. The above outcomes separate for HCV/HIV co-infected patients and HCV mono-infected patients will be presented. A one-way and probabilistic sensitivity analysis to assess the robustness of cost-effectiveness results will also be conducted.

3.0 STUDY DESIGN

A5380 is a phase II single-arm, open-label study to assess the efficacy of FDC G/P in acute HCV-infected participants, with and without HIV-1 coinfection, given for 4 weeks. This study will assess whether G/P confers successful treatment, superior to a cure rate of 80%. The study will entail 2 steps: Step 1—treatment of acute infection with 4 weeks of G/P, and Step 2—re-treatment of participants experiencing post-treatment viremia in Step 1 with 8-16 weeks of G/P with or without RBV with modifications to the retreatment regimen allowed at the discretion of the site PI after discussion with the A5380 CMC.

Prospective participants will be enrolled in Step 1 if diagnosed with acute infection, defined below in section 4.1.3. Both HIV infected and HIV uninfected participants will be included, and participants with HIV who are taking protocol-defined compatible ARVs, as per discretion of the local provider. A minimum of 10 participants with HIV will be enrolled.

Step 1 post-treatment follow-up visits for all participants will occur at 4, 8, 12, and 24 weeks after the last dose of study drug (FDC G/P).

The primary outcome will be SVR12 (i.e., HCV RNA <LLOQ, either TD or TND, at 12 weeks after end of treatment).

Participants experiencing documented viral recurrence before or at the week 16 or SVR12 visit will proceed to Step 2 and be classified as either re-infection or suspected relapse, prior to re-treatment. The type of viral recurrence (suspected relapse versus re-infection) will be determined by the A5380 team chair, co-chairs, and virologist (actg.cmcA5380@fstrf.org) based initially on genotype/subtype information and resistance testing and then reported to the sites by email to inform them of the recommended re-treatment regimen for Step 2. If a re-infection, they will be re-treated with 8 weeks of FDC G/P. If a suspected relapse, they will be re-treated with a treatment regimen of 16 weeks of FDC G/P with or without weight-based RBV, irrespective of genotype. Participants experiencing virologic failure (failure to achieve HCV RNA <LLOQ and confirmed increase in HCV RNA >1 $\log_{10}$ from nadir) will also proceed to Step 2 and will be re-treated with 16 weeks of FDC G/P with or without weight-based RBV. Participants experiencing post-treatment HCV viremia not otherwise defined as re-infection, suspected relapse or virologic failure will also proceed to Step 2 and will be re-treated with 16 weeks of FDC G/P with or without weight-based RBV. At the discretion of the site PI and upon discussion with the A5380 CMC (actg.cmcA5380@fstrf.org), participants experiencing suspected relapse, virologic failure, or undefined post-treatment HCV viremia may be re-treated with an alternative, non-study provided regimen. Retreatment options are outlined in the Manual of Procedures (MOPS).

Participants who meet criteria for Step 2, but opt out of therapy will continue study visits on the Step 1 schedule.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Step 1 Inclusion Criteria

4.1.1 Ability and willingness of participant to provide written informed consent for Step 1.

4.1.2 Men and women age ≥18 years

4.1.3 A documented confirmation of acute HCV infection within 24 weeks prior to entry or HCV reinfection as described below:

Acute HCV infection will be defined as meeting one of the following criteria, depending on whether the participant was never previously infected or previously infected with clearance (treatment induced or natural) and after exclusion of other causes of acute hepatitis:

Never Previously Infected:
New (<24 weeks prior to Step 1 entry) ALT elevation to ≥5X upper limit of normal (ULN) OR >250 U/L in participants with documented normal ALT in the preceding 52 weeks or ≥10 x ULN OR >500 U/L in participants with abnormal or no measured ALT baseline in the 52 weeks prior to study entry with detectable HCV RNA.

OR

Detectable HCV RNA with prior negative anti-HCV antibody (Ab) within 24 weeks prior to study entry or prior undetectable HCV RNA within 24 weeks prior to study entry.

Previously Infected:
For those with evidence of previous infection (as evidenced by positive anti-HCV Ab), documentation of clearance of prior infection either spontaneously with two negative HCV RNA a minimum of 12 weeks apart or after treatment with negative HCV RNA a minimum of 12 weeks after last dose of anti-HCV treatment AND meeting one of the following criteria in addition to exclusion of other causes of acute HCV:

New (<24 weeks prior to Step 1 entry) ALT elevation to ≥5 x ULN OR >250 U/L in participants with documented normal ALT in the preceding 52 weeks or ≥10 x ULN OR >500 U/L in participants with abnormal or no measured ALT baseline in the preceding 52 weeks with detectable HCV RNA.

OR

Detectable HCV RNA with prior undetectable HCV RNA within 24 weeks prior to study entry.

4.1.4 Detectable HCV RNA at the screening visit.

4.1.5 HCV genotype obtained within 24 weeks prior to entry by any US laboratory that has a Clinical Laboratory Improvement Amendments (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.

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

For participants self-reporting as HIV-1 negative, HIV-1 infection testing should be performed at screening via rapid HIV-1 and/or enzyme or chemiluminescence immunoassay (E/CIA) test kit.

OR

HIV-1 infection, documented by any licensed rapid HIV-1 test or HIV-1 E/CIA test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV-1 and/or E/CIA, OR by HIV-1 p24 antigen, OR documented plasma HIV-1 RNA viral load >LLOQ at any time prior to study entry.

NOTE: The term "licensed" refers to a FDA-approved kit, which is required for all IND studies. 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 (World Health Organization) and CDC (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-1 co-infected participants on ART, screening HIV-1 RNA must be <50 copies/mL or <LLOQ of local assay if LLOQ is >50 copies/mL within 28 days prior to entry, as measured by any laboratory that has a CLIA certification or its equivalent or at any network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

NOTE: A single value ≥50 copies/mL but below 200 copies/mL at screening should be repeated within the screening window before screen-fail determination can be made; if repeat values are <50 copies/mL then the participant remains eligible.

4.1.8 For HIV-1 co-infected participants, HIV-1 ART should meet one of the following criteria:

a) ART untreated due to (1) lack of indication per provider (CD4+ T-cell count ≥500 cells/mm^3) or (2) decision by provider and participant to defer ART during the G/P dosing period (4 weeks).

OR

b) On a stable, protocol-defined compatible ART regimen (per sections 2.2 [Rationale for Inclusion of Concomitant ART Regimens] and 5.4.1) for >2 weeks prior to starting G/P with a CD4+ T-cell count >100 cells/mm^3 within 180 days prior to the screening visit. Laboratory testing can be done by any laboratory that has a CLIA certification or its equivalent or at any network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

4.1.9 The following laboratory values obtained within 28 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 GCLP and participates in appropriate external quality assurance programs.

- International normalized ratio (INR) <1.5
  NOTE: INR ≥1.5 x ULN is acceptable in participants with known hemophilia or stable on an anticoagulant regimen affecting INR, at the discretion of the site PI.
- Albumin ≥3.0 g/dL

4.1.10 Female participants of reproductive potential (defined as a person who has not been post-menopausal for at least 24 consecutive months, i.e., who has 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 US clinic or laboratory that has a CLIA certification or its equivalent, or is using a point-of-care (POC)/CLIA-waived test or at any network-approved non-US laboratory or clinic that operates in accordance with GCLP and participates in appropriate external quality assurance programs. The serum, urine, or POC pregnancy test must have a sensitivity of at least 25 mIU/mL.

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

4.1.12 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 contraception 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 spermicide
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormone-based contraceptive (not ethinyl-estradiol containing)
- 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 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.

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

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

- Physician report/letter/operative report or other source documentation in the medical 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

4.2 Step 1 Exclusion Criteria

4.2.1 Received investigational drug or device within 60 days prior to study entry.

4.2.2 Any preceding administration of HCV treatment during the current acute HCV infection episode.

4.2.3 Known preexisting cirrhosis, whether compensated or decompensated.

4.2.4 Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, α1 antitrypsin deficiency, primary sclerosing cholangitis).

4.2.5 Acute HIV-1 infection defined as the phase immediately following infection during which anti-HIV-1 antibodies are not detected and with detectable HIV-1 RNA.

NOTE: Participants with early HIV-1 infection, defined as within the first 6 months of infection and with a positive HIV-1 antibody, should be discussed with the A5380 CMC. These participants may be considered for inclusion in the study on a case-by-case basis with the specific documented approval of the protocol chairs.

4.2.6 Presence of active or acute AIDS-defining opportunistic infections within 30 days prior to study entry.

NOTE: A list of AIDS-defining opportunistic infections as defined by the CDC, can be found in Appendix B of the following document: http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm

4.2.7 Active, serious infection (other than HIV-1 or HCV) requiring parenteral antibiotics, antivirals, or antifungals within 30 days prior to study entry.

4.2.8 Infection with hepatitis B virus (HBV) defined as HBsAg or HBc IgM positive.

4.2.9 Evidence of current acute hepatitis A infection defined as hepatitis A virus (HAV) IgM positive.

4.2.10 Chronic use of systemically administered immunosuppressive agents (e.g., prednisone equivalent to >10 mg/day).

4.2.11 History of solid organ transplantation.

4.2.12 History of a gastrointestinal disorder (or post-operative condition) that could interfere with the absorption of the study drug as determined by the site PI.

4.2.13 History of significant or symptomatic pulmonary disease, cardiac disease, or porphyria as determined by the site PI.

4.2.14 History of clinically significant illness or any other major medical disorder that may interfere with participant treatment, assessment, or compliance with study requirements as determined by the site PI.

4.2.15 For non-antiretroviral medications, use of any prohibited concomitant medications within 28 days prior to study entry.

NOTE: Use of prohibited ARVs within 14 days prior to study entry is not allowed. See section 5.4.1.

4.2.16 Use of daily proton pump inhibitor (PPI) at doses ≥40 mg of omeprazole (or equivalent) within 5 days prior to study entry. See the A5380 protocol specific web page (PSWP) for information on equivalents to omeprazole.

NOTE: PPI can be discontinued or dose reduced to 20 mg/day of omeprazole (or equivalent) at least 5 days prior to study entry.

4.2.17 Known hypersensitivity to glecaprevir or pibrentasvir, the metabolites, or formulation excipients or any other contraindication to the use of G/P.

4.2.18 Pregnant or breastfeeding, including males with pregnant female partner.

4.3 Step 2 Inclusion Criteria

4.3.1 Ability and willingness of participant to provide written informed consent for Step 2.

4.3.2 Completion of Step 1 treatment regimen and meeting any of the below criteria, before or at the week 16 (SVR12) Step 1 visit:

Suspected relapse, defined as HCV RNA <LLOQ (TD or TND) at end of treatment (week 4) or during follow-up, and including confirmation of HCV RNA >LLOQ with the same genotype.

NOTE: Suspected relapse is documented by the email receipt of relapse determination by the designated A5380 team member.

OR

Re-infection, defined as HCV RNA <LLOQ (TD or TND) at end of treatment (week 4) or during follow-up, and including confirmation of HCV RNA >LLOQ with new genotype consistent with a new HCV viral infection.

NOTE: Re-infection is documented by the email receipt of re-infection determination by the designated A5380 team member.

OR

Virologic failure, defined as failure to achieve HCV RNA <LLOQ (TD or TND) and confirmed increase in HCV RNA >1 $\log_{10}$ from nadir.

OR

Post-treatment HCV viremia, defined as HCV RNA >LLOQ at any point after end of treatment (week 4) or during follow-up, not otherwise meeting definition of suspected relapse, re-infection, or virologic failure.

4.3.3 Detectable HCV RNA from the confirmatory sample (see section 6.2.4) collected within 56 days of Step 2 entry.

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

For participants self-reporting as HIV-1 negative, HIV-1 infection testing should be performed prior to Step 2 entry via rapid HIV-1 and/or E/CIA test kit.

OR

HIV-1 infection, documented by any licensed rapid HIV-1 test or HIV-1 E/CIA test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV-1 and/or E/CIA, OR by HIV-1 p24 antigen, OR documented plasma HIV-1 RNA viral load >LLOQ at any time prior to study entry.

NOTE: The term “licensed” refers to a FDA-approved kit, which is required for all IND studies. 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 (World Health Organization) and CDC (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.

4.3.5 The following laboratory values obtained within 56 days prior to Step 2 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 GCLP and participates in appropriate external quality assurance programs.

- INR <1.5
  NOTE: INR ≥1.5 is acceptable in participants with known hemophilia or stable on an anticoagulant regimen affecting INR at the discretion of the site PI.
- Albumin ≥3.0 g/dL
  NOTE: For INR and albumin values, values from the virologic failure/recurrence results in Step 1 can be used and there is no need to draw additional samples.
- For participants receiving RBV, hemoglobin ≥12 g/dL for male, ≥11 g/dL for female.

4.3.6 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 Step 2 entry by any laboratory or clinic that has a CLIA certificate or its equivalent, or is using a POC/CLIA-waived test or at any network-approved non-US laboratory or clinic that operates in accordance with GCLP and participates in appropriate external quality assurance programs. The serum, urine or POC pregnancy test must have a sensitivity of at least 25 mIU/mL.

4.3.7 All participants must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization).

NOTE: Female candidates who are pregnant or breastfeeding are not eligible for Step 2 of the study. A male candidate who has a pregnant female partner is also not eligible for Step 2.

4.3.8 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 contraception simultaneously while receiving protocol-specified medications, and for 6 weeks after stopping the medication. For participants on RBV two forms of birth control, for 6 months after stopping the medications. Such methods include:

- Condoms (either self or require their partner to use one) with spermicide
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Tubal ligation
- Hormone-based contraceptive (not ethinyl-estradiol containing)

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-1 acquisition. Study participants who are sexually active should be advised that they need to consider effective strategies for reducing the risk of HIV-1 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.

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

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

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

4.4 Step 2 Exclusion Criteria

4.4.1 Known preexisting cirrhosis, whether compensated or decompensated discovered since Step 1 entry.

4.4.2 Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, α1 antitrypsin deficiency, primary sclerosing cholangitis).

4.4.3 Acute HIV-1 infection defined as the phase immediately following infection during which anti-HIV-1 antibodies are not detected, and with detectable HIV-1 RNA after enrollment to Step 1.

NOTE: Participants with early HIV-1 infection, defined as within the first 6 months of infection and with a positive HIV-1 antibody, should be discussed with the A5380 CMC. These participants may be considered for participation in Step 2 on a case-by-case basis with the specific documented approval of the protocol chairs.

4.4.4 Presence of active or acute AIDS-defining opportunistic infections within 28 days prior to Step 2 entry.

NOTE: A list of AIDS-defining opportunistic infections as defined by the CDC, can be found in Appendix B of the following document: http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm

4.4.5 Active, serious infection (other than HIV-1 or HCV) requiring parenteral antibiotics, antivirals, or antifungals within 28 days prior to Step 2 entry.

4.4.6 Infection with HBV defined as HBsAg or HBc IgM positive discovered after enrollment to Step 1.

4.4.7 Evidence of acute hepatitis A infection defined as HAV IgM positive discovered after enrollment to Step 1.

4.4.8 Current use of systemically administered immunosuppressive agents (e.g., prednisone equivalent to >10 mg/day).

4.4.9 Diagnosis of a gastrointestinal disorder (or post-operative condition) that could interfere with the absorption of the study drug discovered after enrollment to Step 1, as determined by the site PI.

4.4.10 Significant or symptomatic pulmonary disease, cardiac disease, or porphyria after enrollment to Step 1, as determined by the site PI.

4.4.11 Identification of clinically significant illness or any other major medical disorder after enrollment to Step 1 that may interfere with participant treatment, assessment, or compliance with study requirements.

4.4.12 For non-antiretroviral medications, use of any prohibited concomitant medications within 28 days prior to Step 2 entry.

NOTE: Use of prohibited antiretrovirals within 14 days prior to Step 2 entry is not allowed. See section 5.4.1.

4.4.13 Use of daily PPI doses ≥40 mg of omeprazole (or equivalent) within 5 days prior to Step 2 entry. See the A5380 PSWP for information on equivalents to omeprazole.

NOTE: PPI can be discontinued or dose reduced to 20 mg/day of omeprazole (or equivalent) at least 5 days prior to Step 2 entry.

4.4.14 Discovery of hypersensitivity to glecaprevir or pibrentasvir, the metabolites, or formulation excipients, or any other contraindication to the use of G/P and alternative regimens after enrollment to Step 1.

4.4.15 Pregnant or breastfeeding, including males with pregnant female partner.

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 approvals for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO, and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification 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 Step 1 and Step 2, participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify. An ACTG Screening Checklist must be entered through the 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 completed and 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 A5380 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 A5380 protocol chairs.
- For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the A5380 CMC via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment for all participants in Step 1 of the study is glecaprevir/pibrentasvir.

For participants proceeding to Step 2, study-provided treatment refers to glecaprevir/pibrentasvir with or without RBV only.

NOTE: Participants experiencing HCV suspected relapse, virologic failure, or undefined post-treatment viremia may, at the discretion of the site PI and with approval of the A5380 CMC, be re-treated in Step 2 with a sofosbuvir (SOF)-based triple DAA regimen depending on local standard of care (see A5380 MOPS for additional options). These participants would continue follow-up per protocol based on the duration of their Step 2 treatment regimen.

Only glecaprevir/pibrentasvir and RBV (when administered with glecaprevir/pibrentasvir) will be provided by the study. All other required DAA drugs, chosen by the site PI based on local standards of care for Step 2, will not be provided by the study.

5.1 Regimens, Administration, and Duration

5.1.1 Regimens

Step 1 (4-week duration)
Upon entry, all eligible participants will receive glecaprevir 100 mg/pibrentasvir 40 mg FDC tablets to be taken as 3 tablets orally once daily with food for 4 weeks. The total daily dose administered is glecaprevir 300 mg/pibrentasvir 120 mg.

A prescription must be provided to the site pharmacist at participant entry that includes the Step number, PID, and study identification (SID).

Step 2 (8-16-week duration)
Any participant who experiences viral re-infection, suspected relapse, virologic failure, or undefined post-treatment HCV viremia will proceed to Step 2 for re-treatment. Based on both the classification of recurrence and the site PI preference, participants proceeding to Step 2 will be placed on one of the following re-treatment regimens:

Participants with viral re-infection will be re-treated with regimen 2A.

- Regimen 2A:
  Glecaprevir 100 mg/pibrentasvir 40 mg FDC tablet to be taken as 3 tablets orally once daily with food for 8 weeks.

For participants experiencing virologic relapse, virologic failure, or undefined post-treatment HCV viremia (not otherwise defined as re-infection, relapse, or virologic failure), re-treatment options are either regimen 2B or 2C.

- Regimen 2B:
  Glecaprevir 100 mg/pibrentasvir 40 mg FDC tablet to be taken as 3 tablets orally once daily with food, plus RBV 200 mg tablets taken orally twice daily with food. RBV is to be dosed per Table 5.1.1-1 (Weight-based RBV Dose) and Table 5.1.1-2 (Renal Dosing for RBV) with renal dosing superseding weight-based dosing as applicable. Treatment duration is 16 weeks.
- Regimen 2C:
  Glecaprevir 100 mg/pibrentasvir 40 mg FDC tablet to be taken as 3 tablets orally once daily with food for 16 weeks.

The site PI may choose to re-treat these participants with an alternative SOF-based triple DAA regimen in accordance with the local standard of care. The re-treatment regimen choice will be made by the site PI upon discussion with the A5380 CMC. All products for alternative regimens, except for glecaprevir/pibrentasvir, will need to be obtained locally by the site outside of the

study. An example that may use both study product and non-study product is defined in Regimen 2D. Additional possible DAA regimens to be considered for Step 2 can be found in the A5380 MOPS.

- Regimen 2D:
  Glecaprevir/pibrentasvir plus an appropriate third locally-sourced HCV DAA product for a minimum of 12 weeks, administered in accordance with manufacturer's package insert and per site clinician's discretion. The HCV DAA product selected by the site PI must be discussed with A5380 CMC prior to therapy initiation.

For study products provided through the study in regimens 2A-2D, a new prescription must be provided to the site pharmacist at Step 2 initiation that includes the Step number, PID, and SID. If participant is being prescribed RBV, the prescription must also include weight (kg) and CrCl.

Table 5.1.1-1: Weight-based RBV Dose

Weight (kg)	Morning Dose	Evening Dose
<75 kg	600 mg (3 tablets)	400 mg (2 tablets)
≥75 kg	600 mg (3 tablets)	600 mg (3 tablets)

The total RBV daily dose has been divided into two doses. The dose of RBV will be based on participant's weight at Step 2 entry or at confirmation visit. Changes in weight after Step 2 entry do not require a change in dose. Doses will only be changed for toxicity management.

For Step 2 participants with reduced CrCl, RBV can be dosed based on Table 5.1.1-2 below.

Table 5.1.1-2: Renal Dosing for RBV

Creatinine Clearance	RBV Dose
30-50 mL/min	Alternating doses, 200 mg (1 tablet) daily alternating with 400 mg (2 tablets) daily
Less than 30mL/min and Hemodialysis	200 mg (1 tablet) daily

5.1.2 Administration

Glecaprevir/pibrentasvir is to be administered as three (3) tablets taken orally once daily with food.

Glecaprevir/pibrentasvir should be taken on a regular dosing schedule. If a participant does not take a dose at the regular time, and it is less than 18 hours from the usual time the participant administers the dose, it should be taken as soon as they remember on the same day. Participant should then resume their

usual dosing schedule the next day. If it has been longer than 18 hours from the usual time the participant administers the dose, the missed dose should not be taken, and dosing should resume with the next scheduled dose taken at the participant's usual time.

Participants should not take more than 3 tablets of glecaprevir/pibrentasvir in a day.

RBV is to be taken orally as prescribed twice a day, approximately 12 hours apart, with food. If participants miss a dose of RBV, the missed dose should be taken as soon as possible with food during the same day. If an entire day has gone by, then the missed dose should be skipped, and the normal dosing schedule should be resumed.

Both glecaprevir/pibrentasvir and RBV tablets should not be cut, split, or, crushed.

Participants should not double the next dose of either study product to "make up" the missed dose.

NOTE: All study-required products obtained locally by the site will be administered in accordance with the manufacturer's package insert, per site clinician's discretion.

5.1.3 Duration

For Step 1, participants will take study treatment for a total of 4 weeks.

For participants proceeding to Step 2, treatment will be taken for 8 to 16 weeks based on the indication and the regimen for re-treatment.

5.2 Study Product Formulation and Preparation

5.2.1 Formulation

Glecaprevir 100 mg/pibrentasvir 40 mg (glecaprevir/pibrentasvir) is a film-coated, FDC tablet.

Ribavirin (RBV) 200 mg tablets are light pink to pink, capsule-shaped, film-coated tablets.

5.2.2 Storage

Glecaprevir 100 mg/pibrentasvir 40 mg tablets are to be stored at 15° to 25°C (59° to 77°F).

RBV tablets are to be stored at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep the bottle tightly closed.

5.3 Pharmacy: Study Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

Glecaprevir/pibrentasvir is manufactured and supplied by AbbVie.

Ribavirin (RBV) for the study is manufactured by Aurobindo and purchased with funding support from the ACTG Leadership and Operations Center (LOC).

Glecaprevir/pibrentasvir and RBV will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study drug(s) for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

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

The following medications are considered exclusionary if used within 28 days prior to entry into either Step 1 or Step 2:

- Aliskiren
- Allylisopropylacetylurea

- Amobarbital
- Atorvastatin
- Bosentan
- Carbamazepine
- Comfrey (herbal)
- Dabigatran
- Eltrombopag
- Eslicarbazepine
- Ethinyl estradiol
- Hyoscyamine
- Hyperforin
- Lovastatin
- Lumacaftor/Ivacaftor
- Monacolin K
- Oxcarbazepine
- Pentobarbital
- Phenobarbital
- Phenytoin
- Pimozide
- Primidone
- Rifabutin
- Rifampin
- Rifapentine
- Stress Granule Combination granules (acetaminophen, isopropylantipyrine, allylisopropylacetylurea, caffeine)
- Silodosin
- Simvastatin
- Spasfon (phloroglucinol)
- St John's wort
- Terfenadine
- Troleandomycin
- Vinblastine
- Vincristine

The following medications are considered exclusionary if used within 14 days prior to entry into either Step 1 or Step 2:

- Atazanavir, atazanavir/cobicistat, and atazanavir/ritonavir
- Efavirenz
- Etravirine
- Fosamprenavir/ritonavir
- Indinavir/ritonavir
- Lopinavir/ritonavir
- Nelfinavir
- Nevirapine

- Saquinavir/ritonavir
- Tipranavir/ritonavir

The following medications are considered exclusionary if used within 28 days prior to entry into Step 2 AND RBV is being used in the Step 2 regimen:

- Didanosine
- Stavudine
- Zidovudine

5.4.2 Precautionary Medications

Table 5.4.2-1 Precautionary Medications and Instructions Regarding Use during Study Participation

Medication Category	Precautionary Concomitant Agents	Instructions Regarding Use During Study Participation
Antiarrhythmics	Amiodarone, digoxin, dronedarone	Amiodarone/Dronedarone: monitor for toxicity, ECG monitoring Digoxin: measure digoxin level at baseline, decrease digoxin dose by 50% and continue to monitor digoxin levels
Antibiotics	Erythromycin, Rifaximin	Erythromycin: Consider ECG monitoring if at risk for QTc prolongation Rifaximin: Monitor closely for efficacy of both rifaximin and glecaprevir/pibrentasvir; avoid if possible
Antidiabetic	Glyburide, repaglinide	Monitor blood glucose and for signs/symptoms of hypoglycemia
Antifungals	Ketoconazole, posaconazole	Consider additional LFT monitoring
Anti-gout agents	Colchicine	Consider decreasing colchicine dose
Antihypertensives	Carvedilol, diltiazem, enalapril, eplerenone, irbesartan, olmesartan, telmisartan, verapamil	Monitor heart rate and blood pressure Enalapril: use at lowest dose Eplerenone: start at low dose
Antimalarial	Mefloquine, quinidine, quinine	Monitor for cardiotoxicity (bradycardia, arrest/asystole, PR, QRS, or QT prolongation, depressed contractility), neuropsychiatric effects (psychosis, seizures, anxiety,

Medication Category	Precautionary Concomitant Agents	Instructions Regarding Use During Study Participation
		panic attacks, insomnia), anticholinergic effects (dry mouth, mydriasis, delirium, rigors, fever), nausea/vomiting/diarrhea, and hypotension/pulmonary edema
Antiplatelet	Ticagrelor	Monitor for signs/symptoms of bleeding
Antipsychotics	Aripiprazole, quetiapine	Monitor for toxicities, including CNS sedation, tachycardia, tremors, irritability Quetiapine: ECG monitoring for QTc prolongation if at increased risk
Asthma	Theophylline	Monitor theophylline concentrations and for signs/symptoms of toxicity
Cholesterol-lowering (non-statin)	Ezetimibe, gemfibrozil	Ezetimibe: Consider use of lowest possible ezetimibe dose. Monitor for adverse effects (diarrhea, abdominal pain, arthralgia, fatigue) Gemfibrozil: Consider using lowest possible gemfibrozil dose or holding for duration of treatment if possible. Monitor for adverse effects (GI disturbance, muscle pain)
Corticosteroids	Dexamethasone	Monitor for increased toxicity (blood pressure, blood glucose, mood, weight)
Direct Oral Anticoagulants	Betrixaban, apixaban, edoxaban, rivaroxaban	Consider use of low molecular weight heparins instead of direct oral anticoagulants
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Monitor for ergot toxicity (nausea/vomiting, vasospasms, cardiac toxicity, neurological deficits)
Female hormones	17-beta estradiol, conjugated estrogens, estradiol hemihydrate, estradiol valerate, estriol, estrone	Consider additional liver function test monitoring
HMG CoA reductase inhibitors	Fluvastatin, pitavastatin, pravastatin, rosuvastatin	Patients with high ASCVD risk, consider dose reduction (not to exceed 10mg daily for rosuvastatin) and monitor liver function tests

Medication Category	Precautionary Concomitant Agents	Instructions Regarding Use During Study Participation
		Patients with low ASCVD risk, reduce dose or consider holding HMG CoA reductase inhibitor during GP therapy
Hyperkalemia	Polystyrene sulfonate	Separate administration by at least 3 hours
Immunosuppressants	Cyclosporine, Everolimus, Tacrolimus, Sirolimus	Chronic use of systemically administered immunosuppressive agents is an exclusion criterion for study participation. Cyclosporine: glecaprevir/pibrentasvir not recommended if require cyclosporine doses >100 mg/day Everolimus/sirolimus/tacrolimus: monitor concentrations and adjust doses accordingly
Other cardiac medications	Ranolazine	Consider decreasing ranolazine dose
Pain	Fentanyl, hydrocodone, oxycodone	Consider dosage reduction and closely monitor for respiratory depression
Rheumatoid Arthritis, Ulcerative Colitis, and Crohn's	Methotrexate, sulfasalazine	Methotrexate: Monitor renal function, hepatic function, CBC, respiratory function, and signs/symptoms of adverse effects (nausea, vomiting, diarrhea) Sulfasalazine: Monitor for signs/symptoms of toxicity (tinnitus, vertigo, headache, confusion, drowsiness, sweating, seizures, hyperventilation, dyspnea, vomiting, diarrhea)
Stimulant	Modafinil	May decrease glecaprevir/pibrentasvir concentrations; avoid if possible

Table 5.4.2-2 Precautionary Medications and Instructions Regarding Use during Study Participation (this list only applies to participants on Ribavirin in Step 2)

Medication Category	Precautionary Concomitant Agents	Instructions Regarding Use During Study Participation
Immunosuppressants	Azathioprine	Concomitant use may induce severe pancytopenia and increase risk of Azathioprine induced myelotoxicity. Monitor CBC and platelets weekly for the first month and then twice a month for the 3rd and 4th month and then monthly after that. Both drugs should be discontinued if participant develops pancytopenia.
Antiretrovirals	Abacavir, Tenofovir, lamivudine, emtricitabine	Hepatic decompensation has been reported in cirrhotic HIV/HCV coinfected patients on NRTIs and RBV. Monitor for liver toxicity and anemia. Reduce dose or discontinue Ribavirin if toxicity is suspected.

5.4.3 Colony Stimulating Agents

Under no circumstances are potential participants to be treated with colony stimulating agents (CSA) during Step 1 to elevate hematology laboratory parameters to facilitate entry into Step 2 of the study. CSAs, such as erythropoiesis-stimulating agents or granulocyte colony-stimulating factor, will not be provided by the study.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations (SOE)

Table 6.1-1: SOE: Step 1 - Study Visits for 4-week Treatment and Post-Treatment Follow-up

Evaluation	Screening	Entry (Day 0)	On Treatment		Treatment Completion	Post-treatment					HCV Recurrence/ Virologic Failure Confirmation (see Event-Driven Evaluations in section 6.2.4)	HIV-1 Virologic Breakthrough Confirmation(see Event-Driven Evaluations in section 6.2.4)	Premature Study and /or Treatment Discontinuation Evaluations
			Weeks; See section 6.2.3 for study windows										
			1	2	4	8	12	14	16/SVR12	28			
Documentation of HIV-1 (if applicable)	X												
Documentation of Acute HCV Infection	X												
Documentation of Cirrhosis Status	X												
Documentation of Historical Labs (see section 6.3.4)	X												
Medical History	X												
Medication History	X	X											
Clinical Assessments (see section 6.3.7)	X	X	X	X	X	X	X		X	X	X	X	X
Hematology	X	X									X		
Chemistries	X	X	X	X	X	X	X		X	X	X		X

Evaluation	Screening	Entry (Day 0)	On Treatment		Treatment Completion	Post-treatment					HCV Recurrence/ Virologic Failure Confirmation (see Event-Driven Evaluations in section 6.2.4)	HIV-1 Virologic Breakthrough Confirmation(see Event-Driven Evaluations in section 6.2.4)	Premature Study and /or Treatment Discontinuation Evaluations
			Weeks; See section 6.2.3 for study windows										
			1	2	4	8	12	14	16/SVR12	28			
Liver Function Tests (LFTs)	X	X	X	X	X	X	X		X	X	X		X
Calculated CrCl	X	X			X				X	X	X		X
Coagulation Markers	X	X		X	X	X			X		X		X
Urine Sample for Substance Use Screen		X	X	X	X	X	X		X	X	X		X
FSH	X												
Pregnancy Testing	X	X	X	X	X	X	X		X	X	X		X
Serologies	X	X (see section 6.3.8)									X		
HCV Antibody	X	X (see section 6.3.8)											
CD4+/CD8+ (for participants with HIV-1 infection)	X	X			X				X				X
Stored Plasma and PBMC for Immunologic Studies	X	X			X		X		X	X	X		X
Plasma HCV RNA (screening performed at local lab, see section 6.3.10)	X												
Plasma HCV RNA (real-time, see section 6.3.10)		X	X	X	X	X	X		X	X	X		X

Evaluation	Screening	Entry (Day 0)	On Treatment		Treatment Completion	Post-treatment					HCV Recurrence/ Virologic Failure Confirmation (see Event-Driven Evaluations in section 6.2.4)	HIV-1 Virologic Breakthrough Confirmation(see Event-Driven Evaluations in section 6.2.4)	Premature Study and /or Treatment Discontinuation Evaluations
			Weeks; See section 6.2.3 for study windows										
			1	2	4	8	12	14	16/SVR12	28			
Plasma HCV Genotype (screening performed at local lab unless unavailable, see section 6.3.10)	X										X		
Plasma HIV-1 RNA (for participants with HIV-1 infection) (real-time, see section 6.3.10)	X	X			X					X	X	X	X
Stored Serum for HIV-1/HCV Studies (see section 6.3.10)	X	X	X	X	X	X	X		X	X	X	X	X
Stored Plasma for HIV-1/HCV Studies (see section 6.3.10			X	X		X	X		X	X	X	X	X
Plasma for PK Testing (see section 11.2)		X	X	X	X	X	X		X		X	X	X
Dried Blood Spots (DBS) for PK (see section 11.2)		X			X				X		X	X	X
Optional Hair Sampling for PK (see section 11.2)		X			X				X		X	X	X

Evaluation	Screening	Entry (Day 0)	On Treatment		Treatment Completion	Post-treatment					HCV Recurrence/ Virologic Failure Confirmation (see Event-Driven Evaluations in section 6.2.4)	HIV-1 Virologic Breakthrough Confirmation(see Event-Driven Evaluations in section 6.2.4)	Premature Study and /or Treatment Discontinuation Evaluations
			Weeks; See section 6.2.3 for study windows										
			1	2	4	8	12	14	16/SVR12	28			
IL-28B Genotype and HLA Typing		X (See section 6.3.12; IL-28B genotype/HLA typing may be performed on any PBMC sample collected at any time during the study.)											
Pregnancy Prevention Counseling	X	X			X	X					X		X
Adherence Assessments (see section 6.3.14)		X	X	X	X								X
Study Drug Dispensing/First Dose Observed		X											
Risk Factor Assessment		X	X	X	X	X			X	X			
Health Outcomes Questionnaire (EQ-5D)		X			X				X	X			
Health Care Utilization Questionnaire		X			X				X	X			
Reinfection Prevention Counseling		X			X	X			X	X			
Collection and Updating of Locator Information		X			X	X	X						
Remote Contact Reminder for Week 16 Visit								X					

Table 6.1-2: SOE: Step 2- Repeat Treatment for Suspected Relapse/Virologic Failure/Post-treatment Viremia or Re-infection

Evaluation	Re-Treatment Entry/ Initiation	On-Retreatment (Weeks) R = Step 2 Entry ReTx=Retreatment					Post-Retreatment		HCV Recurrence/Virologic Failure (see Event Driven Evaluations in section 6.2.4) Confirmation	HIV-1 Virologic Breakthrough Confirmation (see Event-Driven Evaluations in section 6.2.4)	Premature Study and /or Treatment Discontinuation Evaluations
		R+2 (RBV regimens only)	R+4	R+8	R+12 (12 & 16 weeks ReTx only)	R+16 (16 weeks ReTx only)	SVR12 visit (R+20, R+24 or R+28, depending on re-treatment duration)	Only for RBV exposed (R+32, R+36 or R+40, depending on re-treatment duration)			
		See section 6.2.3 for study windows									
Evaluation of Step 2 Entry Requirements (see section 6.3.20)	X										
Clinical Assessments (see section 6.3.7)	X	X	X	X	X	X	X	X	X		X
Hematology, Chemistries	X	X	X	X	X	X	X		X		X
LFTs (see section 6.3.8)									X		
Serologies (see section 6.3.8)	X								X		
Calculated CrCl (if on RBV)	X	X	X	X	X	X					X
Pregnancy Testing (see section 6.3.8)	X	X	X	X	X	X	X	X			X

Evaluation	Re-Treatment Entry/ Initiation	On-Retreatment (Weeks) R = Step 2 Entry ReTx=Retreatment					Post-Retreatment		HCV Recurrence/Virologic Failure (see Event Driven Evaluations in section 6.2.4) Confirmation	HIV-1 Virologic Breakthrough Confirmation (see Event-Driven Evaluations in section 6.2.4)	Premature Study and /or Treatment Discontinuation Evaluations
		R+2 (RBV regimens only)	R+4	R+8	R+12 (12 & 16 weeks ReTx only)	R+16 (16 weeks ReTx only)	SVR12 visit (R+20, R+24 or R+28, depending on re-treatment duration)	Only for RBV exposed (R+32, R+36 or R+40, depending on re-treatment duration)			
		See section 6.2.3 for study windows									
CD4+/CD8+ (for participants with HIV-1 infection)	X			X		X	X				X
Stored Plasma and PBMC (see section 6.3.9)	X		X		X	X	X		X		X
Plasma HCV RNA (real-time, see section 6.3.10)	X	X	X	X	X	X	X		X		X
Plasma HCV Genotype (see section 6.3.10)									X		
Plasma HIV-1 RNA (for participants with HIV-1 infection, real-time, see section 6.3.10)			X	X	X	X	X		X	X	X
Stored Serum for HIV-1/HCV Studies (see section 6.3.10)		X	X	X	X		X		X	X	X

Evaluation	Re-Treatment Entry/ Initiation	On-Retreatment (Weeks) R = Step 2 Entry ReTx=Retreatment					Post-Retreatment		HCV Recurrence/Virologic Failure (see Event Driven Evaluations in section 6.2.4) Confirmation	HIV-1 Virologic Breakthrough Confirmation (see Event-Driven Evaluations in section 6.2.4)	Premature Study and /or Treatment Discontinuation Evaluations
		R+2 (RBV regimens only)	R+4	R+8	R+12 (12 & 16 weeks ReTx only)	R+16 (16 weeks ReTx only)	SVR12 visit (R+20, R+24 or R+28, depending on re-treatment duration)	Only for RBV exposed (R+32, R+36 or R+40, depending on re-treatment duration)			
		See section 6.2.3 for study windows									
Stored Plasma for HIV-1/HCV Studies (see section 6.3.10)		X	X	X	X		X		X	X	X
Plasma for PK Testing (see section 11.2)		X	X	X					X	X	X
Pregnancy Prevention Counseling	X	X	X	X	X	X	X				X
Study Drug Dispensing	X		X	X	X						
Risk Factor Assessment	X	X	X	X	X	X	X	X			
Reinfection Prevention Counseling	X					X	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.

For Step 1, screening evaluations to determine eligibility must be completed within 28 days prior to entry unless otherwise specified. For Step 2, participants can enter Step 2 up to 56 days after the confirmatory HCV RNA sample date completed as part of Step 1.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

6.2.2 Entry Evaluations

Entry evaluations must occur at least 24 hours after screening evaluations unless otherwise specified. For Step 1, participants must begin treatment within 24 hours after registration and upon completion of entry evaluations. The first dose of G/P will be provided to the participant and taking the first dose will be observed by study staff.

For participants entering Step 2, treatment must be started within 72 hours of Step 2 entry.

6.2.3 Post-Entry Evaluations

All post-entry evaluations occur in reference to the start of study therapy.

On-Treatment Evaluations
Study visits must be scheduled on the weeks indicated in Tables 6.1-1 and 6.1-2, within the visit windows described below, as appropriate for the visit.

Step 1:
- Weeks 1 and 2 have a window of ±3 days.
- Week 4 has a window of -7 days and +14 days.

Step 2:
- Week R+2 has a window of ±3 days.
- Weeks R+4, R+8, R+12, and R+16 have a window of -7 days and +14 days.

Treatment Completion Evaluations
Clinical assessment and laboratory evaluation, as outlined in section 6.1, will be performed at treatment completion (Step 1: week 4, Step 2: week R+8, R+12, or R+16).

Post-Treatment Evaluations
Following treatment completion, participants will undergo evaluations as outlined in Tables 6.1-1 and 6.1-2, within the study windows, as indicated below.

After the last dose of study drugs, the post-treatment study visits have the following windows:

Step 1:
- Study weeks 8, 12, and 16: -5 days and +21 days
- Study week 28: -7 days and +28 days

Step 2:
- Study week R+20, R+24, or R+28 (12 weeks after re-treatment completion for those not receiving RBV depends on Step 2 treatment duration): -5 days and +28 days
- Study week R+32, R+36, or R+40 completion (for those receiving RBV): -14 days and + 28 days

6.2.4 Event-Driven Evaluations

HCV Viral Recurrence/Virologic Failure
In Step 1, all cases of confirmed HCV recurrence/virologic failure occurring before or at the week 16/SVR12 visit will undergo evaluation for preliminary determination of suspected relapse versus re-infection (see Table 6.1-1, A5380 MOPS, and A5380 Laboratory Processing Chart [LPC]). Viral recurrence is defined as confirmed HCV RNA value >LLOQ after achieving HCV RNA <LLOQ (TD or TND). Virologic failure is defined as failure to achieve HCV RNA <LLOQ (TD or TND) and confirmed increase in HCV RNA >1 $\log_{10}$ from nadir. These participants will enter Step 2. This confirmatory sample should be collected within 56 days of Step 2 entry.

Participants should have this confirmatory evaluation done, per Table 6.1-1, before initiation of Step 2 therapy. Participants should be re-tested with HCV RNA and hepatic panel (LFTs) as soon as possible after viral recurrence or virologic failure to confirm the HCV RNA >LLOQ or >1 $\log_{10}$ from nadir, respectively.

If HCV RNA is >1000 IU/mL, as part of Step 2 entry, each available post-treatment viremic sample will be sent for HCV genotyping and RAS analysis. A stored baseline sample will also be sent for RAS analysis. Results from these assessments will be delivered to the A5380 CMC via email

(actg.cmcA5380@fstrf.org) by the designated Virology Specialty Laboratory (VSL) and initial determination of suspected relapse versus re-infection will be made. If HCV RNA is persistently less than or equal to 1000 IU/mL, the participant may still meet the criteria of virologic failure and/or post-treatment HCV viremia described in section 4.3.1.

Results of repeat HCV genotype and RAS analysis will be delivered to the A5380 CMC (actg.cmcA5380@fstrf.org). If the genotype/subtype has switched, this will be classified as a re-infection. If the same genotype/subtype and there are emergent RASs, this will be initially classified as a suspected relapse. For other situations (e.g., same genotype/subtype without emergent RASs), the classification will be determined later by phylogenetic analysis (with samples sent from the repository, see virologic studies in section 6.3.10), but for Step 2 these will be classified as "undefined post-treatment viremia" but treated as a suspected relapse. Per section 6.3.8, HAV IgM, HBc IgM Ab, total HBcAb, and HBsAg will be done during the Event-driven Evaluations outlined in the SOE with results available prior to Step 2 entry.

Following determination of suspected relapse versus re-infection versus undefined post-treatment viremia, a member of the A5380 CMC will contact the site coordinator and site PI to discuss the re-treatment approach for the participant.

For all participants with recurrence of the same genotype/subtype, stored samples from the repository will be batched and sent for sequencing, phylogenetic analysis, and definitive determination of relapse versus re-infection (see virologic studies in section 6.3.10). Suspected relapse or undefined post-treatment viremia may then be reclassified as confirmed relapse or re-infection for the purposes of exploratory objective 1.4.1.

HIV-1 Virologic Breakthrough

In this study, HIV-1 viral breakthrough is defined as follows (this only applies for participants on ART):

Among participants with HIV-1 RNA <50 copies/mL at study entry, a confirmed increase to ≥200 copies/mL at any time after entry into Step 1 and Step 2.

The increase in plasma HIV-1 RNA should be confirmed with repeat central or local testing as soon as possible (not to exceed 4 weeks); see HIV-1 Virologic Breakthrough Confirmation in Tables 6.1-1 and 6.1-2. For participants with confirmed HIV-1 viral breakthrough (≥200 copies/mL), a plasma specimen should be sent for HIV genotyping and sent to the designated A5380 VSL for evidence of HIV-1 drug resistance. Results will be reported back to sites in real-time from the designated A5380 VSL. See section 6.3.10, Stored Serum and Plasma for HIV-1/HCV Studies.

Clinical management of HIV-1 virologic breakthrough and treatment failure will be

handled by local site PI according to current HIV treatment guidelines and local standard of care. The A5380 CMC should be contacted before switching ART.

HCV medications should be continued unless safety events warrant the discontinuation of these medications, as outlined in section 8.1 of the protocol.

These criteria only apply to participants currently on ART treatment. They do not apply to participants meeting the ART untreated parameters outlined in section 4.1.

6.2.5 Study Completion Evaluations

For those not proceeding to Step 2, the final study visit occurs at study week 28.

For those proceeding to Step 2, the final study visit occurs 12 weeks after re-treatment completion, with extension to 24 weeks after re-treatment completion if the participant receives RBV.

6.2.6 Discontinuation Evaluations

Evaluations for Registered 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 Evaluations
The A5380 CMC must be informed, as soon as possible, when a participant comes off study treatment due to an AE. Participants who permanently discontinue study treatment for toxicity or any other reason, and who have not met the HCV virologic failure criteria below, will also follow the schedule in Table 6.1-2. If applicable, additional or more frequent post-treatment toxicity follow-up may be determined by the site PI.

Participants who prematurely discontinue study treatment (i.e., prior to completion of the last dose of G/P per the assigned dosing period) will complete the premature treatment discontinuation evaluations. Participants will then follow the post-treatment schedule in Table 6.1-2.

NOTE: In Step 2 where applicable: If G/P is discontinued, participants should discontinue RBV. Under no condition should the participant remain on RBV monotherapy. In contrast, participants who discontinue RBV in Step 2 can continue G/P to complete their planned G/P regimen.

HCV Virologic Failure
Participants who experience for HCV virologic failure (see details in section 6.2.4) in Step 1 will have the option to enter Step 2 for re-treatment, otherwise the participants will be followed on study/off treatment through week 28.

Participants who permanently discontinue study treatment for HCV virologic failure (see details in section 6.2.4) in Step 2 will be followed through 12 weeks (or 24 weeks, if RBV given) after the treatment completion. No further treatment will be provided by the study.

Virologic evidence of recurrence, defined as HCV RNA ≤LLOQ at end of treatment but HCV RNA quantifiable (>LLOQ) during follow-up, will require confirmation and should be performed in real time at the designated VSL as soon as possible but within 2 weeks after determination of initial observation. The results will be provided to the co-chairs and site investigators within 2 weeks of specimen receipt.

HCV Virologic Response-Based Treatment Stopping Criteria in Step 2
The following on-treatment HCV virologic response-based treatment stopping criteria will be utilized for all participants in Step 2:

- Confirmed increase in HCV RNA >LLOQ if HCV RNA previously declined to ≤LLOQ (detected or not detected) AND
- Confirmed ≥1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir
- Confirmation will be required for all stopping criteria and should be performed as soon as possible but within 2 weeks after determination of initial observation (see HCV Recurrence/VF Confirmation in Table 6.1-2).

HCV RNA measurement to confirm treatment failure will be performed in real-time at the designated VSL and the results will be provided to the site PI within 2 weeks of specimen receipt. If treatment failure is confirmed, then all study treatment should be stopped. However, participants should be followed as per section 6.2.6.

Pregnancy
Pregnancy will result in immediate and permanent discontinuation of the study medications. Please see section 8.2 for detailed information regarding participant management.

Premature Study Discontinuation Evaluations
Participants who prematurely discontinue from the study will have the study discontinuation evaluations performed prior to being taken off the study.

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/daids-sourcedocpolicy.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 adverse events requirements.

6.3.1 Documentation of HIV-1

Section 4.1.6 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is recorded on the eCRF.

6.3.2 Documentation of Acute HCV Infection

Section 4.1.3 specifies assay requirements for HCV documentation. HCV documentation is not recorded on the eCRF.

6.3.3 Documentation of Cirrhosis Status

Sections 4.2.3 and 4.4.1 specify requirements for known cirrhosis status documentation. Cirrhosis status documentation is not recorded on the eCRF.

6.3.4 Documentation of Historical Labs

For all participants in Step 1, record on eCRFs all available lab values (including specimen dates) for LFTs (AST, ALT, and total bilirubin), HCV RNA, and HCV antibody (Ab) (positive/negative) tests performed within the last 12 months prior to study entry.

6.3.5 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 the past 30 days. In addition, the following diagnoses should be recorded regardless of when the diagnosis was made:

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B

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

6.3.6 Medication History

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history and recorded on the eCRF.

Table 6.3.6-1: Medication History

Medication Category	Complete History or Timeframe
Antiretroviral therapy for HIV treatment	Within 42 days prior to entry
HCV treatment	Complete history
Prescription drugs for treatment of opportunistic infections	Within 42 days prior to entry
Prescription drugs for prophylaxis of opportunistic infections	Within 42 days prior to entry
Other prescription drugs	Within 42 days prior to entry
Non-prescription drugs	Within 42 days prior to entry
Complementary and alternative therapies	Within 42 days prior to entry
Illicit Drug Use	Within 42 days prior to 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.

6.3.7 Clinical Assessments

Complete Physical Examination

A complete physical examination must be performed at screening and is to include at a minimum an examination of the head, neck and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; neurological. The complete physical examination will also include signs and symptoms, diagnoses, and vital signs (height, weight, temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Examination

A targeted physical examination must be performed at entry and all subsequent visits. It should include vital signs (temperature, pulse, and respiratory rate, and

resting blood pressure) and is to be driven by any previously identified or new signs or symptoms including diagnoses that the participant has experienced since the last visit.

Height
Height (in cm) will be collected at entry.

Weight
Weight (in kg) will be collected at Step 1 screening, entry, week 4 (treatment completion), weeks 16 and 28, and in cases of HCV virologic failure or premature study and/or treatment discontinuation evaluations.

Weight (in kg) will be collected at Step 2 entry, weeks R+2, R+4, R+8, R+12 (if on study treatment), R+16 (if on study treatment), and in premature study and/or treatment discontinuation evaluations.

NOTE A: Weight should be done with inner clothing and without shoes.

NOTE B: The weight recorded at entry to each Step will be used as the weight for PK analysis.

Post entry, see section 8.2 for collection requirements for pregnancy.

Diagnoses
Post-entry, record all targeted diagnoses per the A5380 diagnoses list (located on the A5380 PSWP) regardless of grade.

Refer to section 7.2 for AE collection requirements.

Concomitant Medications
Post-entry, the following new and discontinued concomitant medications must be recorded on the eCRFs:

- Sex-hormone medications or sex-hormone analogues or antagonists (see Table 6.3.6-1 for examples).
- Prescription and nonprescription medications taken since the last on-treatment study visit.

Start and stop dates of all prescription and nonprescription medications will be recorded on the eCRF.

Study Treatment and ART Modifications
Record all study drug and ART (for HIV-positive participants) modifications, including initial doses, participant-initiated and/or protocol-mandated modifications, inadvertent and deliberate interruptions of >1 day at each visit. Record any permanent discontinuation of treatment.

6.3.8 Laboratory Evaluations

At Step 1 and Step 2 screening and entry, all laboratory values must be recorded on the eCRF, including repeat testing. For post-entry assessments, record on the eCRF all Grade ≥2 laboratory values; record abnormal laboratory findings as per section 7.2.

Hematology
Hematocrit, hemoglobin (Hb), platelet count, red blood cell count (RBC), white blood cell count (WBC) with differential (absolute and percentage) including lymphocytes, monocytes, neutrophils, eosinophils, basophils, reticulocyte count, and MCV.

Chemistries
Creatinine, glucose, lipase, potassium, and sodium.

Liver Function Tests (LFTs)
Alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), albumin, alkaline phosphatase, total bilirubin, direct bilirubin.

Calculated CrCl
Estimated each time that a creatinine level is determined during the study period per Tables 6.1-1 and 6.1-2.

NOTE: Please refer to the A5380 PSWP for the website link to calculate CrCl using the Cockcroft-Gault calculator.

Coagulation Markers
INR, prothrombin time (PT), activated partial thromboplastin time (APTT).

Urine Sample for Substance Use Screen
Urine substance use screening must be done using a CLIA-waived urine drug use screening tool with these common drugs of abuse: amphetamines, buprenorphine, benzodiazepines, cocaine, ecstasy, methadone, methamphetamine, barbiturates, marijuana, opiates, oxycodone, fentanyl, and phencyclidine. The screening will be assessed by urine test and must include the following ancillary testing, pH and creatinine to help in confirmation of sample against adulterants. The following results would be used as confirmation of an unadulterated human urine sample; pH of 4.5 – 8.0 and urine creatinine ≥20 mg/dL.

Testing will be done per Table 6.1-1 on each scheduled study visit and participants with positive screens will be counseled before and/or at the next scheduled visit with regard to potential impact on medication adherence, health-related risks, as well as in accordance with prevailing local laws.

FSH
For female participants, FSH should be measured at screening if they are believed to not be of reproductive potential but lack medical record.

NOTE: Female participants who have not had menses for at least 24 consecutive months and have an FSH >40 international units (IU) documented by medical record or have documentation of a hysterectomy, bilateral oophorectomy and/or bilateral salpingectomy, do not require an FSH at screening.

Pregnancy Testing
For women with reproductive potential: a serum β-HCG, urine or POC/CLIA-waived test documenting a negative result will be required within 48 hours prior to Step 1 or Step 2 entry. The test should have a sensitivity of at least 25 mIU/mL.

Once a participant has enrolled with a negative documented serum or urine pregnancy test and begins using contraceptives (per sections 4.1.12 and 4.3.8, depending on current step) to prevent pregnancy, further testing per section 6.1 (during study drug dosing and in post treatment follow-up) can be urine testing. Urine test must have a sensitivity of at least 50 mIU/mL.

In the event of a positive urine pregnancy result, participants will be instructed to stop study drugs immediately and return to the clinic as soon as possible for a serum pregnancy test with β-HCG. See section 8.2 for detailed information regarding study management.

For participants taking RBV on Step 2, pregnancy testing will be done per Table 6.1-2, and at the last study visit.

Serologies
HCV Ab, HAV IgM, HBc IgM Ab, total HBcAb, and HBsAg will be done during screening with results available prior to Step 1 entry.

HAV IgM, HBc IgM Ab, total HBcAb, and HBsAg will be done during the Event-driven Evaluations (section 6.2.4) with results available prior to Step 2 entry.

If HCV Ab is negative at Step 1 entry, HCV Ab will be repeated at each subsequent study visit until positive. Once positive, no further HCV Ab testing is required.

If a historical positive HIV Ab or detectable HIV RNA result test result (i.e., used for HIV-1 infection documentation to meet inclusion criterion 4.1.6) is not available, an HIV Ab test will also be done at Step 1 screening with the result available prior to study entry. For those reporting HIV-1 negative status, testing should be sent to confirm (see section 4.1.6).

HCV Ab
HCV Ab must be obtained by any FDA-approved test at any local laboratory that has a CLIA certification or its equivalent. HCV Ab is only to be sent at screening and at a subsequent visit if the result is negative on the preceding visit. Once a single positive Ab is recorded, no further HCV antibody testing is required.

6.3.9 Immunologic Studies

CD4+/CD8+ (For participants with HIV-1 infection only)
Obtain absolute CD4+/CD8+ count and percentages within 28 days prior to entry from 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 IQA certification (non-US sites).

Stored Plasma and PBMC
PBMC will be collected, processed, and shipped to the designated immunology laboratory for analysis of HCV-specific T-cell responses (see A5380 LPC) and for IFN-stimulated gene (ISG)/IFN effector gene (IEG) responses. Based on human leukocyte antigen (HLA) typing results, participants will be screened for the presence of HCV-specific CD4+ and CD8+ T-cell responses using class I and class II HLA multimers. Based on the results HCV-specific T-cell populations will then be analyzed longitudinally using flow cytometry and/or fluorescence-activated cell sorting (FACS) followed by population or single cell RNA sequencing. Additional immune cell populations might be studied if warranted by data emerging during the trial. Findings will be compared to samples from chronic HCV already collected by the protocol immunologist.

Plasma will be analyzed for selected cytokines and chemokines and correlated with ISG/IEG and T-cell responses.

DNA for HLA typing and host polymorphisms: DNA will be extracted from the cell fraction of a PBMC tube and stored for HLA typing (class I and class II) and single nucleotide polymorphism (SNP) testing for key loci.

6.3.10 Virologic Studies

Plasma HCV RNA (screening)
The screening HCV RNA result must be obtained by any FDA-approved test for quantifying HCV RNA at any local laboratory that has a CLIA certification or its equivalent. Screening HCV RNA must be obtained within 28 days prior to study entry.

Plasma HCV RNA (real-time, on-study evaluations)
At the entry and post-entry visits, HCV RNA quantification will be performed as follows:

Plasma HCV RNA real-time testing will be collected, processed, and shipped to the designated testing laboratory (see A5380 LPC for directions). These results will be reported within 2 weeks after specimen receipt for both Steps 1 and 2.

NOTE: For Step 2, an increase in plasma HCV RNA at any time point meeting HCV virologic response-based treatment stopping criteria must be confirmed with repeat testing within 2 weeks of receipt of results. For more information please see section 6.2.4.

Plasma HCV RNA (real-time)
After the treatment is completed in Step 1, for participants entering Step 2 (Viral Recurrence [Reinfection/Suspected Relapse/Undefined Post-Treatment Viremia] or virologic failure): a detectable HCV RNA after the end of treatment after achieving HCV RNA <LLOQ is virologic evidence of recurrence which will require confirmation and should be performed in real-time at the designated testing lab as soon as possible but no later than 2 weeks.

Plasma HCV Genotype
At Step 1 screening, the HCV genotype result will be obtained locally (real-time) from any laboratory that has a CLIA certification or its equivalent. ONLY IF IT IS NOT AVAILABLE LOCALLY should it be done (real-time) at the designated testing laboratory (see A5380 LPC).

At viral recurrence or virologic failure (prior to Step 2 entry), HCV genotype will be performed on stored samples (near-time) at the designated testing lab (see A5380 LPC).

Plasma HIV-1 RNA
For participants with documented HIV-1 infection, a documented plasma HIV-1 RNA level must be noted within 28 days prior to Step 1 study entry from any laboratory that has a CLIA certification or its equivalent. On-study HIV-1 RNA is only required for HIV-1-infected participants and should be performed at the ACTG central laboratory. See the A5380 LPC for processing, shipping, and storage information.

Participants on ART who later experience HIV-1 viral breakthrough while on HIV therapy should be managed as per section 6.2.4.

Stored Serum and Plasma for HIV-1/HCV Studies
Serum and plasma samples will be collected and stored for HCV and potential HIV sequencing and other virology studies. For processing and shipping instructions, refer to the A5380 LPC.

- HIV Genotyping
  Using stored samples for HIV-1/HCV studies above, for participants with confirmed HIV-1 viral breakthrough (≥200 copies/mL), a plasma specimen will be sent to the designated A5380 VSL for evidence of HIV-1 drug resistance. Results will be reported back to sites in real-time from the designated A5380 VSL.

- HCV RAS testing
  Using stored samples for HIV-1/HCV studies above, resistance genotype near-time sequencing will be carried out for NS3 and NS5A genes on participants experiencing confirmed virologic failure or recurrence. Sequencing will be performed on baseline and post-treatment recurrence samples with HCV RNA >1,000 IU/mL.

- Phylogenetic Assessment of Relapse versus Re-infection
  Using stored samples for HIV-1/HCV studies above, viral phylogenies utilizing envelope hypervariable region 1 (HVR1) sequences compared between baseline and viral recurrence time points will be used to confirm determinations of re-infection versus suspected relapse made based on genotype and RAS assessments. This assessment will not be used for determination of eligibility for Step 2. Ultra-deep sequencing will be performed on baseline and post-treatment recurrence samples with HCV RNA >1,000 IU/mL. The genetic diversity threshold for re-infection will be set at nucleotide substitutions per site greater than 3% [43, 59] and verified by cluster analysis. These assessments will be performed by the chairs, co-chairs, and virologist.

6.3.11 PK Sampling

For DBS, hair (optional), and plasma for PK, please refer to the Pharmacology Plan in section 11.0.

6.3.12 IL-28B Genotype and HLA Typing

DNA will be isolated from PBMCs collected during the study; these DNA samples will be analyzed for IL-28B genotype and HLA typing to inform immunologic studies. IL-28B genotype and HLA will be determined by polymerase chain reaction (PCR) amplification by the designated immunology laboratory (see A5380 LPC). For processing and shipping instructions, refer to the A5380 LPC.

The IL-28B genotype and HLA typing will be performed only on participants who consent to this genetic test collection and are subsequently enrolled into the study.

IL-28B genotype/HLA typing only needs to be performed once and may be performed on any PBMC sample collected at any time during the study. At Step 1 entry, samples for IL-28B genotype/HLA typing will be collected.

6.3.13 Pregnancy Prevention Counseling

Counseling on pregnancy prevention will be conducted as per site's standard of care. This information is not recorded on the eCRF.

6.3.14 Adherence Assessments

This study will use a combination of measures of adherence for Step 1 study medication (G/P) and ARVs (if applicable) via the self-reported 4-day recall questionnaire at weeks 1, 2 and 4 for G/P and at entry, and weeks 1, 2 and 4 for ARVs.

Pill counts for G/P should be collected at weeks 1, 2 and 4 and should only cover study medication since the participant's last visit.

Both the 4-day recall and pill counts will only be done as a part of Step 1.

No adherence assessments will be done for Step 2.

The adherence questionnaire is posted on the DMC Portal in the Forms Management Utility.

6.3.15 Study Drug Dispensing/First Dose Observed

For Step 1, study drug will be dispensed at study entry. Study staff will observe the first dose taken by the participant before he/she leaves the site and record this observation on an eCRF.

For Step 2, study drug will be dispensed at Step 2 entry and every 4 weeks as indicated in Table 6.1-2 based on the length of therapy. Due to the different potential lengths of therapy for Step 2, in addition to entry, drug will be dispensed at R+4 for participants receiving 8 weeks of therapy, at R+4 and R+8 for participants receiving 12 weeks of therapy, and at R+4, R+8, and R+12 for participants receiving 16 weeks of therapy.

Participants must be instructed to bring back all packages of study drugs in the original container at the post-entry study visits.

6.3.16 Questionnaires

Questionnaires are posted on the DMC Portal in the Forms Management Utility.

Risk Factor Assessment
As indicated in Tables 6.1-1 and 6.1-2, survey will be administered that will query participants on risk behaviors. The survey may be self-administered, interviewer-administered or a combination of both. At baseline, the survey will ask about risk behaviors in the prior 6 months but at all follow-up visits, the survey will query

about risk behaviors since the prior visit. The questionnaire will capture information related to sexual (e.g., history of unprotected receptive anal intercourse) and injection drug use practices (e.g., history of sharing of injection paraphernalia) as well as other practices that place individuals at a high-risk for HCV acquisition. Participants will be made aware they have the option to decline to answer any of the questions in the survey but still be included in the study. All information from the risk assessment questionnaire will be recorded on the eCRF.

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. Questionnaires will be administered per Table 6.1-1.

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. Responses must be recorded on an eCRF. This questionnaire will be administered per Table 6.1-1.

6.3.17 Reinfection Prevention Counseling

HCV reinfection prevention counseling will be administered to all participants per Tables 6.1-1 and 6.1-2. This information is not recorded on the eCRF. See the A5380 MOPS for further details.

6.3.18 Collection and Updating of Locator Information

Given the limited sample size, it is imperative that additional measures are taken to ensure that retention at SVR12 is as close to 100% as possible. Consequently, locator information will be captured and updated periodically until the SVR assessment for Step 1. At Step 1 entry (day 0), detailed information on the primary mode of contact (e.g., mobile phone, email, social media messaging services, etc.) will be captured along with a secondary mode of contact (e.g.,

mobile phone, email, social media messaging services, etc.). Additionally, information on a second person who may be contacted if the participant cannot be contacted will also be captured. This person could be a spouse, sibling, family member, sexual/injection partner, or a friend.

At Step 1 week 4 (treatment completion) and post-treatment Step 1 weeks 8 and 12, locator information will be confirmed with the participant to ensure that the information provided is up-to-date. If there are any changes in the information, the locator form will be updated accordingly to reflect the changes.

A locator form has been included as part of the study documents available on the A5380 PSWP. It is not mandatory that sites use this form but it is strongly RECOMMENDED that sites use this form to capture and update locator information. It is recognized that some sites may already have site-specific locator forms to track study participants. Sites can opt to use these forms as opposed to the form provided with this protocol if they are more comfortable with the existing form. However, it is REQUIRED that sites capture and update locator information as per Table 6.1-1 by using either the study-specific locator information form or an alternate site-specific locator information form. Locator information is not recorded on the eCRF.

6.3.19 Remote Contact Reminder for Week 16 Visit

Participants will be contacted 2 weeks prior to the week 16 visit via the locator information provided and reminded that they are due for their SVR assessment. If the participant cannot be reached after 3 attempts, the secondary contact will be contacted. This information is not recorded on the eCRF.

6.3.20 Evaluation of Step 2 Entry Requirements

Sections 4.3 and 4.4 specify requirements for Step 2 entry. Recurrence and virologic failure should be documented. Determination of suspected relapse versus reinfection versus undefined post-treatment viremia by communication with the designated team member should be documented. These should be recorded on the eCRF.

The informed consent form for Step 2 must be reviewed and signed by the participant prior to Step 2 entry.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of AEs

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 AE Collection Requirements for This Protocol

From study enrollment, all AEs must be recorded on the eCRFs if any of the following criteria have been met:

- All Grade ≥2 AEs
- All AEs that led to a change in study treatment/intervention regardless of grade or attribution.
- 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.

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 https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Serious Adverse Events (SAEs)
An 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 AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, 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 https://rsc.niaid.nih.gov/clinical-research-sites/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: glecaprevir/pibrentasvir (G/P) FDC and ribavirin (RBV)
- Though not an AE, the study investigator must report to the sponsor or designee, within 3 business days of identification, any pregnancy occurring in a female participant or a female partner of a male participant, during the study or within 24 weeks of the last dose of RBV. Any complication of pregnancy affecting a female participant or female partner of a male participant, and/or fetus, and/or newborn that meets SAE criteria must be reported as an SAE. See section 8.2 for pregnancy reporting requirements.

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 website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is week 0 to week 28 for all participants except those who proceed to Step 2. For individuals who proceed to Step 2, the reporting period would be dependent on the length of their Step 2 regimen. Each Step 2 participant will have expedited AE reporting up to 12 weeks after their last dose of study drug except for RBV for which expedited AE reporting would continue till week 24 after last medication dose. For Step 2 of this study expedited AEs would only be collected on Step 2 participants who are on study drugs (G/P) or G/P and RBV.

- 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

A5380 core team members (including study chairs, medical officer, and statisticians) will monitor the conduct and safety of the study via regular summaries of accrual, AEs, study conduct (including premature study discontinuations and premature study treatment discontinuations), data completeness, and specimen collection, as appropriate. The core team will review the individual participant-level HCV virology data as outlined in section 10.5.

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 standard operating procedures (SOPs), as applicable. Additionally, the DAIDS clinical representative will review aggregated AE summaries prepared every 3 months by the Statistical and Data Analysis Center (SDAC).

The study will undergo interim review at least annually by an ACTG-appointed Study Monitoring Committee (SMC). The first planned interim review will occur when the study week 8 data are available from the first 10 participants or one year after the enrollment of the first study participant, whichever occurs first. 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 10.5 for statistical and other considerations related to interim monitoring.

Detailed plans for study monitoring will be outlined in a Study Progress, Data, and Safety Monitoring Plan (SPDSMP) developed by the Statistical and Data Management Center (SDMC) prior to enrollment of the first participant.

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

It is possible that some participants will experience transient or prolonged AEs during the trial. To minimize the effects of these dosing modifications on the eventual evaluation of the safety, tolerability, and activity of study treatment, the principles in the following sections will be used to determine the appropriate dose adjustment.

Grades 1 and 2 AEs associated with G/P or RBV require no change in study treatment but close follow-up; with the exception that modifications of RBV dosing for Grades 1 and 2 anemia are provided in section 8.1.2.

8.1.1 Management of Side Effects of G/P

Most AEs are expected to be mild in severity. However, if a SAE occurs, administration of G/P may be discontinued due to clinical or laboratory events. For participants also on a ritonavir (RTV)-boosted HIV PI or a cobicistat-containing regimen there is potential for higher exposures.

Dose reduction of G/P will not be allowed in the study. If G/P is stopped for toxicity, it will not be restarted.

All participants must complete weeks 8, 12, 16, and 28 visits (Step 1) or one of the following visits in Step 2 depending on re-treatment duration: week R+20, R+24, or R+28, R+32, R+36, and R+40 visits.

Participants who meet any of the following laboratory criteria should stop treatment with G/P:

- Confirmed elevation of ALT and/or AST >3 x values measured upon study entry
- Confirmed direct bilirubin >2x values measured upon study entry
- Any ≥Grade 3 rash associated with constitutional symptoms
- Any Grade 4 event assessed as related to treatment with G/P

8.1.2 Management of Side Effects of RBV (Step 2 participants with suspected relapse, virologic failure, or undefined post-treatment viremia)

The most common AE of RBV therapy is anemia due to hemolysis. Anemia typically occurs within 1 to 2 weeks of initiating RBV therapy and usually resolves within 4 to 8 weeks of drug discontinuation or dose reduction. Indirect bilirubin elevation is commonly seen in those participants with anemia secondary to RBV-induced hemolysis.

Another major side effect of RBV is its teratogenicity. It is therefore strongly recommended that pregnant women or breastfeeding women and men with pregnant sexual partners not receive RBV. Women who become pregnant on study and men on study whose partners become pregnant must discontinue study treatment and complete the discontinuation evaluations as indicated in section 8.2.

RBV dosing in this study will be based on weight at Step 2 entry (see section 5.0). Dose reduction of RBV is the recommended management for RBV-associated anemia and should be performed according to the product label. Information is summarized in Table 8.1.2-1. It is recommended that sites contact the A5380 CMC with questions regarding difficult anemia management and/or if it is felt RBV discontinuation is required. Participants will continue to take G/P if RBV is temporarily or permanently discontinued.

Table 8.1.2-1: Suggested RBV Dose Reduction in the Event of Anemia

Laboratory Values	Reduce RBV Dose to 600 mg/day if:	Hold RBV if:
Hemoglobin in participants with no cardiac disease	<10 g/dL	<8.0 g/dL
Hemoglobin in participants with history of stable cardiac disease	≥2 g/dL decrease in hemoglobin during any 4-week treatment period	<10 g/dL despite 4 weeks at reduced dose
Symptomatic drop in hemoglobin to be managed at the discretion of the site investigator and can be discussed with the protocol chairs.		

Reintroduction of RBV

If RBV is temporarily stopped due to anemia, the hemoglobin must be rechecked within 2 weeks and at 2-week intervals until stable. Once RBV has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart RBV at 600 mg daily in two divided doses and further increase the dose to 800 mg daily in two divided doses. However, it is not recommended that RBV be increased to the original assigned dose. Please refer to the table below for dosing intervals.

Table 8.1.2-2: Dosing Intervals to Restart RBV

Daily Dose	Morning Dose	Evening Dose
600 mg	400 mg (2 tablets)	200 mg (1 tablet)
800 mg	400 mg (2 tablets)	400 mg (2 tablets)

NOTE A: The half-life of RBV in participants with normal renal function is 290 hours.

NOTE B: The ranges of hemoglobin values used as criteria for triggering dose reduction of RBV do not correspond to those used to grade toxicities in the DAIDS AE Grading Table, corrected Version 2.1, July 2017. Therefore, sites are expected to use specific criteria shown in Table 8.1.2-1 above.

8.2 Pregnancy

Pregnancy and pregnancy outcome will be recorded on the eCRFs. For co-infected participants, pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Telephone: 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.)

Pregnancy Outcomes and Reporting

If a woman has completed the study or chooses to discontinue from the study before the end of the pregnancy, then 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 will result in immediate discontinuation of the study drugs and initiation of counseling regarding the lack of information of safety in pregnancy with G/P and for those in Step 2 receiving RBV, regarding the teratogenicity of RBV. Participants who become pregnant while on study will be followed on study/off treatment until study completion. A visit 6 months following the end of pregnancy will be conducted for evidence of AEs in the participant and infant, and an outcome eCRF will be completed.

In Step 2, male participants taking RBV whose partners become pregnant will undergo treatment discontinuation and remain on study for continued follow-up until the end of the study. They will receive counseling on RBV teratogenicity and the same follow-up visit at 6 months after their partners' delivery as outlined for pregnant women. This same risk of teratogenicity is not seen with G/P, thus pregnancy of female partner in Step 1 is not an indication for treatment discontinuation.

All participants including female partners of male participants who become pregnant while taking the study treatment will have their pregnancy reported to AbbVie via the sponsor.

If a female participant or male participant with a pregnant female partner has completed the study or chooses to discontinue from the study before the end of the pregnancy, site staff should request permission to contact the female participant or male participant with a pregnant female partner 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.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Premature Treatment Discontinuation

- Drug-related toxicity (see section 8.1).
- Pregnancy in a female participant.
- Participant request to discontinue for any reason.
- Requirement for prohibited concomitant medications (see section 5.4).
- Breastfeeding.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.
- For Step 2 only: Pregnancy in female partner of a male participant taking RBV.
- HCV virologic failure during Step 2 (see section 6.2.6).

NOTE: It is important to determine whether the treatment discontinuation is primarily due to an AE, lack of efficacy, or other reason.

9.2 Premature Study Discontinuation

- Request by the participant to withdraw.
- At the discretion of the ACTG, IRB/EC, FDA, NIAID, Office for Human Research Protections (OHRP), any other government agency as part of their duties, investigator, or industry supporter.
- The Study Monitoring Committee (SMC) recommends that the study be stopped early.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5380 is a prospective, phase II, single-arm study in treatment of acute HCV infection in participants with and without HIV-1 coinfection. The study will enroll participants at US and non-US sites. The key study objective is to evaluate the efficacy of a 4-week treatment of a FDC of glecaprevir/pibrentasvir (G/P), using SVR12 as the primary outcome measure. SVR12 is defined as unquantifiable HCV RNA at 12 weeks after treatment discontinuation (week 16 visit).

The study is designed to conclude with reasonable evidence that the true SVR12 proportion is greater than 80% in the study population. This will be assessed by examining if a two-sided 90% confidence interval (CI) for the sample proportion is entirely above 80%. This is equivalent to showing that the SVR12 proportion is higher than 80% in a one-sided test with a type I error of 5%, where the aim is to rule out SVR12 proportions below or equal to 80%. The threshold of 80% was chosen based on past studies (see section 2.2).

The sample size of 44 participants for the evaluation was chosen to provide good power (90%) to show that the SVR12 proportion is not worse than or equal to 80%, assuming that the underlying SVR12 proportion is 95% with the 4-week treatment. The team considers SVR12 proportion of 95% to be plausible based on the results of studies in chronically HCV infected persons using 8 weeks of treatment and considering higher success with acute HCV infection (see section 2.2). This sample size is deemed to provide reasonable precision around the estimated SVR12 proportion to provide useful information in the treatment of acute HCV.

The primary analysis on SVR12 will include all participants who initiate the treatment. As such, participants who discontinue the treatment early for whatever reason will be included in the primary analysis. Similar to the recently completed acute HCV study conducted in the ACTG (A5327), not achieving unquantifiable HCV RNA at the study visit corresponding to the SVR12 evaluation will be considered failure for SVR12 determination in the primary analysis, regardless of the reason. By this definition, early discontinuation of the study prior to the SVR12 visit will be considered a failure

regardless of the reason, and re-infection prior to the SVR12 visit will also be considered a failure. Understanding reasons for SVR failure is important, and reasons for SVR failure will be described for the anticipated small number of non-SVRs. In addition, an important secondary analysis will be an SVR12 analysis that excludes participants who discontinue the study prior to the SVR12 evaluation for reasons clearly not related to study treatment and participants who become re-infected prior to when SVR12 can be assessed. Reasons for discontinuation unrelated to study treatment may include: participant moved away, participant cannot get to the clinic, participant cannot be located. To ensure that the study is well-powered for this important secondary analysis, additional participants may be enrolled if the study is still enrolling participants when the team becomes aware of such early study discontinuations. The maximum replacement number will be 6 for the study, so that study enrollment will not be greater than 50.

The primary outcome at 12 weeks after treatment discontinuation (week 16) may be evaluated for each participant prior to the completion of study. The primary analysis timeline will be driven by the last participant's completion of the primary outcome visit, rather than the study completion date. Results from the primary analysis on SVR12 may be presented publicly, for example at a conference, when the data related to such analysis are complete, prior to study database finalization.

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the study's primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript and results reporting to ClinicalTrials.gov. Outcomes of interest for secondary and exploratory objectives intended for subsequent publications are to be listed under "Other Outcome Measures".

10.2.1 Primary Outcome Measures

10.2.1.1 SVR12 defined as achieving unquantifiable HCV RNA (<LLOQ TD or TND) at the study visit occurring at 12 weeks after treatment discontinuation (week 16). The sample within the visit window for week 12, as defined in section 6.0, will be used. If a participant does not have any HCV RNA measurements in this time period then the participant will be considered as SVR12 failure, unless there are preceding and subsequent HCV RNA measurements that are both LLOQ (either TD or TND).

10.2.1.2 Any reported AE occurring after initiation of study treatment through the study visit occurring 4 weeks after the treatment completion.

10.2.1.3 Tolerability, defined as completion of 4 weeks of treatment without discontinuation due to AEs.

10.2.2 Secondary Outcome Measures

10.2.2.1 HCV RNA <LLOQ (TD or TND) at study visits, using the visit windows as defined in section 6.0.

10.2.2.2 Virologic failure, defined as failure to achieve unquantifiable HCV RNA and confirmed increase in HCV RNA >1 $\log_{10}$ from on-treatment nadir.

10.2.3 Other Outcome Measures

10.2.3.1 Re-infection, defined as confirmed quantifiable HCV RNA during follow-up after achieving unquantifiable HCV RNA at the end of treatment or during follow-up, with phylogenetic results supporting new infection.

10.2.3.2 Relapse, defined as confirmed quantifiable HCV RNA during follow-up after achieving unquantifiable HCV RNA at the end of treatment or during follow-up, with phylogenetic results excluding new infection.

10.2.3.3 HCV resistance profile at study entry. The set of mutations to be considered will be defined prior to analysis based on the latest information.

10.2.3.4 Development of HCV resistance mutation(s) in SVR12 failures.

10.2.3.5 SVR12 for re-treatment, defined as achieving unquantifiable HCV RNA (<LLOQ TD or TND) at the study visit occurring at 12 weeks after treatment discontinuation For the participants receiving 8 weeks of re-treatment, study visit at Step 2 week R+20 will be used for SVR12 evaluation. For the participants receiving 12 weeks of re-treatment, study visit at Step 2 week R+24 will be used for SVR12 evaluation. For the participants receiving 16 weeks of re-treatment, Step 2 week R+28 will be used for the SVR12 evaluation.

10.2.2.6 Substance use.

10.2.2.7 Self-reported adherence measured by the number of missed doses.

10.2.2.8 Adherence measured by the pill count.

10.2.3.9 Serologic and virologic markers of acute immunologic host response (to be defined at the time of assay determination).

10.2.3.10 CD4+ T-cell recovery (to be defined at the time of assay determination).

10.2.3.11 Type I IFN-induced immune dysfunction (to be defined at the time of assay determination).

10.2.3.12 Cost-effectiveness measure (to be determined by assessing the resource use and cost of care).

10.3 Randomization

There is no randomization in this study. All enrolled participants will receive the study treatment. The minimum number of HIV-1-infected participants is 10, and there is no maximum.

10.4 Sample Size and Accrual

The sample size was determined to provide good power to show that SVR12 proportion is greater than 80%. The true SVR12 proportion is assumed to be 95% when treated with 4 weeks of the G/P regimen. With 44 participants, there is at least 90% power to show that proportion achieving SVR12 is greater than 80% in a one-sided exact binomial test with a targeted significance level of 5%. Table 10.4-1 below shows the study power for a range of values for the underlying SVR12 proportion.

Table 10.4-1: Study Power for the Underlying SVR12 Proportion

True SVR12 Proportion	Power
90%	54%
92%	72%
95%	93%
97%	99%

With a sample size of 44 participants, the Wilson confidence interval for the true SVR12 proportion will be entirely above 80% if 40 or more participants achieve SVR12 out of 44 participants. The table 10.4-2 below shows two-sided 90% CIs for various potential observed SVR12 proportions in a sample of 44 participants. The width of the CI indicates precision around the SVR12 estimate.

Table 10.4-2: CIs for Various Potential Observed SVR12 Proportions

Observed SVR12 Proportion	90% CI for the True SVR12 Proportion
86.4% (38/44)	(75.7%, 92.8%)
88.6% (39/44)	(78.4%, 94.4%)
90.9% (40/44)	(81.2%, 95.9%)
93.2% (41/44)	(84.1%, 97.2%)
95.5% (42/44)	(87.2%, 98.5%)
97.7% (43/44)	(90.4%, 99.5%)

Accrual of about three participants per month is expected, to complete enrollment in 15 months. Should accrual of additional participants be needed for a key secondary analysis on SVR12, which excludes participants who are re-infected with HCV or discontinue early for reasons not related to study treatment (see section 10.1), the enrollment period may be extended.

10.5 Data and Safety Monitoring

The study will be monitored by an ACTG SMC, which will review the study at least annually after the first participant is enrolled. The reviews will include information about accrual, baseline characteristics, retention, completeness of key laboratory measurements (HCV RNA), AEs, and available HCV RNA results at study visits. See section 7.4 for an overview of study monitoring. In addition, the following interim monitoring is planned for A5380.

10.5.1 Interim Monitoring Guidelines

HCV RNA results will be closely monitored in the first 10 participants by the A5380 core team (including study chairs, medical officer and statisticians) for consideration of study modification, in case there is evidence of an unacceptable number of participants not achieving unquantifiable HCV RNA, excluding reinfection (referred to as simply “failures” in this interim monitoring section) with the proposed 4 weeks of treatment.

HCV RNA results will be reviewed as the data become available for the first 10 participants. The following guideline will be used to assess failures based on early interim data on 10 participants that may trigger an SMC review:

If 3 or more of the first 10 participants experience failures by the visit occurring 4 weeks after the end of treatment (week 8), further enrollment will be suspended while the core team and the SMC review the data closely and determination is made on the future conduct of the study.

The table below shows the probabilities of meeting the above criteria under various assumed probabilities for failures shown by the visit occurring 4 weeks after the end of treatment, using binomial distributions. We want a high probability of meeting the guideline when the probability of failure is unacceptably high, so that the study can be modified. For example, when the true probability of failure is as high as 50%, then there is 95% probability of meeting the guideline to modify the study. On the other hand, we want a low probability of meeting the guideline when the true probability of failure is low. For example, when the true probability of failure is as low as 5%, then there is only 1% probability of meeting the guideline. When the true probability of failure is 30%, the probability of meeting the guideline to consider modifying the trial is 62%.

Table 10.5.1-1: Probability of Meeting the Guideline

True Probability of Failure	Probability of Meeting the Guideline
0.05	0.012
0.10	0.070
0.15	0.180
0.20	0.322
0.25	0.474
0.30	0.617
0.35	0.738
0.40	0.833
0.45	0.900
0.50	0.945

The criteria described here are meant to serve as a guideline, and the team may request an SMC review at any time for other reasons.

10.5.2 Analysis Plan

For the purpose of the early interim looks, the report will consist of listing of all available HCV RNA results, genotype results, baseline demographics and key clinical characteristics (including HIV status, ALT), study treatment duration, treatment status, and other data that may be related to re-infection. The report will be sent to the A5380 core team (mentioned in sections 7.4 and 10.5.1) frequently for review until the 10th participant has week 8 HCV RNA data available.

10.6 Analyses

The primary efficacy objective will be addressed by estimating the proportion of participants who achieve SVR12 (section 10.2.1.1 describes this primary endpoint). All enrolled participants who receive any study treatment will be included in the primary analysis. A two-sided 90% CI will be calculated around the estimated SVR12 proportion using the Wilson method for binomial data. If this CI is entirely above 80%, then it will be concluded that there is evidence that the underlying SVR12 proportion is greater than 80%.

For the primary safety analysis, the AEs occurring after initiation of study treatment through the study visit occurring 4 weeks after the treatment completion will be summarized. The proportion of study participants with AEs will be estimated with a two-sided 95% CI around the estimate. As a secondary analysis, all reported AEs (which include events that occur after the time frame defined for the primary safety analysis) will be summarized. A two-sided 95% CI will also be provided for the proportion of study participants with AEs. The Wilson method will be used.

As a secondary analysis, SVR12 will be assessed in the analysis set that excludes participants who discontinued the study early for reasons clearly not related to the study

treatment and participants who became re-infected with HCV prior to SVR12 visit. Reasons not related to study treatment include: participant moved away, participant cannot get to the clinic, participant cannot be located. The analysis will use methods similar to the primary analysis. SVR12 results will also be described separately by HIV-1 infection status.

The secondary HCV RNA endpoints (HCV RNA <LLOQ at study visits) will also be assessed with proportion estimates with two-sided 90% CI using the Wilson method, similar to the primary efficacy analysis on SVR12.

Tolerability failures and virologic failures, as defined in section 10.2.2, will be listed and described. A tolerability failure listing will be accompanied by treatment duration and the associated AE(s). Listings on virologic failure will be accompanied by HCV RNA results and any available information on HCV genotype/subtype, RAS and phylogenetic results.

11.0 PHARMACOLOGY PLAN

Within the context of this trial, adherence to G/P and potentially ARVs using a variety of assessments including self-report, pill count, and drug concentrations in plasma, cells, and/or hair will be assessed. Concentration-effect associations (e.g., glecaprevir exposures and acute LFT elevations or the relationship between G/P exposures and likelihood of achieving SVR) may also be investigated. The former is relevant for this study since participants on ritonavir-boosted darunavir and elvitegravir/cobicistat will be included. Exposures of glecaprevir are higher with these ART agents which may theoretically increase the risk for hepatotoxicity. There are limited PK and safety data with G/P and ritonavir-boosted darunavir and elvitegravir/cobicistat in individuals with HIV/HCV coinfection, so this study may provide a unique opportunity to examine any associations between exposures and LFT elevations. Also, though there is not a plan to investigate this prior to limit costs and because what type of ART and substances study participants may use will not be known, samples and data will also be collected that allow the assessment of potential drug interactions with drugs and ART agents with G/P. There is not a pharmacologic basis to expect a significant drug interaction between G/P and drugs, but formal drug interaction studies with substances are lacking.

11.1 Pharmacology Objectives

11.1.1 To evaluate participants' adherence by using several tools, including self-report, pill count and drug concentrations

11.1.2 To assess the pharmacokinetic-dynamic associations for G/P

11.1.3 To evaluate potential drug interactions between common drugs of abuse, ARVs, and G/P.

11.2 Pharmacology Study Design

For Step 1, plasma for PK, DBS samples, and hair samples (optional) will be obtained per Table 6.1-1. Please see A5380 MOPS for details regarding optional hair sample collection. Samples are collected prior to treatment initiation and after discontinuing G/P treatment in the event there is a need to retrospectively evaluate the potential for ART or drug interactions or adherence, but these samples will not be analyzed prior to limit costs and because it is not known what ART or drugs study participants will be taking. Record dose information (date/time) of last three doses of study drug and ARVs on eCRF.

For Step 2, plasma will be obtained per Table 6.1-2. DBS and hair samples will not be collected during Step 2. Record dose information (date/time) of last three doses of study drug and ARVs on eCRF.

Substance use will be assessed using urine screens and participant self-report and potential drug concentrations.

NOTE: The weight recorded at entry to each step will be used as the weight for the corresponding PK analysis.

11.3 Primary and Secondary Data, Modeling, and Data Analysis

To address pharmacology objective 11.1.1, adherence (measured by pill count, self-report, and/or drug concentrations) may be used as a predictor variable in evaluations of associations with viral response, summarized using descriptive statistics, or for ARV, compared before, during, and after G/P treatment.

To address pharmacology objective 11.1.2, we will investigate glecaprevir exposures and LFT elevations or the relationship between G/P exposures and likelihood of achieving SVR.

To address pharmacology **objective** 11.1.3, if we have a sufficient number of participants on a particular ART or drug, we may explore the potential for drug interactions between G/P and these agents.

11.4 Anticipated Outcomes

Pharmacology-related objectives for this study may provide clinical context to study findings (e.g., if adherence contributed to observed SVR rates, or if LFT elevations were associated with glecaprevir exposures) or potentially identify unexpected drug interactions between G/P, ARV, and/or drugs.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form (eCRF) screens 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.

12.2 Role of Data Management

12.2.1 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.

12.2.2 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.

12.3 Clinical Site Monitoring and Record Availability

12.3.1 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 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.

12.3.2 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 ACTG, IRB/EC, FDA, the NIAID, the OHRP, the industry supporters or designee, other local, US, and international regulatory entities for confirmation of the study data.

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix I and II) and any subsequent modifications will be reviewed and approved by the IRB or EC 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.

13.2 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 supporters or designee.

13.3 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 supporters.

14.0 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 supporters prior to submission.

15.0 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 CDC 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.

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APPENDIX I: STEP 1 SAMPLE INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
For protocol: A5380

FINAL VERSON 1.0, 06/07/19: A Phase II Trial of Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection (PURGE-C)

SHORT TITLE: Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection Including Persons with HIV

PART 1 SUMMARY

PURPOSE

The purpose of Part 1 of this study is to see if 4 weeks of the hepatitis C (HCV) drug, glecaprevir/pibrentasvir (G/P), cures your acute HCV. People with acute HCV have a good chance of being cured of the infection when they are treated with a combination of two drugs within the first 6 months of getting HCV.

The study will also look at the safety of 4 weeks of G/P and if it is tolerated by your body.

NUMBER OF PARTICIPANTS

There will be 2 parts of the study for a total of up to 50 participants.

LENGTH OF STUDY

Part 1 of the study will last about 28 weeks for most people. Part 2 of the study will last about 20-40 weeks because additional treatment is required.

For Part 1, you will need to come back to the clinic 9 more times in the first 28 weeks.

REQUIRED ACTIVITIES

Blood and urine collections

- At most visits, some blood will be collected from a vein in your arm. At a few visits, you will be asked to provide a urine sample.

Special procedures

- You will be asked about the best way to reach you by telephone, email, etc., between visits.
- You will be asked questions about potential risks of becoming infected with HCV, and your quality of life.
- Some of your hair will be collected, if you choose.

RISKS The following are possible:

- People outside of the study may find out that you are participating in this study and treat you unfairly.
- Discomfort, lightheadedness, bleeding, swelling, or bruising from drawing blood
- Side effects from the study medication
- Drug resistance, making your HCV more difficult to treat
- If you are living with HIV, drug interactions with your HIV drugs while taking the study medication.
- If you have hepatitis B (HBV) and HCV, reactivation of HBV.

BENEFITS You may be cured of your HCV but no guarantee can be made.

OTHER CHOICES Instead of being in this study, you have the option of continuing with your current treatment, starting a new treatment under the care of your regular doctor or other health care provider, or no treatment at all. Your participation in this study is completely voluntary.

INTRODUCTION

You are being asked to take part in this research study because you have a recent infection with the hepatitis C virus (HCV, a virus that affects the liver). You may also be living with human immunodeficiency virus (HIV, the virus that causes AIDS). 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 Part 1 of this study, we want you to know about Part 1 of the study.

This is a consent form. It gives you information about Part 1 of 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 Part 1 of this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

People who are recently infected with a new case of HCV are often considered to have acute HCV. People with acute HCV have a good chance of being cured of the infection when they are treated with a combination of two drugs within the first 6 months of being diagnosed. This study is being done to see if 4 weeks of the HCV drug, glecaprevir/pibrentasvir (G/P), cures your HCV, and if 4 weeks of G/P is safe for you and can be tolerated by your body. This study will include up to two parts:

Part 1 (shorter course of treatment- 4 weeks) - You will take 3 tablets of G/P by mouth daily for 4 weeks. If you are not cured of HCV from this 4-week treatment, or you are infected again, you will have the option to enroll into Part 2.

Part 2 (longer course of treatment- more than 4 weeks, and the treatment may differ from Part 1) - If you require retreatment approximately 12 weeks after completing the treatment in Part 1, you will take 3 tablets of G/P by mouth daily for either 8, 12, or 16 weeks. It is possible another drug named ribavirin (RBV) will be added to G/P. The length of treatment will be decided from various lab tests. It is possible that the study doctor will suggest a different HCV drug based on your local standard of care. You are not signing up for Part 2 at this time. A separate consent form will be obtained in the event you become eligible for Part 2.

The medications that is provided in this study is approved by the Food and Drug Administration (FDA) for use in persons who have been diagnosed with HCV.

You will be monitored for safety and viral response (how your body is responding to treatment and whether the amount of HCV in your body is decreasing) while on treatment. After completing treatment, you will be evaluated to see how your body responded to treatment at various time points up to 24 weeks in each part of the study.

This is a consent form for Part 1 of the study. You may be asked to join Part 2 of the study if, after treatment in Part 1, you still have HCV. Details on Part 2 of the study will be reviewed with you should that occur, and you will be asked to sign another consent form. Right now, you are not signing up for Part 2 of the study.

WHAT DO I HAVE TO DO IF I AM IN STEP 1 OF THIS STUDY?

If you would like to be in this study, after you have read and signed this informed consent form, you will come to the clinic for a screening visit to make sure you meet the requirements for joining the study. You may have as little as 2.5 tablespoons to as much as 11 tablespoons of blood collected at any one visit. Over the course of the study, the amount of blood collected from you will be within approved limits.

If you are also living with HIV, you will continue taking your current anti-HIV drugs (antiretrovirals [ARVs]- medications to control HIV) if you are receiving them. If you are not currently on ARVs and your provider does not think you will need ARVs for the next 4 weeks, this is also acceptable. If your HIV regimen includes atazanavir, efavirenz, etravirine, fosamprenavir/ritonavir, indinavir/ritonavir, lopinavir/ritonavir, nelfinavir, nevirapine, saquinavir/ritonavir, or tipranavir/ritonavir, you will need to be switched to another HIV regimen. You will need to be sure that your HIV provider discusses all changes to your HIV regimen with the study doctor. See section I for a description of the study visits.

After the entry visit, you will be given your study medication (G/P) for all 4 weeks of treatment to take home. You will need to store the medications in a safe place at room temperature (between 15º to 25ºC [59º to 77ºF]). You will take three pills every day for 4 weeks. After you have completed 4 weeks of treatment with G/P, you will continue to have follow-up visits for 24 weeks.

Everyone who enters this study will take a fixed-dose combination (FDC) of G/P, which will be given for free by the study. If you have HIV, your ARVs will not be provided by the study. These will be provided by your regular non-study HIV provider.

While you are in Part 1 of this study, you will need to be seen in the clinic about 9 times during the study. The study staff will tell you about how long each visit could be. You will have blood drawn for study related tests during each visit both to monitor your response to the study medication and to look for any side effects that may be caused by the medication.
For both parts of the study, you may need to make extra visits to the clinic if you have side effects or if you switch or take new ARVs. 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 when they are available.

A5380 Part 1 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.

Appendix I Table 1: Part 1 Study Schedule

Evaluation or Test	Screening	Entry	Post-Entry Visits			Unplanned Visits	HCV Virologic Failure Confirmation	HIV Virologic Failure (Breakthrough) Confirmation	Early Discontinuation
			Weeks 1 and 2	Week 4	Weeks 8, 12, 14, 16, 28				
Consent	✓								
Documentation of HIV, HCV, and Cirrhosis Status, and Past Labs	✓								
Medical & Medication History	✓	✓							
Clinical Assessments	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood Collection & Laboratory Testing	✓	✓	✓	✓	✓	✓	✓	✓	✓
Urine Sample for Substance/Drug Use Test		✓	✓	✓	✓	✓	✓		✓
Pregnancy Test	✓	✓	✓	✓	✓		✓		✓

Evaluation or Test	Screening	Entry	Post-Entry Visits			Unplanned Visits	HCV Virologic Failure Confirmation	HIV Virologic Failure (Breakthrough) Confirmation	Early Discontinuation
			Weeks 1 and 2	Week 4	Weeks 8, 12, 14, 16, 28				
Blood Collection for Pharmacokinetic (PK) Studies		✓	✓	✓	✓ (wks 8, 12, 16)	✓	✓	✓	
Optional Hair Collection for PK Studies		✓		✓	✓ (wk 16)	✓	✓	✓	✓
Pregnancy Prevention Counseling	✓	✓		✓	✓ (wk 8)	✓			✓
Adherence Assessments		✓	✓	✓					✓
HCV Risk Factors Assessment		✓	✓	✓	✓ (wks 8, 16, 28)				
Health Outcomes Questionnaire		✓		✓	✓ (wks 16, 28)				
Health Care Utilization Questionnaire		✓		✓	✓ (wks 16, 28)				
Study Medication Distribution		✓							
HCV Reinfection Prevention Counseling		✓		✓	✓ (wks 8, 16, 28)				
Contact Information		✓		✓	✓ (wks, 8, 12)				
Reminder for Week 16 Visit					✓ (wk 14)				

I. Description of Part 1 Study Visits

Part 1 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 several tests, including blood tests, to make sure that you qualify to join this study. Some of the blood taken will be shipped to a testing lab. Your new HCV diagnosis and approximately how long you've been diagnosed with HCV will be confirmed. This visit will take about 1-2 hours. At this visit:

- Your HIV status will be confirmed. If there is no record available, another HIV test will be done. You may have to sign a separate consent form before this is done.
- Your HCV diagnosis status will be confirmed. HCV RNA (to measure the level of the HCV in the blood) and genotype (to determine the genetic makeup of your HCV) will also be done. If available, information about cirrhosis (liver damage) status will be collected.
- Your lab results from the past 12 months (if available) will be documented for liver function and HCV tests.
- You will be asked questions about your medical history and any medications you are taking or have taken in the past.
- You will have a complete physical exam, including vital signs (temperature, pulse, respiration rate [the number of breaths you take in a minute], and blood pressure), and weight.
- You will have blood drawn to see if you are diagnosed with the hepatitis A or B virus (an infection of the liver); for routine lab tests for safety; for virologic studies (to help study the virus); for serologic studies (to study how your immune system responds HCV); if you are living with HIV, to measure the amount of HIV in your blood, and to measure your CD4+ and CD8+ cell counts (cells that help fight infection). Some of the blood you provide will be stored for future protocol-required testing.
- If you are a woman and able to get pregnant, some of your blood or urine will be tested for pregnancy. You will also receive counseling on pregnancy prevention. Men will also be counseled on ways to not impregnate a woman while taking study medication.
- For female participants, who report not being able to get pregnant, and have no medical record to confirm, follicle stimulating hormone-release factor (FSH) will be measured.

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 at birth, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4+ T-cell count, 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.

Part 1 Entry

If all of the results from your screening tests show that you are eligible and you decide to take part, you will be enrolled in this study.

- You will be asked about your health and any changes in your medicines since your last visit. You will have a brief physical exam including vital signs, height, and weight.

- If you are a woman and able to get pregnant, some of your blood or urine will be tested for pregnancy.
- You will provide a urine sample to look for the use of drugs.
- You will have blood drawn for routine lab tests for safety, virologic, immunologic (to test how your body fights infection), and pharmacokinetic studies (to look at your body's response to the study medication). If you are living with HIV, blood will be drawn to measure the amount of HIV in your blood, and to measure your CD4+ and CD8+ cell counts. Some of the blood you provide will be stored for future protocol-required testing.
- You will provide a hair sample for PK studies (this helps us learn more about how your body handles the study medication). This is optional.
- You will receive 4 weeks of study medication (G/P) to take home with you.
- You will receive adherence counseling as described below.
- You will be asked questions about how well you take your ARVs (if applicable).
- If you are a woman and able to get pregnant, you will be counseled on ways to not become pregnant while taking study medication. Men will also be counseled on ways to not impregnate a woman while taking study medication.
- You will be asked questions about the use of drugs.
- You will be asked questions about risk factors for HCV.
- You will receive counseling on how not to become re-infected with HCV.
- 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. 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.

Study Medication

At your entry visit (for Part 1), the study staff will give you your study medication for the whole 4-weeks of treatment to take home. You will need to store the medications in a safe place at room temperature (between 15º to 25 ºC [59º to 77ºF]).You need to take the study medication G/P for Part 1 with food. You will take three pills every day for 4 weeks. If you forget to take the study medication at the correct time, you may take it later in the day as soon as you remember. Then the next day you should continue with the usual schedule that you take the study medication. You should always take all 3 pills together. If you miss doses entirely, simply resume 3 pills the next day and do not ever double the dose (do NOT take 6 pills). Do not split or crush the pills or the split the medication doses. After you have completed 4 weeks of treatment with G/P, you will continue to have follow-up visits for 24 weeks.

Everyone who enters this study will take a FDC of G/P, which will be given for free by the study. For those who are living with HIV, your ARVs will not be provided by the study. These will be provided by your regular non-study HIV provider.

Part 1 Post-entry Visits

After your entry visit, you will come to the clinic at weeks 1, 2, 4 (end of treatment), 8, 12, 16, and 28. These visits will last about 1-1½ hours each.

Reminder for Week 16 Visit

Study staff will contact you at week 14 in Part 1, to schedule your week 16 visit.

During Most Study Visits for Part 1

- You will be asked about your health and any changes in your medicines since your last visit.
- You will have a brief physical exam including vital signs and weight (weight only done Weeks 4, 16, and 28).
- You will have blood drawn for routine lab tests for safety, virologic, immunologic, pharmacokinetic, and serologic studies (if needed); to measure the amount of HCV in your blood. If you are living with HIV, the amount of HIV in your blood and your CD4+ and CD8+ counts will be measured. Some of the blood you provide will be stored for future protocol-required testing.
- If you are a woman and able to get pregnant, some of your blood or urine will be tested for pregnancy at all on-treatment and post-treatment visits and study discontinuation.
- You will provide a urine sample to look for the use of drugs.
- You will provide a hair sample for PK studies at weeks 4 and 16. This is optional.
- You will be asked questions about how well you take your ARVs (if applicable) at weeks 1, 2, and 4.
- All participants, male and female, will be counseled on the risk of the study medication in pregnancy and on how to prevent pregnancy while taking study medication at weeks 4, and 8.
- You will be asked questions about the use of drugs at weeks 1, 2, 4, 8, 16, and 28.
- You will be asked questions about risk factors for HCV at weeks 1, 2, 4, 8, 16, and 28.
- You will receive counseling on how not to become re-infected with HCV at weeks 4, 8, 16, and 28.
- Study staff will update your contact information at weeks 4, 8, and 12. This contact information will be used to remind you about upcoming study visits. If study staff are unable to reach you after two tries, they will try to reach you via your second contact.

Unplanned visits

During the study, you may have to come back to the clinic for extra visits for testing of any lab results that are not normal, or to follow up on a specific side effect or symptom.

HCV Virologic Failure Confirmation

If laboratory tests show there is evidence of virologic failure (the amount of HCV in your blood is still detectable when tested), you will be asked to return to the clinic to confirm your lab results. At this visit:

- You will have a brief physical exam including vital signs and weight.
- You will have blood drawn for routine lab tests for safety, serologic, virologic, immunologic, and pharmacokinetic studies, and to measure the amount of HCV in your blood, for an HCV resistance test (resistance means that the drugs are not likely to fight the HCV in your body). If you are living with HIV, the amount of HIV in your blood will be measured. Some of the blood you provide will be stored for future protocol-required testing.
- A urine sample will be taken for the substance use screen.
- If you are a woman and able to get pregnant, some of your blood or urine will be tested for pregnancy. You will also receive counseling on pregnancy prevention. Men will also be counseled on ways to not impregnate a woman while taking study medication.
- You will be asked to stay on the study and complete all of the study visits.

- If you choose, you will provide a hair sample for PK studies.

HIV Virologic Failure (Breakthrough) Confirmation
If laboratory tests show there is evidence of HIV virologic failure (the amount of HIV in your blood is still detectable when tested) you will be asked to return to the clinic to confirm your lab results. At this visit:

- You will have a brief physical exam including vital signs.
- You will have blood drawn for routine lab tests for safety and pharmacokinetic studies and to measure the amount of HIV in your blood, for an HIV resistance test (resistance means that the drugs are not likely to fight the HIV in your body).
- If you choose, you will provide a hair sample for PK studies.
- You will be asked to stay on the study and complete all of the study visits.

Early discontinuation
If HCV virologic failure is confirmed, you will then complete an early discontinuation visit. You will have the option to enroll in Part 2 of the same study after your discontinuation evaluations have been completed in Part 1. There are three types of discontinuation (early discontinuation of Part 1, stopping study treatment early, or leaving the study early) in which you will be asked to come to the clinic for an extra visit.

1. *Early discontinuation of Part 1*
   You stop taking medications or stop follow up in Part 1 for HCV virologic failure and have the option to transition to Part 2.

2. *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 some tests. You would not have the option to enter Part 2.

3. *Leave study early*
   You or your doctor decides that you will no longer stay in the study or you are notified that the study is stopped early. You will be asked to complete some evaluations before being taken off the study. You would not have the option to enter Part 2.

II. Description of Part 1 Study Evaluations

Consent
After you read this consent form and have had a chance to ask questions about the study, you will sign this consent form if you want to continue to be tested to see if you qualify for the study.

Documentation of HCV, HIV, cirrhosis status, and previous labs
Study staff will check your medical records for the availability of test results for HCV, HIV, and cirrhosis. Study staff will also check your medical records for the availability of liver function tests from the previous 12 months.

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

Physical examination
You will have a physical exam. The study staff will check the different systems in your body such as head, neck, eyes, ears, nose, throat, mouth and tongue, chest (excluding breasts) for respiratory, heart for cardiovascular, 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 not be recorded at every visit.

Medical and medication history
You will be asked questions about your health and any medicines you have taken or are taking now. Once you are on treatment, 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. These may include: routine safety lab tests such as hematology (the study of blood), coagulation markers (how your blood clots), kidney and liver function, and HCV viral load (a test that shows how much HCV is in your blood). For those who are living with HIV, HIV viral load (a test that shows how much HIV is in your blood), and CD4+/CD8+ counts (a test that shows how many infection-fighting cells you have in your blood) will be done.

Resistance testing
Blood will be drawn and stored for future HCV/HIV resistance testing that is required for this study. A resistance test is used to determine if the HCV/HIV viruses still respond to your medications.

Genetic testing
Some of your blood cells will be tested to see if your responsiveness to the therapy is associated with different genes related to the immune system that fights viruses. You will not receive the results of these studies because they will be done in the future.

Your initials below confirm your voluntary decision to give permission for the collection, storage, and use of your blood for this genetic testing.

You do not have to give permission for storage of these samples. This will not affect your participation in the study, and you may withdraw your permission for genetic testing sample storage at any time.

_____ YES _____ NO

PK Studies
Blood will be drawn and hair samples taken to measure the levels of the drugs in your blood and to understand how the drugs interact with your body and how your body responds to the drugs. Hair sampling is optional.

Your initials below confirm your voluntary decision to give permission for the collection, storage, and use of your hair samples.

You do not have to give permission for storage of these samples. This will not affect your participation in the study, and you may withdraw your permission for hair sample storage at any time.

_____ YES _____ NO

Pregnancy test
If you are a woman who is able to become pregnant, you will have blood or urine taken for pregnancy testing, or have a Point of Care (POC) (a test with results available the same day) test done, prior to study entry. After you enter the study, you will be asked to provide blood or urine samples for pregnancy testing.

Urine Sample for Substance/Drug Use
Urine sample for substance use screening will be done at study entry, and at every Part 1 study visit, HCV virologic failure confirmation, and early discontinuation visits.

Pregnancy prevention counseling
All participants, male and female, will be counseled on the risk of the study medication in pregnancy and how to prevent pregnancy.

Adherence counseling and assessment
You will be asked about how well you take your medications. The study staff will give you information and encouragement to help you take your medications as prescribed.

Study medication distribution
You will be given a 4-week supply of study medication at entry. You will be asked to store the study medication as instructed on the medicine bottle label and to bring any leftover study medication back to the clinic at week 4.

Questionnaires
You will be asked to fill out the following questionnaires:

Risk Factor Assessment
You will be asked questions about drug use, sexual habits, and other risk factors for getting HCV.

Health Outcomes Questionnaire
You will be asked questions about how you are feeling and how you are doing with your daily activities.

Health Care Utilization Questionnaire
You will also be asked questions if you have stayed at a hospital or been to an emergency room.

HCV Reinfection 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. Study staff will talk with you about how you could become re-infected with HCV after being cured and ways to decrease risk of reinfection.

Contact Information
Study staff will ask you about the best way to reach you when they need to contact you remotely. 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.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your blood will be stored and used for study-required pharmacologic, immunologic, and virologic testing. For non-US locations, biological specimens will be shipped and/or stored outside of the country from which they are collected.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.

Some blood that is collected from you during the study may be left over after all required study testing is done. This blood will be stored and, if you give your consent below, may be used for ACTG-approved research. This means that researchers who are not part of the protocol team may use your samples without asking you again for your consent. As noted above, none of your samples will have any private information about you on their labels.

You may decide whether this “extra” blood may be stored and, if so, whether additional testing may be performed on it. None of this testing will be used for commercial profit.

At this time, we do not know whether any of the research will include testing of your genes or your DNA (your own genetic information). We do not know whether a type of testing called whole genome sequencing, or WGS, might be done. In WGS, researchers look at all of your genes and at almost all of your DNA. In “standard” genetic testing, researchers look at specific

genes or subsets of genes, but not at all genes. Some possible genetic testing is described below.

For each of the questions below, choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selections.

Research Without Human Genetic Testing – OPTIONAL (Research on leftover blood; no human genetic testing)

If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my blood.

OR

____ (initials) I understand but I do not agree to this storage or possible use of my blood.

Research With Human Genetic Testing – OPTIONAL (Human genetic research on leftover blood)

If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that includes human genetic testing, and may include whole genome sequencing (WGS).

____ (initials) I understand and I agree to this storage and possible use of my blood.

OR

____ (initials) I understand but I do not agree to this storage or possible use of my blood.

Sharing Genetic Data - OPTIONAL

Genetic Research Databases: If you agreed to possible genetic testing of your blood above, researchers may want to share genetic information (with protection of your identity) with other researchers around the world, so that they can learn more about the causes and treatment of diseases. They may store this information in dbGaP, a genetic database maintained by the National Institutes of Health, as well as in other protected databases.

____ (initials) I understand and I agree to this possible sharing of my genetic data.

OR

____ (initials) I understand but I do not agree to this possible sharing of my genetic data.

HOW MANY PEOPLE WILL TAKE PART IN PART 1 OF THIS STUDY?

Up to 50 people (men and women age 18 years and older) will take part in Part 1 of this study.

HOW LONG WILL I BE IN PART 1 OF THIS STUDY?

You will be in Part 1 of this study for approximately 28 weeks. If you are not cured of HCV or are infected again with HCV in Part 1, and you agree, you will enter Part 2 of the study, and you will be in Part 2 for 20-40 weeks.

WHY WOULD THE DOCTOR TAKE ME OFF PART 1 OF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- the study is cancelled.
- a Study Monitoring Committee (SMC) recommends that the study be stopped early (An SMC is an outside group of experts who monitor the study for safety).
- 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 medication without your permission if:
- you become pregnant.
- you are breastfeeding.
- continuing the study medication may be harmful to you.
- you need a treatment that you may not take while on the study.
- you are not able to take the study medication as required by the study.
- you have not had, or are not able to have the required study visits and evaluations.

If you must stop taking the study medication earlier than indicated by the study, the study doctor will ask you to remain on the study and complete post-discontinuation visits from the date that you took the last dose of study medication.

<u>If I have to permanently stop taking study medication during Part 1 of the study, or once I leave the study, how can I get study medication?</u>
If you must permanently stop taking study medication 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 G/P through the study.

WHAT ARE THE RISKS OF THE STUDY?
No clinical safety issues specifically related to G/P have been identified to date in HCV mono-infected or HIV-1/HCV co-infected participants without cirrhosis or with compensated cirrhosis (the liver is heavily scarred but can still perform many important bodily functions).

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 diagnosed with HCV and/or living with 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 Medication
The drugs used in this study may have side effects, some of which are listed below. Please note that this list does not include all the side effects seen with this medication. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning study medication side-effects, please ask the medical staff at your site. To assist you in understanding your risk of side effects we have included reported percentages of these events in clinical studies of the medications concerned.

Glecaprevir/pibrentasvir (G/P)
- Headaches- 9-16%
- Fatigue- 11-14%
- Diarrhea- 3-7%
- Nausea- 6-12%
- Asthenia (abnormal physical weakness or lack of energy) – 7%
- Pruritic skin (itchy skin) – 17%
- Abnormal liver function tests- 3.5%

There is a risk of serious and/or life-threatening side effects when some non-study medications are taken with the study medication. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and 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. If you believe you are having side effects from any of the study medications make sure to immediately inform your study team.

Bradycardia, or slow heart rate, may happen in persons who are taking digoxin (a medicine that is used to treat heart failure and heart rhythm problems) particularly for those with a heart disorder and/or advanced kidney disease. Because of this risk the dose of digoxin must be reduced by about half in persons taking G/P and be closely monitored. It is also not recommended to take G/P with cholesterol lowering medications such as simvastatin, lovastatin, or atorvastatin. Other cholesterol lowering medications such as fluvastatin, pravastatin, pitavastatin, and rosuvastatin can be used but either at lower doses or at the same dose with careful monitoring; you will need to check with your doctor.

Drug interactions that increase the levels of medicine in your blood may increase the chances of side effects. Drug interactions that could affect the levels of G/P or HIV medicines in your blood could cause changes in liver enzymes and other abnormal blood tests. For certain ARVs, we may ask you to change them to another medication to reduce this risk. Drug interactions that lower the levels of glecaprevir or pibrentasvir in your blood may decrease your chances for a cure of hepatitis C and/or cause drug resistance (the virus changes form and drugs that used to work, no longer work).

For those persons taking HIV medicines, efavirenz can lower the levels glecaprevir or pibrentasvir in your blood and affect the potency of this drug in the fighting hepatitis C virus. The HIV medication atazanavir when it is taken together with G/P can cause increases in liver enzymes and the combination should be avoided. Study staff will review the list of all medications that should not be taken while in this study. Examples of other medications that should not be taken with G/P include:

- St. John's wort
- Carbamazepine
- Rifampin
- Ethinyl estradiol containing birth control pills

Drug resistance may prevent other medicines from working in the future. HCV viral load will be monitored regularly to ensure that evidence of early failure of the HCV regimen is identified quickly. Development of resistance after failing G/P has not been studied that well. However, studies so far suggest that use of G/P could select for mutations (permanent changes in genetic material) in the NS3 and NS5A gene which could cause varying levels of resistance to glecaprevir and pibrentasvir. The impact of these resistance associated mutations is still not known.

Some people with HCV and HBV coinfection receiving therapy for HCV with direct-acting antivirals (DAA) like G/P have experienced reactivation of the HBV. Some of these cases have led to severe hepatitis, liver failure and death. This has been reported in people who are positive for HBsAg (HBV surface antigen [a foreign substance in your body that cause antibodies {cells that fight infection} to develop]) and those who appear to have resolved HBV infection by lab tests. If you have ever been diagnosed with HBV let your study doctor/nurse know.

ARE THERE RISKS RELATED TO DELAYING HIV THERAPY?

You are not required to be on ARVs to enter this study. If you are not on ARVs at the time you are diagnosed with HCV and you and your doctor do not think you need to start ARVs, you will not be excluded from the study. Also, it is not recommend**ed** that the start of HIV therapy be delayed for entry into the study if your doctor feels they are medically necessary. Although the dosing period of the study HCV medication is short, a delay in necessary HIV therapy could allow for progression of HIV disease, which can increase your risk of opportunistic infections and long-term effects of living with HIV. If you have any concerns about these risks, you should discuss them with your provider.

WHAT IF I AM DIAGNOSED WITH HIV DURING THIS STUDY?

If you are diagnosed with HIV during this study, study staff will tell you about any available care. Study staff will counsel you about HIV. They will also tell you how to lower the risks of giving HIV to others. Researchers may ask you to continue with this study.

ARE THERE RISKS RELATED TO PREGNANCY?

The drugs or drug combinations in this study may be unsafe for unborn babies. Therefore, becoming pregnant is not allowed. If you are having sex that could lead to pregnancy, you must agree not to become pregnant. If you become pregnant, you will be followed after delivery.

Because of the potential risk involved and due to the uncertainty of risk to the fetus, you and your partner must use birth control. In Part 1, you must use one of the birth control methods, listed below, while receiving study medication, and for 6 weeks after stopping the medication.

- Condoms (either self or require their partner to use one) with spermicide
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormone-based contraceptive (not ethinyl-estradiol containing)
- Tubal ligation

If you can become pregnant, you must have a pregnancy test within 48 hours before starting the study medication. The test must show that you are not pregnant. Pregnancy tests will also be performed at most study visits.

If you are man who gets a woman pregnant, then you will be asked to report this event to study staff. You may also be asked to report on your partner's pregnancy outcomes.

Some of the methods listed above may not prevent the spread of HIV to other people. If you are living 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.

If you think you may be pregnant or are a male who impregnates a female at any time during the study, tell your study staff right away. Pregnancy will result in immediate discontinuation of the study medications. You will be followed on study until study completion. You will be asked to return to the clinic 6 months after the end of your pregnancy to follow up on any side effects. Pregnancy complications and/or pregnancy outcomes will be reported to the company that makes G/P, AbbVie, by way of the sponsor (NIAID). If you are also living with HIV and become pregnant while on study, pregnancy complications and/or pregnancy outcomes will be reported to the Antiretroviral Pregnancy Registry.

It is not known if G/P is present in breast milk in women who are breastfeeding. Studies done in animals however show that there are low concentrations of the drug in breast milk in laboratory

rats. This did not appear to affect these animals. Breastfeeding is not allowed while on G/P.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you (your HCV may be cured), but no guarantee can be made. Your health may be watched more closely than usual while you are in this study, which may help you to feel better. 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 living with HIV. Also, the benefits of limiting the potential transmission of HCV to others, benefits others in society and saves in cost of treatment for others.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study, you have the choice of:

- treatment with other prescription drugs currently available to you
- treatment with other experimental regimens, if you qualify
- no treatment; some people may clear HCV on their own over the first year of infection

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 medications, 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. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research 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 that an incentive of USD XX will be provided to participants in addition to routine compensation if they complete the post-treatment* w*eek 12 visit within the visit window.*]

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 A5380 Part 1

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

APPENDIX II: STEP 2 SAMPLE INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
For protocol: A5380

FINAL Version 1.0, 06/07/19: A Phase II Trial of Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection (PURGE-C)

SHORT TITLE: Glecaprevir/Pibrentasvir Fixed-dose Combination Treatment for Acute Hepatitis C Virus Infection Including Persons with HIV

PART 2 SUMMARY

PURPOSE

The purpose of Part 2 of this study is to see if longer treatment cures your hepatitis C (HCV). People with acute HCV have a good chance of being cured of the infection when they are treated with a combination of two drugs within the first 6 months of getting HCV.

NUMBER OF PARTICIPANTS

There will be 2 parts of the study for a total of up to 50 participants.

LENGTH OF STUDY

Part 2 of the study will last about 20-40 weeks.

You will need to come back to the clinic up to 8 more times in the next 20-40 weeks.

REQUIRED ACTIVITIES

Blood and urine collections
At most visits, some blood will be collected from a vein in your arm. At a few visits, you will be asked to provide a urine sample.

Special procedures
You will be asked questions about potential risks of becoming infected with HCV.

RISKS

The following are possible:

- People outside of the study may find out that you are participating in this study and treat you unfairly.
- Discomfort, lightheadedness, bleeding, swelling, or bruising from drawing blood
- Side effects from the study medications
- Drug resistance, making your HCV more difficult to treat

- If you are living with HIV, drug interactions with your HIV drugs while taking the study medications.
- If you have hepatitis B (HBV) and HCV, reactivation of HBV.

BENEFITS You may be cured of your HCV but no guarantee can be made.

OTHER CHOICES Instead of being in this study, you have the option of continuing with your current treatment, starting a new treatment under the care of your regular doctor or other health care provider, or no treatment at all. Your participation in this study is completely voluntary.

INTRODUCTION

You are being asked to continue to take part in Part 2 of this research study because your HCV was not cured in Part 1 of the study or you may have been infected again after getting cured. 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 Part 2 of this study, we want you to know about Part 2 of the study.

This is a consent form. It gives you information about Part 2 of 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 Part 2 of this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

As mentioned in Part 1 of this study, people who are recently infected with a new case of HCV are often considered to have acute HCV. People with acute HCV have a good chance of being cured of the infection when they are treated with a combination of two drugs within the first 6 months of being diagnosed. However, after 4 weeks of the HCV drug, glecaprevir/pibrentasvir (G/P), in Part 1 of this study, the HCV is present again in your blood. It is also possible that you may have been infected again with hepatitis C after you were cured in Part 1. Therefore, this Part 2 of the study is being done to see if a longer course of treatment will cure your HCV. In Part 2 of this study, you will take 3 tablets of G/P by mouth daily for either 8, 12, or 16 weeks. It is possible another drug named ribavirin (RBV) will be added. The length of treatment will be decided from various lab tests. It is also possible that the study doctor will suggest a different HCV drug.

The medication that is provided in this study is approved by the Food and Drug Administration (FDA) for use in persons who have been diagnosed with HCV.

You will be monitored for safety and viral response (how your body is responding to treatment and whether the amount of HCV in your body is decreasing) while on treatment. After completing treatment, you will be evaluated to see how your body responded to treatment at various time points up to 24 weeks of the study.

WHAT DO I HAVE TO DO IF I AM IN PART 2 OF THIS STUDY?

If you decide to be in Part 2 of this study, after you have read and signed this informed consent form, you will come to the clinic for an entry visit to make sure you meet the requirements to continue treatment for your HCV in this part of the study.

You may have as little as 2.5 tablespoons to as much as 11 tablespoons of blood collected at any one visit. Over the course of the study, the amount of blood collected from you will be within approved limits.

If you are also living with HIV, you will continue taking your current anti-HIV drugs (antiretrovirals [ARVs]- medications to control HIV) if you are receiving them. If you are not currently on ARVs and your provider does not think you will need ARVs for the next 8, 12, or 16 weeks, this is also acceptable. If your HIV regimen includes atazanavir, atazanavir/cobicistat, and atazanavir/ritonavir, efavirenz, etravirine, fosamprenavir/ritonavir, indinavir/ritonavir, lopinavir/ritonavir, nelfinavir, nevirapine, saquinavir/ritonavir, or tipranavir/ritonavir, you will need to be switched to another HIV regimen. You will need to be sure that your HIV provider discusses all changes to your HIV regimen with the study doctor. See section I for a description of the study visits.

After the entry visit, you will be given your study medication for the first 4 weeks of treatment to take home. Study medication (G/P and possibly RBV) will be given to you for free by the study. If you have HIV, your ARVs will not be provided by the study. These will be provided by your regular non-study HIV provider. Your study physician may also decide to treat your HCV based on local standard of care, and these medications would not be provided by the study. Details on study medication for Part 2 of this study can be found below under Description of Part 2 Study Visits. After you have completed 8, 12, or 16 weeks treatment with G/P, you will continue to have follow-up visits for 24 weeks (depending in whether you also take RBV). Alternatively, your study doctor may choose a sofosbuvir-containing regimen for you. If so, you may continue to have follow-up visits in the study.

While you are in Part 2 of the study, you will need to be seen in the clinic about 5-8 times. The number of required clinic visits will depend on which HCV medications you are taking and the length of treatment. The study staff will tell you about how long each visit could be. You will have blood drawn for study-related tests at each visit to monitor your response to the study medications and to look for any side effects that may be caused by the medications.

You may need to make extra visits to the clinic if you have side effects or if you switch or take new ARVs. 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 when they are available.

A5380 Part 2 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.

Appendix II, Table 1: Part 2 Study Schedule

Evaluation or Test	Entry	Post-Entry Visits		Unplanned Visits	HCV Virologic Failure Confirmation	HIV Virologic Failure (Breakthrough) Confirmation	Early Discontinuation
		On-treatment Visits	Off-treatment Visits				
Clinical assessments	✓	✓	✓	✓	✓		✓
Blood collection & laboratory testing	✓	✓	✓	✓	✓	✓	✓
Blood Collection for PK Studies		✓		✓	✓	✓	✓
Pregnancy test	✓	✓	✓				✓
Pregnancy prevention counseling	✓	✓	✓				✓
Re-infection Prevention Counseling	✓	✓	✓				✓
Questionnaire	✓	✓	✓	✓			✓
Distribution of Study Medication	✓	✓					

I. Description of Part 2 Study Visits

Part 2 Entry

Once HCV confirmation results are available for the study doctor to review and it is confirmed that you meet all the other eligibility criteria, you will be enrolled into Part 2 of the study. This visit will take about 1-2 hours. At this visit:

- Documentation of Step 2 eligibility will be confirmed.
- Your HIV status will be confirmed.
- You will be asked about your health and any changes in your medicines since your last visit. You will have a brief physical exam including vital signs and weight.
- If you are a woman and able to get pregnant, some of your blood or urine will be tested for pregnancy. Such women will also be counseled on ways to not become pregnant while taking study medications. Men will also be counseled on ways to not impregnate a woman while taking study medications.

- You will have blood drawn to see if you are diagnosed with the HAV or HBV (an infection of the liver), for routine lab tests for safety, for virologic studies (to help study the virus), and immunologic studies (to test how your body fights infection). If you are living with HIV, you will have your blood drawn to measure the amount of HIV in your blood, and to measure your CD4+ and CD8+ cell counts (a test that shows how many infection-fighting cells you have in your blood). Some of the blood you provide will be stored for future protocol-required testing.
- You will receive study medications to take home with you.
- You will be asked questions about risk factors for HCV.
- You will receive counseling on how not to become re-infected with HCV.
- You will agree to continue taking combination ARVs as prescribed throughout the entire study.

Study Medication

At your Part 2 entry visit, study staff will give you your study medications for the first 4 weeks of treatment to take home. You will need to store the medications in a safe place at room temperature (between 15º to 25ºC [59º to 77ºF]). You would need to take the study medication, G/P, with food. You will take three pills every day for 8, 12, or 16 weeks, as instructed by the study doctor/nurse. If you forget to take the study medication at the correct time, it may be taken later in the day as soon as you remember. Then the next day you should continue with the usual schedule that you take the study medications. You should always take all 3 pills together. If you miss doses entirely, simply resume 3 pills the next day and do not ever double the dose (do NOT take 6 pills). Do not split the pills or the medication doses. After you have completed 8, 12, or 16 weeks of treatment with G/P as may be determined by your study investigator, you will continue to have follow-up visits for 24 weeks (depending in whether you also take RBV).

Some participants who enroll in Part 2 will also take RBV, which will be provided by the study. If you need to take RBV, it must be taken with food for it to work well. RBV should be taken twice a day. All other HCV medications other than these will be used at the discretion of your study provider based on local standard of care in discussion with the study team. These other medications will not be provided by the study and as such any risks related to other alternate regimens will not be covered under this consent. If you and your study doctor choose that option in Part 2 you could still remain on the study on that regimen and continue all required study visits up to 12 weeks after completing your given regimen.

Part 2 Post-entry Visits

After your entry visit for Part 2, you will come to the clinic at weeks 2, 4, 8, 12, and 16, and weeks 20, 24, or 28 (depending on study regimen chosen by your doctor), and weeks 32, 36, or 40 (if necessary). These visits will last about 1-1½ hours each.

- For this part of the study, there will be about 4 study medication regimens with varying visit schedules. Study staff will talk to you about this visit schedule according to the drug regimen chosen for you.

During Most Study Visits for Part 2

- You will be asked about your health and any changes in your medicines since your last visit.
- You will have a brief physical exam including vital signs and weight.

- You will have blood drawn for routine lab tests for safety, virologic, immunologic, and pharmacokinetic (to look at your body's response to the study medication) studies; and to measure the amount of HCV in your blood. If you are living with HIV, the amount of HIV in your blood and your CD4+ and CD8+ counts will be measured. Some of the blood you provide will be stored for future protocol-required testing.
  If you are a woman and able to get pregnant, some of your blood or urine will be tested for pregnancy at all on-treatment and post-treatment visits and study discontinuation.
- All participants, male and female, will be counseled on the risk of the study medications in pregnancy and on how to prevent pregnancy while taking study medications.
- You will be asked questions about drug use, sexual habits, and other risk factors for getting HCV.
- You must return any remaining study medication before your last study visit.

Unplanned visits
During the study, you may have to come back to the clinic for extra visits for testing of any lab results that are not normal, or to follow up on a specific side effect or symptom. During any unplanned visits, you may have the following tests done: clinical assessments, blood collection (including for PK studies) and laboratory testing, and complete a questionnaire.

HCV Virologic Failure Confirmation
If laboratory tests show there is evidence of virologic failure (the amount of HCV in your blood is still detectable when tested), you will be asked to return to the clinic to confirm your lab results. At this visit:
- You will have a brief physical exam including vital signs and weight done.
- You will have blood drawn for routine lab tests for safety, virologic, immunologic, and pharmacokinetic studies, to measure the amount of HCV in your blood, and for an HCV resistance test (resistance means that the drugs are not likely to fight the HCV in your body). If you are living with HIV, to measure the amount of HIV in your blood. Some of the blood you provide will be stored for future protocol-required testing.
- You will be asked to stay on the study and complete all of the study visits.

HIV Virologic Failure (Breakthrough) Confirmation
If laboratory tests show there is evidence of HIV virologic failure (the amount of HIV in your blood is still detectable when tested), you will be asked to return to the clinic to confirm your lab results. At this visit:
- You will have blood drawn for pharmacokinetic studies, HIV RNA (to measure the level of the HIV in the blood) and for an HIV resistance test (resistance means that the drugs are not likely to fight the HIV in your body; also known as genotyping) will also be done.
- You will be asked to stay on the study and complete all of the study visits.

Early discontinuation
If HCV virologic failure is confirmed, you will then complete an early discontinuation visit. There are two types of discontinuation (stopping study treatment early or leaving the study early) in which you will be asked to come to the clinic for an extra visit. Participants in Step 2 who have

HCV virologic failure confirmed will be followed through 12 weeks (or 24 weeks, if RBV is given) after treatment completion or is discontinued, and no further treatment will be provided by the study.

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 some tests.

2. *Leave study early*
   You or your doctor may decide that you will no longer stay in the study or you are notified the study is stopped early. You will be asked to complete some evaluations before being taken off the study.

II. Description of Part 2 Study Evaluations

Clinical Assessments
You will have a brief physical exam. The study staff will check your vital signs such as temperature, pulse, blood pressure, respiratory rate, and weight. 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. These may include: routine safety lab tests such as hematology (the study of blood), kidney and liver function; and HCV viral load (a test that shows how much HCV is in your blood). For those who are living with HIV, HIV viral load and CD4+/CD8+ counts.

Resistance testing
Blood will be drawn and stored for future HCV/HIV resistance testing that is required for this study. A resistance test is used to determine if the HCV/HIV viruses still respond to your medications.

PK Studies
Blood will be drawn to measure the levels of the drugs in your blood and to understand how the drugs interact with your body and how your body responds to the drugs.

Pregnancy test
If you are a woman who is able to become pregnant, you will have blood or urine taken for pregnancy testing, or have a Point of Care (POC) test (a test with results available the same day) test done prior to study entry. After you enter the study, you will be asked to provide blood or urine samples for pregnancy testing.

Pregnancy prevention counseling
All participants, male and female, will be counseled on the risk of the study medications in pregnancy and how to prevent pregnancy.

Study medication distribution
Due to the longer treatment course (compared to Part 1 of the study), you will be given a 4-week supply of study medication at your return study visits as indicated based on the length of therapy. You will be asked to bring any leftover study medication back to the clinic up to week 16 (depending on your drug regimen in Part 2).

Questionnaire
You will be asked to fill out the following questionnaire:

Risk Factor Assessment
You will be asked questions about drug use, sexual habits, and other risk factors for getting HCV.

HCV Reinfection 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. Study staff will talk with you about how you could become re-infected with HCV after being cured and ways to decrease risk of reinfection.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your blood will be stored and used for study-required pharmacologic, immunologic, and virologic testing. For non-US locations, biological specimens will be shipped and/or stored outside of the country from which they are collected.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.

Some blood that is collected from you during the study may be left over after all required study testing is done. This blood will be stored and, if you give your consent below, may be used for ACTG-approved research. This means that researchers who are not part of the protocol team may use your samples without asking you again for your consent. As noted above, none of your samples will have any private information about you on their labels.

You may decide whether this “extra” blood may be stored and, if so, whether additional testing may be performed on it. None of this testing will be used for commercial profit.

At this time, we do not know whether any of the research will include testing of your genes or your DNA (your own genetic information). We do not know whether a type of testing called whole genome sequencing, or WGS, might be done. In WGS, researchers look at all of your genes and at almost all of your DNA. In "standard" genetic testing, researchers look at specific genes or subsets of genes, but not at all genes. Some possible genetic testing is described below.

For each of the questions below, choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selections.

Research Without Human Genetic Testing – OPTIONAL (Research on leftover blood; no human genetic testing)

If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my blood.

OR

____ (initials) I understand but I do not agree to this storage or possible use of my blood.

Research With Human Genetic Testing – OPTIONAL (Human genetic research on leftover blood)

If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that includes human genetic testing, and may include whole genome sequencing (WGS).

____ (initials) I understand and I agree to this storage and possible use of my blood.

OR

____ (initials) I understand but I do not agree to this storage or possible use of my blood.

Sharing Genetic Data - OPTIONAL

Genetic Research Databases: If you agreed to possible genetic testing of your blood above, researchers may want to share genetic information (with protection of your identity) with other researchers around the world, so that they can learn more about the causes and treatment of diseases. They may store this information in dbGaP, a genetic database maintained by the National Institutes of Health, as well as in other protected databases.

____ (initials) I understand and I agree to this possible sharing of my genetic data.

OR

____ (initials) I understand but I do not agree to this possible sharing of my genetic data.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

The number of people who enroll in Part 2 will depend upon participants' responses to the study medication in Part 1.

HOW LONG WILL I BE IN PART 2 OF THIS STUDY?

You will be in Part 2 of this study for approximately 20-40 weeks.

WHY WOULD THE DOCTOR TAKE ME OFF PART 2 OF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- the study is cancelled.
- a Study Monitoring Committee (SMC) recommends that the study be stopped early (An SMC is an outside group of experts who monitor the study for safety).
- 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 medications without your permission if:
- you experience HCV treatment failure.
- you become pregnant.
- if you are a male whose female partner becomes pregnant (only if you are taking RBV).
- you are breastfeeding.
- continuing the study medications may be harmful to you.
- you need a treatment that you may not take while on the study.
- you are not able to take the study medications as required by the study.
- you have not had, or are not able to have, the required study visits and evaluations

If you must stop taking the study medication earlier than indicated by the study, the study doctor will ask you to remain on the study and complete the post discontinuation visits from the date that you took the last dose of study medication.

<u>If I have to permanently stop taking study medications during Part 2 of the study, or once I leave the study, how can I get study medications?</u>
If you must permanently stop taking study medications 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 G/P through the study.

WHAT ARE THE RISKS OF THE STUDY?

No clinical safety issues specifically related to G/P have been identified to date in HCV mono-infected or HIV-1/HCV co-infected participants, without cirrhosis or with compensated cirrhosis (the liver is heavily scarred but can still perform many important bodily functions).

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 diagnosed with HCV and/or living with 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 Medications
The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning study medication side-effects, please ask the medical staff at your site. To assist you in understanding your risk of side effects we have included reported percentages of these events in clinical studies of the medications concerned.

Glecaprevir/pibrentasvir (G/P)
- Headaches- 9-16%
- Fatigue- 11-14%
- Diarrhea- 3-7%
- Nausea- 6-12%
- Asthenia (abnormal physical weakness or lack of energy) – 7%
- Pruritic skin (itchy skin) – 17%
- Abnormal liver function tests- 3.5%

Ribavirin (RBV)
Since RBV was given with IFN in most previous studies the risk of side-effects described here may be much lower than what could happen to you.
- Anemia (low iron in your blood) - 12%
- Severe hypersensitivity (your body's inability to tolerate RBV) - up to 1%
- Severe skin reactions (Stevens Johnson Syndrome)- up to 1%
- Liver Failure – up to 1%
- Bone marrow suppression (decrease in production of cells responsible for providing immunity, carrying oxygen, and/or those responsible for normal blood clotting) – up to 10%

- Pancreatitis (inflammation of the pancreas [the organ responsible for releases digestive enzymes into the small intestine to aid the digestion of food, and releases the hormones insulin and glucagon into the bloodstream, which help the body control how it uses food for energy.]) – up to 1%
- Pulmonary pneumonitis (infection of the lungs that causes inflammation of the lung tissue) – up to 1%

RBV must always be taken along with another hepatitis C medication; RBV alone is not effective for treatment of hepatitis C. RBV has been shown to cause birth defects in all animals that are exposed to this drug. Participants who are put on this medication in this study must agree to be on/use two different forms of birth control. Both men and women taking this drug must take extra care to avoid pregnancy while they are taking this drug and for 6 months after the last dose of RBV. Additional pregnancy testing will be done if you are a woman of child bearing potential taking this drug. RBV can also cause severe anemia which could cause life threatening heart attacks in people with underlying heart disease.

Interactions between RBV and the HIV drugs didanosine (DDI), stavudine (D4T) or zidovudine (AZT) can cause increased risk of side effects of these drugs and as such if you are on any of these medications, your HIV provider would need to change your regimen if you need to take RBV in Part 2.

There is a risk of serious and/or life-threatening side effects when some non-study medications are taken with the study medication. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and 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. If you believe you are having side effects from any of the study medications make sure to immediately inform your study team.

Bradycardia, or slow heart rate, may happen in persons who are taking digoxin (a medicine that is used to treat heart failure and heart rhythm problems) particularly for those with a heart disorder and/or advanced kidney disease. Because of this risk the dose of digoxin must be reduced by about half in persons taking G/P and be closely monitored. It is also not recommended to take G/P with cholesterol lowering medications such as simvastatin, lovastatin, atorvastatin. Other forms of cholesterol lowering medications such as fluvastatin, pravastatin, pitavastatin, and rosuvastatin can be used either at lower doses or at the same dose with careful monitoring; you will need to check with your doctor.

Drug interactions that increase the levels of medicine in your blood may increase the chances of side effects. Drug interactions that could affect the levels of G/P or HIV medicines in your blood could cause changes in liver enzymes and other abnormal blood tests. For certain HIV medications, we may ask you to change them to another medication to reduce this risk. Drug interactions that lower the levels of glecaprevir or pibrentasvir in your blood may decrease your chances for a cure of hepatitis C and/or cause drug resistance (the virus changes form and drugs that used to work, no longer work).

For those persons taking HIV medicines, efavirenz can lower the levels of glecaprevir or pibrentasvir in your blood and affect the potency of this drug in fighting hepatitis C virus. The HIV medication atazanavir when it is taken together with G/P can cause increases in liver enzymes and the combination should be avoided. Examples of other medications that should not be taken with G/P include:

- St. John's wort
- Carbamazepine
- Rifampin
- Ethinyl estradiol containing birth control pills

Drug resistance may prevent other medicines from working in the future. HCV viral load will be monitored regularly to ensure that evidence of early failure of the HCV regimen is identified quickly. Development of resistance after failing G/P has not been studied that well. However, studies so far suggest that use of G/P could select for mutations (permanent changes in genetic material) in the NS3 and NS5A gene which could cause varying levels of resistance to glecaprevir and pibrentasvir. The impact of these resistance associated mutations is still not known.

Some people with HCV and HBV coinfection receiving therapy for HCV with direct-acting antivirals (DAA) like glecaprevir/pibrentasvir have experienced reactivation of HBV. Some of these cases have led to severe hepatitis, liver failure and death. This has been reported in people who are HBsAg (HBV surface antigen [a foreign substance in your body that cause antibodies {cells that fight infection} to develop]) and those who appear to have resolved HBV infection by lab tests. If you have ever been diagnosed with HBV let your study doctor/nurse know.

ARE THERE RISKS RELATED TO DELAYING HIV THERAPY?

You are not required to be on ARVs to enter Part 2 of this study. If you are not on ARVs at the time of your HCV diagnosis and you and your doctor do not think you need to start ARVs, you will not be excluded from the study. Also it is not recommend that that of ARVs is delayed for entry into the study if your doctor feels they are medically necessary. Although the dosing period of the study HCV medications is limited, a delay in necessary HIV medications could allow for progression of HIV disease, which can increase your risk of opportunistic infections and long-term effects of living with HIV. If you have any concerns about these risks, you should discuss them with your medical provider.

WHAT IF I AM DIAGNOSED WITH HIV DURING THIS STUDY?

If you are diagnosed with HIV during this study, study staff will tell you about any available care. Study staff will counsel you about HIV. They will also tell you how to lower the risks of giving HIV to others. Researchers may ask you to continue with this study.

ARE THERE RISKS RELATED TO PREGNANCY?

The drugs or drug combinations in this study may be unsafe for unborn babies. There is also evidence that the use of RBV can result in birth defects. Therefore, becoming pregnant is not allowed. If you are having sex that could lead to pregnancy, you must agree not to become pregnant. Note that if you become pregnant or if you are a man whose female partner becomes pregnant, the study medications will be stopped, and you will be followed after delivery.

Because of the potential risk involved and due to the uncertainty of risk to the fetus, you and your partner must use birth control. You must use one form of the birth control methods listed below, while receiving study medication and for 6 weeks after stopping the medication. If you are taking RBV in Part 2, you must use two forms of birth control up to 6 months after your last RBV dose:

- A condom (male or female) with spermicide
- Diaphragm or cervical cap with spermicide
- An intrauterine device (IUD)
- Tubal ligation
- Hormone-based contraceptives

If you can become pregnant, you must have a pregnancy test within 48 hours before starting the study medications. The test must show that you are not pregnant. Pregnancy tests will also be performed at most study visits.

Some of the methods listed above may not prevent the spread of HIV to other people. 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.

If you think you may be pregnant at any time during the study or if you are a man whose female partner becomes pregnant, tell your study staff right away. Pregnancy will result in immediate discontinuation of the study medications. You will be followed on study until study completion. You will be asked to return to the clinic 6 months after the end of your pregnancy to follow up on any side effects. In addition, pregnancy complications and/or pregnancy outcomes will be reported to the company that makes G/P, AbbVie, by way of the sponsor (NIAID). If you are also living with HIV and become pregnant while on study, pregnancy complications and/or pregnancy outcomes will be reported to the Antiretroviral Pregnancy Registry.

It is not known if G/P is present in breast milk in women who are breastfeeding. Studies done in animals however show that there are low concentrations of the drug in breast milk in laboratory rats. This did not appear to affect these animals. Breastfeeding is not allowed while on G/P. It is not known if RBV is present in breast milk, however because of possible side effects to breast fed babies, breastfeeding is not recommended in women taking RBV.

If you are a man whose female partner becomes pregnant, then you will be asked to report this event to study staff and discontinue therapy. You may also be asked to report on your partner's pregnancy outcomes.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you (your hepatitis C may be cured), but no guarantee can be made. Your health may be watched more closely than usual while you are on the study, which may help you to feel better. 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 living with HIV. Also, the benefits of limiting the potential transmission of HCV to others, benefits others in society and saves in cost of treatment for others.

WHAT OTHER CHOICES DO I HAVE BESIDES PART 2 OF THIS STUDY?

Instead of being in this study, you have the choice of:
- treatment with other prescription drugs currently available to you
- treatment with other experimental regimens, if you qualify
- no treatment; some people may clear HCV on their own over the first year of infection

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 medication, 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. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research 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 that an incentive of USD XX will be provided to participants in addition to routine compensation if they complete the post-treatment* w*eek 12 visit within the visit window.*]

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 A5380 Part 2

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