A5348

Phase II Trial of Retreatment Strategies for Difficult-to-Treat Hepatitis C Virus (HCV)-Infected Individuals Who Have Failed Prior Direct Acting Antiviral (DAA)-Based Regimens

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

DAIDS ES # 12046

This file contains the current ACTG A5348 protocol, which includes the following document:

- Letter of Amendment #1, dated 11 April 2016
- Protocol Version 1.0, dated 29 September 2015

Letter of Amendment #1 for:

A5348

Phase II Trial of Retreatment Strategies for Difficult-to-Treat Hepatitis C Virus (HCV)-Infected Individuals Who Have Failed Prior Direct Acting Antiviral (DAA)-Based Regimens

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

DAIDS ES # 12046

Letter of Amendment Date: 11 April 2016

DATE: April 11, 2016

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

FROM: A5348 Protocol Team

SUBJECT: Letter of Amendment #1 for Protocol A5348, Version 1.0, 09/29/15 entitled "Phase II Trial of Retreatment Strategies for Difficult-to-Treat Hepatitis C Virus (HCV)-Infected Individuals Who Have Failed Prior Direct Acting Antiviral (DAA)-Based Regimens"

The following information impacts the A5348 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation.

The following information may also impact the Sample Informed Consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this Letter of Amendment (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 a 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 the required LOA registration documents have been received and are complete. A LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

The following are changes to A5348, Version 1.0, 09/29/15:

1. Schema, Population, second paragraph (first sentence) has been revised to read:

   The first 15 HIV co-infected participants taking ritonavir-boosted HIV protease inhibitor **and tenofovir disoproxil fumarate (TDF)** ~~tenofovir~~ are required to participate in the PK study.

2. Section 1.3.1 has been revised to read:

   To assess the impact of LDV/SOF and ritonavir-boosted HIV protease inhibitor (PI/r) **and TDF** coadministration on the pharmacokinetics (PK) of tenofovir (TFV).

3. Section 1.3.2 has been revised to read:

   To assess the impact of LDV/SOF and HIV PI/r **and TDF** coadministration on any associated clinical events attributed to elevated tenofovir levels, including renal toxicity (defined as the development of ≥ Grade 2 renal dysfunction or development of new or worsened proteinuria or glucosuria).

4. Section 2.2, Rationale, 6th paragraph (second sentence) has been revised to read:

   Other studies are planned outside of the ACTG which will evaluate retreatment strategies for SOF-failures; however, they exclude HIV/HCV coinfected persons and do not address the important drug-drug interaction of ledipasvir with concomitant **TDF** ~~tenofovir~~ - and ritonavir-boosted protease inhibitors.

5. Section 2.2, Rationale, PK evaluation of tenofovir concentrations on participants on PI/r, 1st sentence has been revised to read:

   When given with TDF, LDV/SOF increases tenofovir concentrations.

6. Section 2.2, Rationale, PK evaluation of tenofovir concentrations ~~on~~ **in** participants on PI/r, has been revised to read:

   LDV/SOF increases tenofovir concentrations. The extent of the increase in tenofovir concentrations is most concerning for persons on PI/rs. In healthy volunteers, LDV/SOF increases tenofovir C_{max} by 46-47% and C_{tau} 38- 47% when administered as tenofovir disoproxil fumarate (TDF)/FTC/atazanavir (ATV)/r versus TDF/FTC/ATV/r alone. LDV/SOF increases tenofovir C_{max} by 46-64% and C_{tau} 52-59% when administered with TDF/FTC/DRV/r versus TDF/FTC/DRV/r alone [17]. Staggering the LDV/SOF by 12 hours from HIV protease inhibitors did not substantially change the increase in tenofovir exposure. Independent of HCV treatment, RTV-boosted ATV and darunavir increase tenofovir concentrations by 29-37% (tenofovir package insert) and 22-37% (tenofovir package insert), respectively. Due to anticipated increases in tenofovir with LDV/SOF and

PI/r coadministration, the current LDV/SOF package insert recommends selecting alternative ARV, if feasible, or monitoring for tenofovir-associated adverse reactions [10]. However, there can be significant downsides of changing stable ARV, including potential loss of HIV virologic suppression, toxicity of new regimens and delay in HCV treatment. As that both LDV/SOF and PI/rs increase tenofovir levels in healthy volunteers, a PK evaluation of the impact of LDV/SOF on tenofovir concentrations in HIV/HCV coinfected patients on PI/r based ARV is warranted with concomitant assessment of any clinical impact of elevated tenofovir levels, such as development of renal dysfunction. Given the limited duration of HCV treatment (12-24 weeks), it is reasonable to conduct the PK evaluation as part of the overall study with close monitoring of participants' renal function, as recommended, rather than prior to this study. The antiretroviral tenofovir alanfenamide (TAF) ~~is anticipated to have~~ **appears to have** less impact on renal function [18] **than TDF** and may be less impacted by drug interactions with LDV/SOF. **In a healthy volunteer pharmacokinetic study,** ~~LDV/SOF given with TAF did not affect TAF or tenofovir concentrations. Coadministration~~ **of LDV/SOF with the fixed dose combination of rilpivirine (RPV)/emtricitabine (FTC)/TAF increased TFV AUC concentration with a geometric mean ratio of 1.75 (1.69, 1.81). However, tenofovir concentrations (AUC 467ng/mL and C_{max} 25 ng/mL) were well below concentrations seen with TDF-containing ART in the absence of HCV treatment. LDV/SOF coadministration with elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF (Genvoya) resulted in increased tenofovir concentration with GMR for AUC of 1.27 (1.23, 1.31) and C_{max} 1.17 (1.12, 1.22); however, as with RAL/FTC/TAF, overall tenofovir concentration remained low (<500 ng/mL)** [19]**. Thus, coadministration of LDV/SOF with TAF containing regimens such as TAF/FTC, RPV/TAF/FTC, and EVG/COBI/TAF/FTC is not anticipated to lead to significant drug-drug interactions, as indicated in the prescribing information [**20**]. Due to the limited impact of LDV/SOF on tenofovir concentrations with TAF-containing regimens, PK evaluation of TFV concentrations will be restricted to participants HIV PI/r with TDF-containing ART only.** ~~However, once approved TAF will not be available to all HIV/HCV coinfected patients due to cost and accessibility. Thus it~~ **It** is important to understand the extent and clinical relevance of the tenofovir-ledipasvir drug interaction in HIV coinfected patients taking HIV protease inhibitors as TDF-based ARV remains a ~~current~~ mainstay of current ARV treatment.

7. Section 3.0, Study Design, second paragraph has been revised to read:

   The first 15 participants on ARV regimens with a HIV PI/r with **TDF-containing ART** ~~tenofovir~~ will be required to participate in the PK component in order to participate in the study. These first 15 participants on PI/r with ~~tenofovir~~ **TDF** who enroll to the study will undergo semi-intensive PK sampling (pre-dose, hour 1 and hour 4) at weeks 0 and 4 for quantification of tenofovir in plasma. After the first 15 participants have enrolled, subsequent participants taking HIV PI/r with ~~tenofovir~~ **TDF** may opt out of the PK evaluations but still participate in the study. **PK evaluation of tenofovir concentrations will be restricted to participants on ritonavir-boosted HIV protease inhibitors with TDF-containing ART only; TAF-containing ART regimens will not be part of the PK evaluation.**

8. Section 3.0, Study Design, third paragraph has been revised to read:

   Fifteen slots will be held for participants across the study arms whose ARV regimen contains an HIV PI/r plus ~~tenofovir~~ **TDF** for the first 3 months after the study opens to enrollment. After 3 months, these slots will no longer be reserved to allow expeditious completion of study. Up to 25 participants whose ARV regimen does not contain PI/r plus ~~tenofovir~~ **TDF** or who are not taking ARVs will be enrolled to the study during the first 3 months of study enrollment. After the first 3 months, additional participants whose ARV regimen does not contain a PI/r plus ~~tenofovir~~ **TDF** or who are not taking ARV may be enrolled. The study may end up with fewer than 15 participants whose ARV regimens contain HIV PI/r plus ~~tenofovir~~ **TDF** and more than 25 participants without, including participants who are not taking ARVs.

9. Section 4.1.5 c, Inclusion Criteria, NOTE has been revised to read:

   Approved ARV is limited to efavirenz, rilpivirine, raltegravir, dolutegravir, **TDF**, **EVG/COBI/TAF/FTC (Genvoya), TAF/FTC, RVP/TAF/FTC (Odefsey),** abacavir, 3TC/FTC, RTV-boosted atazanavir, **and** RTV-boosted darunavir (both 800 mg QD and 600 mg BID permitted).

10. Section 4.1.6, Inclusion Criteria has been revised to read:

    For the first 15 participants taking ~~tenofovir~~ **TDF** and a PI/r as part of their ARV regimen, willingness and intent to participate in PK component.

    NOTE: In the event that 15 participants on PI/r and ~~tenofovir~~ **TDF** have enrolled into A5348, participation in the PK evaluation will be optional for subsequent participants.

11. A note has been added to clarify electrocardiogram inclusion criterion in Section 4.1.11. The revised language now reads:

    4.1.11 Screening electrocardiogram (ECG) without clinically significant abnormalities as determined by the investigator within 42 days prior to study entry.

    NOTE: **ECG abnormalities that are not of clinical concern for underlying heart conditions that may be exacerbated by ribavirin are not exclusionary.**

12. Section 6.1, Schedule of Events, footnotes #3 and 6 has been revised to strike "~~tenofovir~~" and replace with **TDF**.

13. Section 6.3.6, Clinical Assessments, Complete Physical has been revised, removing standardized blood pressure. The revised language reads as follows:

    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 exam will also include diagnoses, signs, and symptoms and vital signs (temperature, pulse, respiratory rate, and resting blood pressure).

    ~~NOTE: Blood pressure will be measured following the current ACTG Standardization of Blood Pressure Measurement SOP.~~

14. Section 6.3.7, Laboratory Evaluations, Urinalysis has been revised to strike "~~tenofovir~~" and replace with **TDF**.

15. Section 6.3.11, Tenofovir PK Samples, first sentence has been revised and now reads:

    The tenofovir PK sampling evaluations will be only required for the first 15 participants, and consenting participants thereafter, who are taking ritonavir-boosted protease inhibitor and **TDF-containing ART** ~~tenofovir~~.

16. Section 7.1.3.1, Specific Guidance for Creatinine Clearance, fifth bullet has been revised to strike "~~tenofovir~~" and replace with **TDF**.

17. Section 9.3, Randomization and Stratification has been revised and now reads:

    The study is randomized to Arm A and Arm B and stratified by the cirrhosis status. Initially, 15 slots will be reserved for participants taking a PI/r and ~~tenofovir~~ **TDF-containing** regimen across the two study arms. This will be lifted 3 months after the study is open to accrual, so that the accrual progress is not constrained by the PK objective on tenofovir.

    The first 15 participants whose ARV regimen contains HIV PI/r plus ~~tenofovir~~ **TDF** who enroll to the study must be willing to participate in PK sampling (pre-dose, hour 1 and hour 4) at weeks 0 and 4. After 15 such participants have contributed PK samples, participation in the tenofovir PK sampling is optional. Study accrual may conclude with fewer than 15 participants whose ARV regimen contains HIV PI/r plus ~~tenofovir~~ **TDF**, since the reservation of 15 slots will be lifted 3 months after the study is open to accrual. There is no minimum or maximum for such participants.

18. Section 10.3, Pharmacology Sample Size Considerations, last sentence was revised and reads as follows:

    However, because expeditious completion of the study is key, the study enrollment may be completed without the required number of participants on ritonavir-boosted HIV protease inhibitor plus ~~tenofovir~~ **TDF.**

19. Sample Informed Consent, What do I have to do if I am in this study, fourth paragraph (first sentence) has been revised to clarify the number of visits. The revised statement now reads:

    While you are in this study, you will need to be seen in the clinic about ~~11~~**10** times (~~14~~ **13** times for those in Group B) during the study.

20. Sample Informed Consent, What do I have to do if I am in this study, Genetic Testing, second paragraph (first sentence) was revised to clarify use of genetic specimens. The revised statement now reads:

    Please initial below if you agree to have any of your blood used for ACTG-approved future ~~unspecified~~ genetic testing **related to HCV and HIV research.**

21. Sample Informed Consent, What do I have to do if I am in this study, has been modified to add a section for consenting to pharmacokinetic testing, before the Optional Tests section.

    The added language reads as follows:

    Pharmacokinetic Evaluation
    Participants who are taking an HIV protease inhibitor with ritonavir along with tenofovir disoproxil fumarate (TDF) as part of HIV treatment are eligible to participate in the pharmacokinetic evaluation at entry and week 4.The first 15 participants who are taking an HIV protease inhibitor with ritonavir along with TDF will be required to participate in this PK evaluation; after the first 15 participants eligible for this evaluation enroll, participation in the PK evaluation will be optional. If you qualify for and participate in the PK evaluation, you will have blood drawn at entry to look at drug concentration in your blood. Additional blood samples will be obtained at 1 and 4 hours after your observed dose of HIV medications. These evaluations will be repeated at the week 4 visit.

Consent to participate in the PK evaluation (Only for participants on HIV ritonavir-boosted protease inhibitor and TDF):

Please initial below if you agree to participate in the PK evaluation at entry and week 4. Please note that participation is *required* for the first 15 participants who qualify and are enrolled in the study, which means that you will not be able to participate in the study if you are one of the first 15 participants and you meet the criteria, but do not want to participate in the PK evaluation.

_____ YES _____ NO

22. Sample Informed Consent, What do I have to do if I am in this study, II. Description of Study Visits, Pharmacokinetic Evaluations at Entry (first sentence) has been modified to clarify TDF use. The revised sentence now reads:

    If you are taking part in the PK testing, and are taking an HIV ritonavir-boosted protease inhibitor and ~~tenofovir~~ **TDF** as part of your HIV regimen, you will have an extra evaluation (PK testing) done at the entry visit.

23. Sample Informed Consent, What do I have to do if I am in this study, II. Description of Study Visits, Post-Entry Visits, third paragraph (fifth sentence) has been revised to clarify those participating in PK use. The revised sentence now reads:

    If you are participating in the PK studies, you ~~You~~ will have blood drawn several times for PK testing.

24. Sample Informed Consent, What do I have to do If I am in this Study, III. Description of Study Evaluations, Sample Collections and Laboratory Testing, Blood Sample PK (first and second sentences) has been revised to clarify use of TDF. The revised statements read as follows:

    If you are taking ~~tenofovir~~ **TDF-containing HIV medication** and an HIV ritonavir-boosted protease inhibitor (atazanavir or darunavir) and you give permission to participate in the PK evaluation, you will have blood collected three times at each of two visits, which will last 4 hours each. The PK samples will be used to measure the levels of the HIV medicines (first PK visit and week 4) and study drugs (week 4 only) in your blood since there is limited information available about the interaction between ~~tenofovir~~ **TDF**, HIV protease inhibitors and the study drugs. You will not take your study medications or HIV medications that morning until you arrive at the clinic and are instructed to do so. Your visit will last 4 hours total.

25. Sample Informed Consent, What are the Risks of the Study, Risk of Study Drug, second paragraph:

    For those persons taking HIV medicines, there is no clear risk of drug interactions between HIV medicines and sofosbuvir. Although sofosbuvir has not been studied with all HIV medicines, it has been studied with all first-line HIV medication drug classes and there are no recognized clinically significant interactions. This is also true for ledipasvir with the exception of one of the HIV medications named ~~tenofovir~~ **TDF**. Ledipasvir increases tenofovir levels in your body. With most other HIV drug combinations this increase is not felt to lead to significant risk unless your kidneys don't work normally. However, if ~~tenofovir~~ **TDF** and ledipasvir are used with HIV protease inhibitors that are combined with ritonavir, (which is used to increase the level of your HIV drugs in your blood stream), the potential risk of kidney toxicity may be higher. The combination of HIV protease inhibitors and ledipasvir and ~~tenofovir~~ **TDF** has not been studied in HIV-infected patients. For this reason there will be monitoring of the kidney function for all participants in this study.

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

A5348

Phase II Trial of Retreatment Strategies for Difficult-to-Treat Hepatitis C Virus (HCV)-Infected Individuals Who Have Failed Prior Direct Acting Antiviral (DAA)-Based Regimens

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

Sponsored by:

The National Institute of Allergy and Infectious Diseases

Industry Support Provided by Gilead Sciences, Inc.

non-IND Protocol

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FINAL Version 1.0
September 29, 2015

ACTG
AIDS CLINICAL TRIALS GROUP

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STUDY MANAGEMENT

All questions concerning this protocol should be sent to actg.coreA5348@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5348@fstrf.org. A response should generally be received within 24 hours (Monday-Friday).

Protocol E-mail Group
Sites should contact the Computer Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5348 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 coenrollment, contact the protocol team.

- Send an e-mail message to actg.coreA5348@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

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

- Send an e-mail message to actg.coreA5348@fstrf.org (ATTN: David Wyles [virologist] or Jennifer Kiser [pharmacologist]).

Data Management
For nonclinical questions about transfers, inclusion/exclusion criteria, case report forms (CRF), the CRF schedule of events, randomization/registration, delinquencies, and other data management issues, contact the data manager. CRFs can be downloaded from the FSTRF website at www.fstrf.org.

- For transfers, reference the Patient Transfer from Site to Site SOP 119, and contact Melissa Mineo directly.
- For other questions, send an e-mail message to actg.coreA5348@fstrf.org (ATTN: Melissa Mineo).
- Include the protocol number, PID, and a detailed question.

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

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

Computer and Screen Problems
Contact the SDAC/DMC programmers.

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

STUDY MANAGEMENT (Cont'd)

Protocol Document Questions
For questions concerning the protocol document, contact the clinical trials specialist.
- Send an e-mail message to actg.coreA5348@fstrf.org (ATTN: KaSaundra Oden).

Copies of the Protocol
To request a hard copy of the protocol, send a message to ACTGNCC@s-3.com (ATTN: Diane Delgado) via e-mail. Electronic copies can be downloaded from the ACTG Web site (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, contact the clinical trials specialist KaSaundra Oden (koden@s-3.com) or ACTG Site Coordination group at actgsitecoordination@s-3.com.

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call Bijal Patel, protocol pharmacist, at 240-421-8445.

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

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

Phone Calls
Sites are responsible for documenting any phone calls made to A5348 team members.
- Send an e-mail to actg.teamA5348@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

3TC	lamivudine
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
ARV	antiretroviral
AST	aspartate aminotransferase (also SGOT)
ATV	atazanavir
AUC	area under the curve
$AUCt_{au}$	area under the plasma concentration versus time curve over the dosing interval
BMI	body mass index
CrCl	creatinine clearance
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval (tau)
CTP	Child-Turcotte-Pugh
d4T	stavudine
DAA	direct acting antiviral
ddI	didanosine
DRV	darunavir
ECG	electrocardiogram
EFV	efavirenz
E_{max}	maximal effect
FDA	US Food and Drug Administration
FTC	emtricitabine
GT	genotype (viral)
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
ICH	International Conference on Harmonisation
IFN	interferon
IL-28B	IL-28B gene
ISGs	IFN stimulated genes
ITT	intention-to-treat
LDV	ledipasvir
LLOQ	lower limit of quantification
Hg	mercury
MCV	mean corpuscular volume
PBMC	peripheral blood mononuclear cell(s)
PEG	pegylated interferon
P-gp	P-glycoprotein

GLOSSARY OF PROTOCOL-SPECIFIC TERMS (Cont'd)

PI	protease inhibitor
PI/r	ritonavir-boosted protease inhibitor
PK	pharmacokinetic
QD	once daily
r	low dose ritonavir (booster)
RAL	raltegravir
RAV	resistant variants
RBV	ribavirin
RPV	rilpivirine
RTV	ritonavir
RVR	rapid virologic response
SAE	severe adverse event
SIM	simeprevir
SOF	Sofosbuvir, GS-7977
SVR	sustained virologic response
SVR4	sustained virologic response 4 weeks after completion of HCV antiviral therapy
SVR12	sustained virologic response 12 weeks after completion of HCV antiviral therapy
SVR24	sustained virologic response 24 weeks after completion of HCV antiviral therapy
TAF	tenofovir alanfenamide
TD	target detected
TDF	tenofovir disoproxil fumarate (prodrug of tenofovir)
TFV	tenofovir
TND	target not detected
t½	an estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λz)
ULN	upper limit of the normal range
WBR	weight-based RBV

SCHEMA

A5348

Phase II Trial of Retreatment Strategies for Difficult-to-Treat Hepatitis C Virus (HCV)-Infected Individuals Who Have Failed Prior Direct Acting Antiviral (DAA)-Based Regimens

DESIGN	Phase II randomized, open-label trial of 12 weeks of ledipasvir/sofosbuvir (LDV/SOF) with weight-based ribavirin (RBV) versus 24 weeks of LDV/SOF for retreatment of participants with hepatitis C virus (HCV) infection and HIV coinfection who have previously failed prior SOF-based regimens. Participants will be followed for an additional 24 weeks after completion of study treatment.
DURATION	Up to 36 weeks in Arm A and up to 48 weeks in Arm B
SAMPLE SIZE	40 participants total, 20 participants per arm
POPULATION	Genotype (GT) 1 HCV infected men and women, age ≥ 18 years, with HIV infection, who have previously been treated for HCV infection with SOF-based treatment, including SOF/RBV +/- pegylated interferon (PEG) and SOF/simeprevir (SIM), and who experienced virologic failure. The first 15 HIV co-infected participants taking ritonavir-boosted HIV protease inhibitor and tenofovir are required to participate in the PK study. See section 3.0 for clarification on enrollment during the first 3 months after the study opens.
STRATIFICATION	Participants will be randomized 1:1 in an open label fashion to one of the two specified treatment regimens. Participants will be stratified by cirrhosis status.
REGIMEN	Arm A: 12 weeks of LDV 90 mg/SOF 400 mg fixed dose tablets once daily (QD), with weight-based RBV: 1000 mg/day for weight < 75 kg, 1200 mg/day for weight ≥ 75 kg. Arm B: 24 weeks of LDV 90 mg/SOF 400 mg fixed dose tablets QD.

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 12 weeks of ledipasvir (LDV)/sofosbuvir (SOF)/ribavirin (RBV) and 24 weeks of LDV/SOF alone result in an estimated 90% sustained virologic response (SVR) 12 weeks after stopping HCV antiviral therapy (SVR12) for each regimen when used for HCV retreatment after sofosbuvir failure.

1.1.2 12 weeks of LDV/SOF/RBV and 24 weeks of LDV/SOF alone will be safe and well tolerated.

1.2 Primary Objectives

1.2.1 To assess the proportion of participants who attain SVR12 in each study arm.

1.2.2 To evaluate safety and tolerability of each study regimen.

1.3 Secondary Objectives

1.3.1 To assess the impact of LDV/SOF and ritonavir-boosted HIV protease inhibitor (PI/r) coadministration on the pharmacokinetics (PK) of tenofovir (TFV).

1.3.2 To assess the impact of LDV/SOF and HIV PI/r coadministration on any associated clinical events attributed to elevated tenofovir levels, including renal toxicity (defined as the development of ≥ Grade 2 renal dysfunction or development of new or worsened proteinuria or glucosuria).

1.3.3 To assess the proportion of participants who attain SVR4 (i.e., SVR 4 weeks after stopping HCV antiviral therapy) and SVR24 (i.e., SVR 24 weeks after stopping HCV antiviral therapy) in each study arm.

1.3.4 To evaluate baseline predictors of SVR12, including cirrhosis, prior treatment response (relapse, partial response, null responder), HCV genotype (GT)-1a vs. 1b, race, and IL-28B status.

1.3.5 To evaluate the association between LDV/SOF adherence and SVR12 in both arms.

1.3.6 To evaluate the impact of baseline HCV resistance mutations on the SVR12 attained with retreatment with LDV/SOF (+/- RBV).

1.3.7 To evaluate emergence of HCV resistance mutations in participants who fail to attain SVR12 with retreatment with LDV/SOF (+/- RBV).

1.3.8 To evaluate kinetics of HCV RNA during treatment (weeks 1, 2, 4, 8, 12, and in Arm B, weeks 16, 20, and 24) and 4, 12, and 24 weeks after treatment discontinuation.

1.3.9 To assess the influence of LDV/SOF based retreatment on HIV-specific parameters, including maintenance of HIV-1 RNA < 50 copies/mL for participants on antiretrovirals and CD4+ cell count during treatment.

1.3.10 To evaluate differences in SVR12 among participants receiving specific antiretroviral (ARV) therapy regimens compared to those taking no ARV on SVR12.

1.3.11 To compare the SVR12 proportions, safety, and tolerability in the two arms.

2.0 INTRODUCTION

2.1 Background

There is a pressing need to understand appropriate retreatment options for HCV-infected patients who fail direct acting antiviral (DAA)-based regimens. To date, over 100,000 prescriptions have been written for SOF (Gilead, *personal communication*). Recent data from the multicenter HCV-Target 2.0 cohort of over 2,000 participants indicate that the SOF-based treatment defined as SOF/RBV, SOF/pegylated-interferon (PEG)/RBV or SOF/simeprevir (SIM) +/- RBV have led to SVR4 in 70-92% of HCV genotype (GT) 1 patients, depending on the regimen used and presence of cirrhosis [1]. Thus, there are a growing number of individuals who have failed SOF-based regimens and are in need of a retreatment strategy, the majority of which are anticipated to be HCV GT1, given the US distribution of genotypes. While failure of a SOF-based regimen is uncommon, those failing a SOF-based regimen represent some of the most difficult to treat patients, given failure of one of the most potent current treatment options and limited data to guide retreatment. In addition, given current restrictions on access to HCV treatment in the US, many patients accessing SOF-based treatment already have advanced fibrosis and need access to curative therapy as soon as possible to reduce disease progression and HCV related complications. Therefore, it is a priority to identify effective, accessible retreatment strategies for this hard to treat population. Further, there are no data to inform retreatment strategies for HIV-infected individuals with SOF failure, who have traditionally represented a harder to treat group and are impacted by DAA-ARV interactions.

Retreatment of SOF-failure with SOF-based regimens

There is precedent for retreatment after SOF-failures with SOF-containing regimens (see Table 2-1). The majority of patients failing SOF regimens do not fail with NS5B resistance mutations. When NS5B mutations have rarely occurred, several patients with the NS5B mutation S282T or L159F mutations have been successfully retreated with SOF- based therapy for 12 weeks or longer [2-4]. Deep sequencing analysis of one SOF

failure demonstrated disappearance of S282T at weeks 24 and 48, suggests the potential for SOF use after SOF resistance [2].

Table 2-1: Successful interferon-sparing SOF-based retreatments of SOF-failures

Parent Trial Name; Failed treatment regimen; Reference	Genotype	SVR12	Successful Re-Treatment Regimen
ELECTRON; SOF monotherapy x 12 weeks; [2]	2b	1/1 (100%)	SOF/RBV x 12 weeks
LONESTAR; LDV/SOF x 8 weeks; [3]	1a	1/1 (100%)	LDV/SOF + RBV x 24 weeks
SPARE; SOF/RBV x 24 weeks; [4, 5]	1	14/14 (100%)	LDV/SOF without RBV x 12 weeks
ELECTRON-2; LDV/SOF/RBV x 6 weeks (8 patients), SOF/RBV x 12 weeks (10), SOF/GS-9669/RBV x 12 weeks (1); [6]	1	19/19 (100%)	LDV/SOF + RBV x 12 weeks
SOF/PEG/RBV x 12 weeks (25 patients), SOF/RBV x 24 weeks (20); [7]	1	45/45 (100%)	LDV/SOF + RBV x 12 weeks

While these data are compelling because of the uniformly high response rates, numbers were small, no patients received past treatment with SOF/SIM, and the retreatment regimens varied. Importantly, none of these retreatment data are from HIV coinfected individuals. Therefore, a LDV/SOF-based strategy should be investigated further as a promising, currently available retreatment regimen for HIV-coinfected individuals who have failed prior SOF-containing therapy.

2.2 Rationale

We propose a phase II retreatment study of HCV GT1 HIV coinfected patients who have previous virologic failure on a SOF-based regimen. SOF-failures represent a challenging group to retreat as they have already failed one potent regimen, and in many cases may have failed prior regimens as well. Given the current restrictions by many insurers on access to SOF-based treatment, patients accessing SOF often have advanced fibrosis and thus are in immediate need of available curative therapy. While overall SOF-failures represent a small percentage of HCV-infected patients, it is a priority to identify curative, immediately available strategies for this growing difficult-to-treat population, enriched for advanced fibrosis. Furthermore, there is an additional need for data to inform SOF retreatment of HIV/HCV coinfected persons within this hard-to-treat population.

Studying SOF/RBV, SOF/PEG/RBV and SOF/SIM failures together is rational, since the prior SOF-treatment is the most salient consideration when choosing retreatment with a LDV/SOF strategy. In addition, the combination of LDV/SOF retreatment has proven highly efficacious in a small number of patients with failure of each of these SOF-based regimens, as outlined in Table 2-1.

Participants will be randomized in an open-label fashion to 12 weeks of LDV/SOF with weight-based RBV vs. 24 weeks of LDV/SOF alone. A small number of previous SOF failures have been successfully retreated with 12 weeks of LDV/SOF alone. However, given what is known about the population that has received and failed SOF-based regimens since approval, this protocol will be enriched with traditionally difficult-to-treat patients including those with null response to prior regimen and cirrhosis. Therefore, 12 weeks of LDV/SOF alone will not be evaluated, given the difficult-to-treat population.

SOF failures represent an uncommon occurrence; therefore, the sample size will be constrained by the pool of participants with this infrequent, yet important, event. Therefore, we will limit the sample size to 20 participants per arm, a number which can be feasibly enrolled in a timely manner to generate meaningful data about each treatment strategy. The COSMOS study evaluating simeprevir and sofosbuvir had treatment arms of similar size and provided groundbreaking data with an immediate impact on HCV clinical practice [3]. COSMOS comprised 168 difficult to treat individuals with either advanced fibrosis (METAVIR F3-4) or prior null response to interferon/ribavirin with more limited fibrosis (F0-2) to receive sofosbuvir and simeprevir, with or without ribavirin, for 12 to 24 weeks. Participants were assigned to 1 of 8 treatment arms ranging from 14 to 27 persons per arm. COSMOS demonstrated that cirrhotic and treatment-experienced patients could still attain a high SVR with an all oral DAA regimen in as short as 12 weeks with a therapy that was generally safe and well tolerated. The multiple small arms provided important data on the regimen performance, impact of RBV, and treatment duration in different populations. COSMOS led to a swift uptake of the investigational regimen, particularly in these harder-to-treat populations with cirrhosis or prior null response for which data had been lacking.

Given the limited retreatment options currently available for patients failing SOF-based treatment, an SVR12 of 70% or greater would represent an important, immediately available retreatment option for this hard-to-treat group, many of whom are anticipated to have advanced fibrosis, which prompted initial therapy. While the preliminary data support the expectation of a high SVR12 rate, cure rates exceeding 70% would be clinically acceptable in this harder to treat population. This threshold is deemed acceptable in consideration of the lower bound of the confidence intervals from several LDV/SOF retreatment studies to date, which have reported high SVRs of 95-98% [6, 7] with a lower confidence interval bounds of down to approximately 85% [7, 8]. Given that data are sparse for retreatment of SOF/RBV +/- PEG failures and non-existent for SOF-SIM failures and for HIV/HCV coinfected patients and we expect the study to be enriched for traditionally hard-to-treat patients, we have relaxed the null response rate from what is considered acceptable for an initial treatment regimen or even PI-based failure retreatment in the DAA era [4, 6, 7]. As a phase II study, this protocol will not be powered for direct comparison of SVR12 between the 12 and 24-week arms. Randomization will help to distribute and control for heterogeneous patient

characteristics between the two treatment arms.

This study will provide much needed pilot data evaluating retreatment strategies of LDV/SOF for prior SOF-failures in HIV/HCV coinfection, including those with cirrhosis. Other studies are planned outside of the ACTG which will evaluate retreatment strategies for SOF-failures; however, they exclude HIV/HCV coinfected persons and do not address the important drug-drug interaction of ledipasvir with concomitant tenofovir- and ritonavir-boosted protease inhibitors. This study will add to the HCV mono-infection studies. In addition, the data from this study will be useful in the future design of a larger conclusive efficacy study based on these initial retreatment strategies.

Rationale for length and composition of retreatment regimens

In the ION-2 study, cirrhotic patients with prior PEG/RBV failure had improved SVR12 with an extended treatment duration of LDV/SOF for 24 weeks(22/22,100% SVR12) compared to 12 weeks of LDV/SOF (19/22, 86% SVR12) [9], leading to the current recommendation for 24 weeks of LDV/SOF in treatment-experienced cirrhotics [10]. However, several studies have now demonstrated that the addition of RBV to 12 weeks of LDV/SOF mitigated the suboptimal SVR12 associated with 12 weeks of LDV/SOF in treatment-experienced patients. In pooled data from phase II and III LDV/SOF studies with 352 treatment experienced, compensated cirrhotic patients, 12 weeks of LDV/SOF/RBV led to SVR12 of 96% compared to SVR12 90% with 12 weeks of LDV/SOF alone [11]. Similarly, in the SIRIUS study, compensated cirrhotic participants with prior HCV PI failure randomized to 12 weeks of LDV/SOF/RBV attained a 96% SVR12 (74/77), comparable to the 97% (75/77) SVR12 with 24 weeks of LDV/SOF alone [8]. In addition, extended treatment or addition of RBV may overcome the negative impact of baseline NS5a resistance mutations, which are uncommon but may contribute to lower SVR in harder-to-treat populations with prior SOF regimen failures. In ION-3 patients with high level baseline NS5a resistance (>100 fold), 24 weeks of LDV/SOF resulted in 100% SVR12, while SVR12 was 69.2% with 12 weeks of LDV/SOF alone[12]. Thus, both 12 weeks of LDV/SOF/RBV and 24 weeks of LDV/SOF alone are promising retreatment strategies, including in the hardest to treat populations such as cirrhotics. Inadequate data exist on the use of either strategy in SOF-failures, and thus there is equipoise about which strategy is preferable. Twelve weeks of LDV/SOF/RBV is attractive given the shorter duration and therefore reduced cost of therapy; however, 24 weeks of LDV/SOF avoids inclusion of RBV, which increases pill burden and is associated with additional toxicity.

Rationale for evaluation of HIV/HCV coinfected participants

Trials of IFN-sparing, DAA HCV treatment have increasingly demonstrated that HIV coinfection has not negatively affected SVR rates. SVR12 rates with 12 weeks of LDV/SOF have been 96%-98% among HIV/HCV coinfected individuals [12, 13], similar to SVR12 of 95-99% attained with 12 weeks of LDV/SOF in HCV monoinfected patients [14, 15]. However, some questions remain about equivalent efficacy in subgroups of HIV/HCV coinfected patients. In the ION-4 study, the overall SVR12 was 96% with 12 weeks of LDV/SOF in HIV/HCV coinfected participants. However, all 10 relapses occurred in black participants, who had an overall SVR of 90%, raising questions about

decreased efficacy in some subgroups, the etiology of which is not yet clear[13]. In addition, in the ALLY-2 study, 8 weeks of sofosbuvir and the NS5a daclatasvir led to a 76% SVR12 rate [16], substantially lower than the SVR12 rate of 94% with the similar combination of polymerase/NS5a inhibitor of LDV/SOF for 8 weeks in monoinfected patients[14]. The reasons for the decreased SVR12 may be due to a number of factors including ARV/DAA drug interactions but the results do raise the question of a differential response in HIV/HCV coinfection with some regimens and subgroups. Thus, while overall HIV coinfected patients have demonstrated similar SVR rates to HIV mono-infected counterparts, it is a priority to evaluate LDV/SOF retreatment in HIV/HCV coinfection as there are no data examining LDV/SOF to treat HIV-infected patients with prior SOF failure.

Interaction between LDV/SOF and HIV antiretrovirals

Consideration of the PK interactions between HCV and HIV treatment is critical. LDV/SOF has minimal interactions with ARV, but is not devoid of interactions. SOF, a uridine nucleotide analogue, is not metabolized by cytochrome P450 (CYP) enzymes, nor does it inhibit or induce any CYP enzymes. SOF is a substrate for membrane efflux transporters, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) [12]. LDV is a substrate for P-gp and an inhibitor of P-gp, BCRP, and organic anion transporting polypeptide (OATP) 1B1/3. Most of a LDV dose is excreted unchanged (70%), the other 30% is metabolized primarily by CYP3A4. Potent inducers of P-gp or BCRP (e.g., tipranavir) should not be used with LDV/SOF as LDV/SOF concentrations may be reduced [13].

PK evaluation of tenofovir concentrations in participants on PI/r

LDV/SOF increases tenofovir concentrations. The extent of the increase in tenofovir concentrations is most concerning for persons on PI/rs. In healthy volunteers, LDV/SOF increases tenofovir C_{max} by 46-47% and C_{tau} 38- 47% when administered as tenofovir disoproxil fumarate (TDF)/FTC/atazanavir (ATV)/r versus TDF/FTC/ATV/r alone. LDV/SOF increases tenofovir C_{max} by 46-64% and C_{tau} 52-59% when administered with TDF/FTC/DRV/r versus TDF/FTC/DRV/r alone [17]. Staggering the LDV/SOF by 12 hours from HIV protease inhibitors did not substantially change the increase in tenofovir exposure. Independent of HCV treatment, RTV-boosted ATV and darunavir increase tenofovir concentrations by 29-37% (tenofovir package insert) and 22-37% (tenofovir package insert), respectively. Due to anticipated increases in tenofovir with LDV/SOF and PI/r coadministration, the current LDV/SOF package insert recommends selecting alternative ARV, if feasible, or monitoring for tenofovir-associated adverse reactions [10]. However, there can be significant downsides of changing stable ARV, including potential loss of HIV virologic suppression, toxicity of new regimens and delay in HCV treatment. As that both LDV/SOF and PI/rs increase tenofovir levels in healthy volunteers, a PK evaluation of the impact of LDV/SOF on tenofovir concentrations in HIV/HCV coinfected patients on PI/r based ARV is warranted with concomitant assessment of any clinical impact of elevated tenofovir levels, such as development of renal dysfunction. Given the limited duration of HCV treatment (12-24 weeks), it is reasonable to conduct the PK evaluation as part of the overall study with close monitoring of participants' renal function, as recommended, rather than prior to this study. The antiretroviral tenofovir

alanfenamide (TAF) is anticipated to have less impact on renal function [18], and may be less impacted by drug interactions with LDV/SOF. However, once approved, TAF will not be available to all HIV/HCV coinfected patients due to cost and accessibility. Thus it is important to understand the extent and clinical relevance of the tenofovir-ledipasvir drug interaction in HIV coinfected patients taking HIV protease inhibitors as TDF-based ARV remains a current mainstay of current ARV treatment.

Rationale for inclusion of cirrhotic patients

Cirrhotic patients are at the highest risk for death and complications due to liver disease. HIV/HCV coinfected patients who have failed SOF-containing regimens thus represent a difficult-to-treat population with a critical unmet need for therapy. Cirrhotic patients were represented in the small trials of SOF-failures, 7/14 (50%) of 24 week SOF/RBV-relapsed participants [5] and 15/51 (29%) of SOF-experienced participants [7]. All participants attained SVR12. Side effects were minimal, including the absence of Grade 4 adverse events (AEs).

Treatment strategies for NS5a failures

There is a need to examine strategies for retreatment of NS5a failures, given the US approval of two NS5 containing regimens, LDV/SOF and the NS5a ombitasvir containing triple regimen of ombitasvir/paritaprevir/dasabuvir. Current limited data suggest that LDV/SOF without RBV led to virologic breakthrough in 18-40% of patients, and was negatively impacted by the presence of preexisting NS5a mutations, which occur commonly at the time of NS5a failure [19]. Therefore, NS5a failures are not included in the current retreatment strategy of LDV/SOF +/-RBV.

However, we may include a second cohort comprised of NS5a failures in a future protocol when we can secure the best available, optimized retreatment regimen. This may be composed of sofosbuvir, the NS5a GS-5816 +/- RBV, or a triple class approach (NS5a, HCV polymerase inhibitor, HCV protease inhibitor).

Quantifying LDV/SOF adherence

Clinical trials indicate high rates of SVR from SOF-based HCV treatment. However, a number of patients still fail to achieve SVR. Several factors (virologic, immunologic, etc.) may contribute to therapeutic failure, but adherence is the primary reason medications fail to work as prescribed. There are very limited data on medication adherence with DAAs. LDV/SOF concentrations were measured and found to be undetectable in participants with HCV viral rebound in the FISSION, VALENCE, PHOTON-1, ION-1 and ION-2 studies. Thus, nonadherence appears to exist in the treatment of HCV, even in highly selected patient populations in clinical trials, and the contribution of nonadherence to SVR has not been determined.
In this study, we will use LDV and SOF metabolite concentrations as an objective measure of adherence and determine the contribution of LDV/SOF adherence to the likelihood of SVR.

2.3 Study Agent: Efficacy and Safety

LDV/SOF

LDV/SOF is an all-oral, once daily treatment regimen for chronic HCV infection. As of 21 March 2014, 23 clinical studies have been initiated with LDV/SOF alone or in combination with RBV, including 344 healthy participants and 3,504 participants with chronic HCV infection.

Ribavirin

RBV is a guanosine analogue that inhibits the in vitro replication of a wide range of RNA and DNA viruses [14]. RBV monotherapy has little or no effect on the replication of HCV but can result in normalization of serum ALT activity and improvement in liver histology. When combined with IFN or PEG therapy, RBV decreases substantially the relapse rate seen after cessation of IFN therapy [16, 17].

RBV is a known teratogen (US Food and Drug Administration [FDA] category X). Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 6 months following completion of treatment. A comprehensive review of RBV is contained in the package insert/summary of product characteristics.

2.3.1 Clinical efficacy in participants with GT-1 HCV infection and HIV coinfection

The efficacy data for LDV/SOF in GT-1 and 4 HCV infections are derived from the Phase III ION-4 study, which was a multicenter, open-label, single arm study of LDV/SOF for 12 weeks. The trial included HCV treatment-naïve and treatment-experienced (55%) participants and included 20% of participants with cirrhosis. Participants were required to be on ARVs and have evidence of HIV viral suppression. The allowable ARVs included TDF plus efavirenz (EFV), raltegravir (RAL), or rilpivirine (RPV). Overall, the study population was 82% male, 34% self-reported black race, 24% IL-28B CC genotype, and 98% GT-1 (75% 1a, 23% 1b, 8% GT-4). The overall SVR12 was 96% (96% GT-1 and 100% GT-4). Virologic failures included 10 participants with relapse after end of therapy and 2 participants with breakthrough due to nonadherence. One participant was lost to follow-up after achieving SVR4 although this participant did return for SVR24 visit. There was one death for an unrelated event (infectious endocarditis in IDU). There was no difference in SVR12 for treatment-naïve (95%), treatment-experienced (97%), cirrhosis (94%), no cirrhosis (96%), treatment-experienced with cirrhosis (98%). In a multivariable analysis only self-reported black race was associated with a lower SVR12 (90%). This association of lower SVR12 and race was not observed in the mono-infected Phase III program. Further investigations to explain this observation in ION-4, including population PK across race, ARV regimen, relapse and a candidate gene study of the CYP2B6 polymorphism, were negative. Deep sequencing was completed on all participants and NS5A

resistant variants (RAV) were identified at baseline in 20% of participants; this did not associate with lower SVR12 (94% with RAVs at baseline vs 96% without). Ten of the 12 virologic failures in the study had RAV at failure, 4 of these were relapsers who had the RAVs at baseline.

2.3.2 Clinical Efficacy in HCV Mono-infection

The primary efficacy data for LDV/SOF in GT-1 HCV infection in the clinical efficacy section is derived from 3 Phase III ION studies (GS-US-337-0102 [ION-1], GS-US-337-0109 [ION-2], and GS-US-337-0108 [ION-3]). Studies GS-US-337-0102 and GS-US-337-0109 evaluated treatment with LDV/SOF±RBV for 12 or 24 weeks in treatment-naive and treatment-experienced participants, respectively, who were infected with GT-1 HCV. Both studies enrolled up to 20% of HCV-infected participants who had documented compensated cirrhosis. Study GS-US-337-0108 evaluated LDV/SOF±RBV treatment for 8 weeks and LDV/SOF treatment for 12 weeks in noncirrhotic treatment-naïve participants with GT-1 HCV infection [13].

Additional data from Phase II studies provide clinical efficacy information for retreatment of virologic failures to prior SOF-based regimens (Studies 13-I-0066 [SYNERGY] and GS-US-337-0118 [LONESTAR]).

Efficacy data across the Phase III ION studies were not pooled or grouped with the exception of those for noncirrhotic treatment-naive participants from the LDV/SOF 12-week groups in Studies GS-US-337-0102 and GS-US-337-0108. These two studies had data for LDV/SOF 12-week groups pooled for purposes of subgroup analysis of noncirrhotic treatment-naive participants. With the exception of this one subset of participants, different participant populations were enrolled in each study.

2.3.3 Participant Disposition

Of the 1,952 participants who received at least one dose of study drug in the LDV/SOF Phase III ION studies, 98.1% completed their assigned study treatment, and 0.7% of participants discontinued study treatment due to an AE. Two participants discontinued treatment due to lack of efficacy, and, in both cases, PK data suggested study drug noncompliance (Studies GS-US-337-0102 and GS-US-337-0109).

2.3.4 Demographics and Baseline Disease Characteristics

Overall, demographic characteristics were generally similar across all treatment groups in the LDV/SOF Phase III ION population; however, because Study GS-US-337-0102 enrolled 40.8% of participants in Europe, notable differences in demographics between the US and Europe compared with groups in Studies GS-US-337-0109 and GS-US-337-0108 were observed for race and body mass index (BMI) as follows: in the US, a higher percentage of participants were black or African-American (19.5% US vs. 2.3% Europe) and had a BMI ≥30 kg/m^2

(27.3% US vs. 9.3% Europe). Overall, baseline disease characteristics were generally similar across all treatment groups. A total of 11.5% of participants had cirrhosis at screening: 15.7% and 20.0% of participants had cirrhosis at screening in Studies GS-US-337-0102 and GS-US-337-0109, respectively. No participants had cirrhosis at screening in Study GS-US-337-0108. The majority of participants had GT-1a (73.9%) or 1b (25.5%) HCV infection; 5 participants had GT-1 (no subtype per the protocol-specified clinical assays) HCV infection, 2 participants had GT-4 HCV infection, and 5 participants had no GT determined by the protocol-specified clinical assays. The 7 participants who had either GT- 4 HCV infection or no genotype determined for their HCV infection were randomized in violation of the clinical study protocols [20].

2.3.5 Study GS-US-337-0102 (ION-1): Treatment-Naive Participants

In Study GS-US-337-0102, both 12-week groups met the primary efficacy endpoint of an SVR12 rate that was superior to the historical control rate of 60% ($p<0.001$) and the prespecified interim criteria of SVR12 ≥90% in participants with and without cirrhosis separately. The SVR12 rates were 97.7% for the LDV/SOF 12-week group and 97.2% for the LDV/SOF+RBV 12-week group.

Participants with and without cirrhosis achieved high rates of SVR12: SVR12 rates in participants with cirrhosis were 94.1% in the LDV/SOF 12-week group and 100% in the LDV/SOF+RBV 12-week group; SVR12 rates in participants without cirrhosis were 98.3% in the LDV/SOF 12-week group and 96.7% in the LDV/SOF+RBV 12-week group.

In the LDV/SOF 12-week group, only one participant relapsed and four participants did not have a post treatment week 12 visit and were classified as failures. The participant who relapsed had IL-28B TT alleles, cirrhosis, and the baseline NS5A resistance-associated variant (RAVs) L31M, and relapsed at the post treatment week 4 visit; the participant had completed 12 weeks of LDV/SOF without any dose interruptions. In the LDV/SOF+RBV 12-week group, no participants relapsed and six participants did not have a post treatment week 12 visit and were classified as failures. Across all 4 treatment groups, one participant in the LDV/SOF 24-week group had on-treatment virologic failure at week 8 (breakthrough), associated with documented study drug noncompliance.

Several host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, cirrhosis, high BMI, GT-1a, high viral load, non-CC IL-28B allele) had no notable impact on SVR12 rates. The presence of baseline LDV-associated NS5A RAVs in 78 participants also had no notable impact on SVR12 rates.

2.3.6 Study GS-US-337-0108 (ION-3): Treatment-Naive Participants

All treatment groups met the primary efficacy endpoint of an SVR12 rate that was statistically significantly higher ($p<0.001$) than the adjusted historical SVR null rate of 60%. The SVR12 rates were 94.0% for the LDV/SOF 8-week group, 93.1% for the LDV/SOF+RBV 8-week group, and 95.4% for the LDV/SOF 12-week group.

The 8-week RBV-free LDV/SOF regimen was noninferior to the 8-week RBV-containing regimen and the 12-week LDV/SOF regimen, as demonstrated by lower bound 95.0% CI of −3.9% and lower bound 97.5% CI of −6.4%, respectively, based on the requirement that the lower bound of the CI of the difference between two treatment groups was greater than the prespecified noninferiority margin of −12%.

The addition of RBV to an 8-week treatment course of LDV/SOF or extension of the LDV/SOF treatment duration from 8 to 12 weeks did not substantially increase the observed SVR12 rates. Relapse rates were similar in the 8-week treatment groups, but were lower in the LDV/SOF 12-week group.

The overall virologic failure rate was low (LDV/SOF 8 Weeks: 5.1%, LDV/SOF+RBV 8 weeks: 4.2%, and LDV/SOF 12 weeks: 1.4%). No resistance to SOF or LDV was detected in 21 and 7 of the 23 relapsed participants, respectively. Virologic failure was associated with single-class LDV resistance in 16 (69.6%) of the relapse participants. The substitutions V321A and L159F in NS5B were each detected in one participant with GT-1a HCV infection at low levels at relapse. E237G, a conserved site substitution in NS5B, but distant from the active site, was detected in two GT-1a participants at virologic failure. Eleven participants who achieved SVR4 did not achieve SVR12: five participants in the LDV/SOF 8-week group (three relapsed, one lost to follow-up, and one withdrew consent); four participants in the LDV/SOF+RBV 8-week group (three relapsed, one lost to follow-up) and two participants in the LDV/SOF 12-week group (two participants had visits that had not occurred at time of data cut and were considered lost to follow-up).

Prespecified analyses of subgroups indicated that the SVR12 rates across the three treatment groups were generally consistent with those observed in the overall population, with high SVR12 rates observed in most subgroups.

For the 8-week treatment groups, exact univariate logistic regression analysis was used to assess the relationship between relapse and 10 prognostic factors (treatment with vs. without RBV, age, sex, race, ethnicity, HCV GT-1 subtype, baseline HCV RNA viral load, BMI, IL-28B alleles, and gamma-glutamyl transferase). Among the 10 factors included in the analysis, two were found to be significant ($p<0.05$). These were male sex and having a baseline HCV RNA viral load ≥800,000 IU/mL. Of note, the analysis showed that the absence of RBV in an 8-week regimen consisting of LDV/SOF was not a significant predictor of relapse. Additionally, several other host and viral factors that have traditionally

been predictive of, or associated with, relapse (eg, age >65 years, black or African-American, Hispanic or Latino, high BMI, non-CC IL-28B alleles) were not found be significant in this analysis. Subsequent exact multivariate regression analysis identified only one factor, male sex, to be the most predictive of relapse, among the limited number of participants who relapsed. Although the SVR12 rate was numerically lower among male participants than female participants, the majority of male participants (92.6%, 225 of 243 participants) and female participants (98.9%, 178 of 180 participants) achieved SVR12 after 8 weeks of therapy (see Table 2-2).

Table 2-2: 8-week LDV/SOF and LDV/SOF+RBV Regimen

	ION-3	ION-3	ION-3	ION-1	ION-1
	LDV/SOF 8-Week N=215 (%)	LDV/SOF+ RBV 8-Week N=216 (%)	LDV/SOF 12-Week N=216 (%)	LDV/SOF 12-Week N=214 (%)	LDV/SOF+ RBV 12-Week N=217 (%)
Treatment-Naïve Total					
SVR12	202/215 (94)	201/216 (93)	206/216 (95)	209/214 (98)	211/217 (97)
95% CI	89.9 - 96.7%	88.8 – 96.1	91.7 – 97.8	94.6 – 99.2	94.1 – 99.0
P-value*	<0.001	<0.001	<0.001	<0.001	<0.001
Treatment-Naïve Noncirrhotic					
SVR12	202/215 (94)	201/216 (93)	206/216 (95)	177/180 (98)	178/184 (97)
95% CI	89.9 – 96.7	88.8 – 96.1	91.7 – 97.8	95.2 – 99.7	93.0 – 98.8
Treatment-Naïve Cirrhotic					
SVR12	NA	NA	NA	32/34 (94)	33/33 (100)
95% CI	--	--	--	80.3 – 99.3	89.4 - 100

*Compared to historic control of 60%

2.3.7 Clinical Efficacy Conclusions

In the LDV/SOF Phase III clinical program, LDV/SOF±RBV treatment was evaluated for 12 or 24 weeks in treatment-naive and treatment-experienced participants in studies GS-US-337-0102 and GS-US-337-0109, respectively, with GT-1 HCV infection. Both studies enrolled up to 20% HCV-infected participants who had documented compensated cirrhosis. Study GS-US-337-0108 evaluated LDV/SOF±RBV treatment for 8 weeks and LDV/SOF treatment for 12 weeks in noncirrhotic treatment-naive participants with GT-1 HCV infection. Across all studies, LDV/SOF demonstrated a high degree of efficacy with point estimates for SVR12 >93% in participants with GT-1 HCV infection.

Across the three Phase III studies, the addition of RBV to the LDV/SOF regimen did not substantially increase the SVR rate. When the SVR rates are considered, extending the duration of LDV/SOF treatment from 8 to 12 weeks in noncirrhotic treatment-naive participants in Study GS-US-337-0108 and 12 to 24 weeks in noncirrhotic or cirrhotic treatment-experienced participants in Study GS-US-337-0109 would not enhance the observed SVR12 rates for the majority of participants. Concordance analysis between SVR12 and SVR24 in treatment-naïve and treatment-experienced participants receiving LDV/SOF for 12 or 24 weeks was 100% in the Phase III Studies GS-US-337-0102 and GS-US-337-0109. There was no clinically meaningful impact on SVR12 rates or relapse when participants took LDV/SOF with or without food in any study.

Comprehensive analyses showed that no genotypic or phenotypic resistance to either SOF or LDV was detected in eight of 37 participants (22%) at virologic failure in the Phase III studies. Virologic failure was associated with single-class LDV phenotypic resistance in 29 of 37 participants (78%). Low levels of V321A and L159F in NS5B, two substitutions previously identified to be SOF treatment-emergent substitutions with no phenotypic resistance to SOF, were detected in one participant with GT-1a HCV infection at relapse by deep sequencing. In addition, E237G, a conserved site substitution in NS5B, but distant from the active site, was observed in two participants with GT-1a HCV infection and one participant with GT-1b infection at virologic failure. The clinical significance of these NS5B substitutions is unknown. No genotypic or phenotypic resistance to SOF was detected in the remaining participants.

Overall, pre-existing baseline NS5A RAVs have a poor predictive value for virologic failure when participants are treated with a dual combination of SOF and LDV. Among all participants who had baseline NS5A RAVs, an SVR12 rate of 89.5% (34/38 participants) or 92.1% (82/89 participants) was observed among participants treated with LDV/SOF for 8 or 12 weeks, respectively. Nevertheless, among participants with baseline NS5A RAVs, there were slight reductions in SVR12 observed, associated with NS5A RAVs expressing higher levels of LDV resistance within the treatment-experienced population. From a clinical perspective, the lack of a high predictive value between viral sequence and treatment outcome coupled with the observation that a large majority of participants with NS5A RAVs achieve SVR12 appears to preclude the clinical utility of baseline sequencing.

2.3.8 Clinical Safety

The primary safety data for this clinical safety section are derived from the three Phase III LDV/SOF ION studies (GS-US-337-0102 [ION-1], GS-US-337-0109 [ION-2], GS-US-337-0108 [ION-3]) with supporting safety data from other studies as appropriate. The ION-4 safety analysis confirmed the clinical safety reported in the rest of the ION program.

2.3.9 Adverse Events

Treatment-emergent AEs were any events with onset dates on or after the date of the first dose of any study drug up to 30 days after the last dose of any study drug.

2.3.10 Overall Summary of Adverse Events

Table 2-3 presents an overall summary of AEs reported in the three Phase III ION studies. Of the participants in these studies, 79.1% had at least one AE and 4.7% had at least one Grade 3 or 4 AE. In addition, 2.6% of participants had at least one SAE, with only 0.3% of participants experiencing a treatment-related SAE (section 2.3.12).

Overall, <1% of participants receiving LDV/SOF with or without RBV (0.7%) had an AE leading to discontinuation of LDV/SOF. The only AEs that led to discontinuation of LDV/SOF in >1 participant were palpitations and anxiety (2 participants each) (section 2.3.14).

A higher proportion of participants in the RBV-containing (LDV/SOF+RBV) treatment groups (13.5%) had AEs leading to dose modification or interruption of any study drug than participants in the RBV-free (LDV/SOF) treatment groups (0.6%).

No treatment-emergent deaths were reported in the three Phase III studies. One non-treatment-emergent death was reported in a participant who had an SAE of hepatic failure secondary to HCV infection and alcohol use on post treatment Day 38. The participant died of liver failure on post treatment Day 121 (Section 2.3.13).

The difference in the AE profile of RBV-free (LDV/SOF) and RBV-containing (LDV/SOF+RBV) treatment groups was also evaluated. The percentage differences for the 8-, 12-, or 24-week treatment durations and overall risk differences (adjusted for treatment duration based on Mantel-Haenszel proportions) were calculated for the AE brief summary and for AEs and treatment-related AEs that occurred in at least 5% of participants within any treatment group. The addition of RBV to the treatment regimen was associated with an increase in the total incidence of AEs for all treatment durations. Overall, when adjusted for treatment duration, the addition of RBV increased the risk of a participant experiencing any AE by 11.1%, the risk of a participant experiencing any treatment-related AE by 25.7%, and the risk of a participant experiencing any AE leading to modification or interruption of any study drug by 13.0%. For Grade 3 or 4 AEs, Grade 3 or 4 treatment-related AEs, SAEs, treatment-related SAEs, AEs leading to permanent discontinuation of any study drug, AEs leading to permanent discontinuation of LDV/SOF, and AEs leading to interruption of LDV/SOF, the risk differences between the LDV/SOF and LDV/SOF+RBV treatment regimens were small (<5%). The majority of AEs attributable to the addition of RBV to LDV/SOF were Grade 1 to 2 in severity.

The ION-4 reported 77% of participants with AEs, 4% with Grade 3-4 (only four of the 14 were reported as related to the study regimen), eight with severe AE (including two diagnoses of hepatocellular carcinoma and two diagnoses of portal vein thrombosis). No participant discontinued treatment due to AE. Eleven percent of participants had a Grade 3-4 laboratory abnormality but these were all transient and asymptomatic (elevated glucose in diabetic participants, elevated lipase and creatinine kinase). All participants maintained stable CD4 throughout the study and no participant had confirmed HIV virologic rebound. Common AEs (≥ 5%) included headache (25%), fatigue (21%), diarrhea (11%), nausea (10%), arthralgia (7%), and upper respiratory tract infection (5%). This is quite similar to Tables 2-3 and 2-4 below. Due to the drug-drug interaction of LDV and TDF leading to increased serum tenofovir levels, all participants had close renal monitoring at all study visits. There was no clinically or statistically significant increase in serum creatinine or decrease in creatinine clearance (CrCl) during the study. Four participants met the study protocol defined criteria of confirmed, treatment-emergent, renal insufficiency (creatinine ≥ 0.4 mg/dL). Two of these participants were simply monitored and in the absence of any evidence of tubular toxicity no changes were made in ARVs. One participant entered the study on RAL and had baseline CrCl of approximately 50 mL/min. With worsening CrCl but no evidence of tubular toxicity, this participant had dose reduction of TDF as per package insert. The fourth participant also entered the study with evidence of chronic kidney disease (CKD) with CrCl of approximately 80 mL/min and baseline 4+ glucosuria and 2+ proteinuria. This participant had worsening renal function on study and due to the concern for tubular damage at baseline, the decision was made to switch this participant off of TDF to RAL. The participant completed the study on EFV, RAL and lamivudine (3TC) without difficulty and achieved SVR12.

Table 2-3 Overall Summary of Adverse Events in LDV/SOF Phase III Safety Population

Number (%) of Participants Experiencing Any:	ION-3 LDV/SOF 8 Week N=215	RBV-Free Regimens (ION-1, 2, 3) Overall (N=1080)	RBV-Containing Regimens (ION-1, 2, 3) Overall (N=872)
AE	145 (67%)	800 (74%)	745 (85%)
Grade 3 or 4 AE	2 (0.9%)	46 (4.3%)	45 (5.2%)
Treatment-Related AE	82 (38%)	484 (44.8%)	617 (70.8%)
Grade 3 or 4 Treatment-Related AE	0	11 (1.0%)	27 (3.1%)
SAE	4 (1.9%)	34 (3.1%)	17 (1.9%)
Treatment-Related SAE	0	4 (0.4%)	1 (0.1%)
AE Leading to Permanent Discontinuation of Any Study Drug	0	6 (0.6%)	11 (1.3%)
AE Leading to Permanent Discontinuation of LDV/SOF	0	6 (0.6%)	7 (0.8%)
AE Leading to Modification or Interruption of Any Study Drug	0	6 (0.6%)	118 (13.5%)
AE Leading to Interruption of LDV/SOF	0	6 (0.6%)	7 (0.8%)
Treatment-Emergent Death	0	0	0

2.3.11 Frequent Adverse Events Final

Table 2-4 presents the AEs reported for at least 5% of participants in any treatment group by preferred term in the three Phase III ION studies. Overall, the three most frequently reported AEs were fatigue (29.3%), headache (23.1%), and nausea (13.5%). All of these events were reported more commonly in participants receiving LDV/SOF+RBV compared with participants receiving LDV/SOF: fatigue (38.0% vs. 22.2%), headache (26.1% vs. 20.6%), and nausea (17.4% vs. 10.4%).

The majority of AEs reported in at least 5% of participants occurred more commonly in participants receiving LDV/SOF+RBV compared with participants receiving LDV/SOF. Furthermore, irrespective of treatment duration (8 vs. 12 vs. 24 weeks), the AEs with a ≥5% risk difference were generally similar across the three treatment durations (8 vs. 12 vs. 24 weeks). Therefore, a pooled analysis, which adjusted for treatment duration, was used to identify AEs occurring at ≥5% incidence in participants receiving LDV/SOF+RBV compared with participants receiving LDV/SOF. These AEs were fatigue, insomnia, anemia, nausea, dyspnea, irritability, cough, rash, pruritus, and headache. All of these events were associated with the expected safety profile of RBV [15; 18-19].

When evaluated at the system-organ-class level, numerically higher percentages (difference of >5%) of participants receiving LDV/SOF+RBV than participants receiving LDV/SOF experienced AEs within the following system organ classes: blood and lymphatic system disorders (10.7% vs. 1.5%); gastrointestinal disorders (39.6% vs. 30.6%); general disorders and administration site conditions (52.5% vs. 33.8%); infections and infestations (23.7% vs. 18.4%); nervous system disorders (36.9% vs. 27.8%); psychiatric disorders (29.6% vs. 16.2%); respiratory, thoracic, and mediastinal disorders (25.2% vs. 11.5%); and skin and subcutaneous tissue disorders (29.7% vs. 14.3%). No system organ class had an incidence of AEs higher (>5%) in participants receiving LDV/SOF compared with participants receiving LDV/SOF+RBV.

Longer treatment duration (8 vs. 12 vs. 24 weeks) was associated with an increase in the total incidence of AEs, both in the LDV/SOF groups (67.4%, 72.4%, and 81.3%, respectively) and LDV/SOF+RBV groups (76.4%, 85.4%, and to 91.5%, respectively).

When comparing the LDV/SOF groups by treatment duration, the differences in the incidence of any individual AE between 8 and 12 weeks of treatment or between 12 and 24 weeks of treatment were small (<5%); headache was the only AE with increased incidence of ≥5% when the treatment durations increased from 8 to 12 weeks.

When comparing the LDV/SOF+RBV groups by treatment duration, most of the differences in the incidence of any individual AE between 8 and 12 weeks of treatment were small (<5%); insomnia, cough, asthenia, and dyspnea were exceptions with increased incidence of ≥5% when the treatment durations increased from 8 to 12 weeks. Similarly, the differences in the incidence of any individual AE between 12 and 24 weeks of treatment were small (<5%), with the exception of headache, which had an increased incidence of ≥5% when the treatment duration increased from 12 to 24 weeks.

Table 2-4: Adverse Events in at Least 5% of Participants in Any Treatment Group by Preferred Term in the LDV/SOF Phase III Safety Population

	ION-3 LDV/SOF 8 Week N=215	RBV-Free Regimens (ION-1, 2, 3) Overall (N=1080)	RBV-Containing Regimens (ION-1, 2, 3) Overall (N=872)
Number (%) of Participants Experiencing Any AE:	145 (67%)	800 (74%)	745 (85%)
Fatigue	45 (21%)	240 (22.2%)	331 (38%)
Headache	30 (14%)	222 (20.6%)	228 (26.1%)
Nausea	15 (7%)	112 (10.4%)	152 (17.4%)
Insomnia	11 (5.1%)	82 (7.6%)	155 (17.8%)
Diarrhea	15 (7%)	88 (8.1%)	67 (7.7%)
Irritability	3 (1.4%)	46 (4.3%)	95 (10.9%)
Rash	3 (1.4%)	47 (4.4%)	94 (10.8%)
Arthralgia	9 (4.2%)	68 (6.3%)	66 (7.6%)
Cough	3 (1.4%)	42 (3.9%)	90 (10.3%)
Pruritus	2 (0.9%)	33 (3.1%)	78 (8.9%)
Dizziness	6 (2.8%)	47 (4.4%)	61 (7%)
Constipation	9 (4.2%)	53 (4.9%)	42 (4.8%)
Myalgia	7 (3.3%)	47 (4.4%)	48 (5.5%)
Asthenia	1 (0.5%)	38 (3.5%)	56 (6.4%)
Anemia	2 (0.9%)	5 (0.5%)	84 (9.6%)
Muscle Spasms	3 (1.4%)	28 (2.6%)	57 (6.5%)
Back Pain	6 (2.8%)	43 (4.0%)	40 (4.6%)
Dyspnea	0	12 (1.1%)	69 (7.9%)
Anxiety	5 (2.3%)	30 (2.8%)	49 (5.6%)
Nasopharyngitis	3 (1.4%)	38 (3.5%)	41 (4.7%)
Vomiting	6 (2.8%)	24 (2.2%)	40 (4.6%)
Dry Skin	1 (0.5%)	10 (0.9%)	43 (4.9%)
Dyspnea Exertional	0	6 (0.6%)	35 (4%)

2.3.12 Serious Adverse Events in Phase III ION Studies

Overall in the Phase III ION studies (GS-US-337-0102, GS-US-337-0109, and GS-US-337-0108), few participants (2.6%, 51 of 1952 participants) had any SAE. The only SAEs reported in >1 participant across all treatment groups were noncardiac chest pain (three participants), and chest pain, colitis, gastroenteritis, hand fracture, hypertension, intervertebral disc protrusion, and pneumonia (two participants each), suggesting that no trends in SAE type or onset time were observed. Only five participants (0.3%) had an SAE that was considered related to study drug by the investigator: anemia, development of factor VIII inhibitor,

mesenteric vein thrombosis, salpingitis, and headache. These events are described below:

1. A participant in the LDV/SOF+RBV 12-week group had two separate treatment-related SAEs of anemia; both events were Grade 3, led to interruption of the RBV dose, and resolved.
2. A participant with cirrhosis in the LDV/SOF 24-week group had a treatment-related SAE of mesenteric vein thrombosis; this event was Grade 3, led to the interruption of the LDV/SOF dose, and resolved.
3. A participant with a medical history of hemophilia A in the LDV/SOF 24-week group, who had received factor VIII supplementation prior to and during the study, had a treatment-related SAE of development of factor VIII inhibitor; this event was Grade 3, led to the discontinuation of LDV/SOF, and was ongoing at the time of the data cut.
4. A participant in the LDV/SOF 24-week group had a treatment-related SAE of salpingitis; this event was Grade 3, did not lead to a dose change for LDV/SOF, and resolved.
5. A participant in the LDV/SOF 24-week group had a treatment-related SAE of headache; this event was Grade 3, occurred on post treatment Day 6, and was ongoing at the time of the data cut.

2.3.13 Deaths

Participants in Phase III ION Studies

One treatment-emergent death was reported in the LDV/SOF Phase III Safety Population. This participant was in the ION-4 trial and was discontinued from the study at week 4 due to hospitalization for severe staphylococcal aureus infective endocarditis resulting in multi-organ failure and death in a participant actively using intravenous drugs.

One non-treatment-emergent death was reported in Study GS-US-337-0102. This participant, who had received LDV/SOF for 12 weeks and achieved SVR12, was reported to have died of hepatic failure on post treatment Day 121. This participant had an SAE of hepatic failure secondary to HCV infection and alcohol use on post treatment Day 38; this event was considered not related to study drug by the investigator.

2.3.14 Discontinuations Due to Adverse Events: Participants in Phase III ION Studies

Overall, the incidence of AEs leading to permanent discontinuation of any study drug was low across all treatment groups (0.9%, 17 of 1952 participants). Anemia, anxiety, fatigue, and rash were the only AEs leading to permanent discontinuation of any study drug in >1 participant (two participants each); these were reported in the LDV/SOF+RBV treatment groups and are consistent with the expected safety profile of RBV [15; 18-19].

All participants who discontinued LDV/SOF were required to discontinue the entire study treatment regimen (i.e., for the RBV-containing [LDV/SOF+RBV] groups, RBV was also discontinued). Across treatment groups, palpitations and anxiety were the only AEs leading to discontinuation of LDV/SOF reported in >1 participant (2 participants each). All of these events were Grade 1 or 2 in severity and resolved following the discontinuation of LDV/SOF.

2.3.15 Clinical Safety Conclusions

The LDV/SOF Phase III clinical program compared the safety and tolerability of LDV/SOF with and without RBV for treatment durations of 8, 12, and 24 weeks. A total of 1952 participants received at least one dose of study drug and 98.1% of these participants completed their assigned study treatment.

Across the LDV/SOF Phase III safety population, treatment with LDV/SOF was generally safe and well tolerated. The incidence of AEs leading to permanent discontinuation of any study drug was low (0.9%) across all regimens, with no AEs leading to permanent discontinuation of any study drug that occurred in >1 participant in the LDV/SOF treatment groups; the only AEs leading to permanent discontinuation of any study drug in >1 participant in the LDV/SOF+RBV treatment groups included AEs consistent with the expected safety profile of RBV (anemia, anxiety, fatigue, and rash [2 participants each]) [15; 18-19]. Across the LDV/SOF Phase III Safety Population, the three most frequently occurring AEs were fatigue, headache, and nausea. A higher incidence of each event was reported in participants receiving LDV/SOF+RBV compared with participants receiving LDV/SOF: fatigue (38.0% vs. 22.2%), headache (26.1% vs. 20.6%), and nausea (17.4% vs. 10.4%).

The addition of RBV to LDV/SOF increased the number of AEs experienced by participants. Overall, AEs were 11.1% and treatment-related AEs were 25.7% more likely to occur in the RBV-containing (LDV/SOF+RBV) groups compared with the RBV-free (LDV/SOF) groups. In addition, the need for study drug modification or dose interruption due to any AE was 13.0% more frequent in the RBV-containing (LDV/SOF+RBV) groups compared with the RBV-free (LDV/SOF) groups. The specific AEs that increased in the presence of RBV were fatigue, insomnia, anemia, nausea, dyspnea, irritability, cough, rash, pruritus, and headache.

For both RBV-free (LDV/SOF) and RBV-containing (LDV/SOF+RBV) regimens, increasing treatment duration from 8 to 12 weeks and from 12 to 24 weeks resulted in small but consistent increases in the incidence of AEs, but did not change the observed AE profile.

No treatment-emergent deaths were reported in the LDV/SOF Phase III safety population and few participants (2.6%) had any SAE. The only SAEs reported in >1 participant across all treatment groups were noncardiac chest pain (three participants), and chest pain, colitis, gastroenteritis, hand fracture, hypertension, intervertebral disc protrusion, and pneumonia (two participants each), suggesting

that no trends in SAE type or onset time were observed. Only five participants (0.3%) had an SAE that was considered related to study drug by the investigator.

Grade 4 laboratory abnormalities were reported in only 1.0% of participants for both the RBV-free (LDV/SOF) and RBV-containing (LDV/SOF+RBV) groups. Grade 3 laboratory abnormalities were reported in 5.4% of participants in the RBV-free (LDV/SOF) groups and 11.4% of participants in the RBV-containing (LDV/SOF+RBV) groups. The increased incidence of Grade 3 laboratory abnormalities in the RBV-containing (LDV/SOF+RBV) groups compared with Grade 3 laboratory abnormalities in the RBV-free (LDV/SOF) groups was driven largely by hemoglobin abnormalities. The addition of RBV to a LDV/SOF treatment regimen contributed substantially to the incidence of anemia that required dose modification or discontinuation (hemoglobin <10 g/dL). A small number of participants with changes in non-hematologic laboratory parameters met the criteria for Grade 3 and 4 laboratory abnormalities. The most common Grade 3 or 4 chemistry laboratory abnormalities across all treatment groups were increased lipase (1.7%) and increased serum glucose (1.5%). In participants with Grade 3 or 4 increased lipase, no case of Grade 3 or 4 increased lipase was associated with clinical signs or symptoms of pancreatitis. Only one case of pancreatitis occurred in the entire Phase III program; this event occurred post treatment in a participant with a history of chronic pancreatitis and was not associated with a Grade 3 or 4 increased lipase. Among participants who experienced a Grade 3 or 4 increased serum glucose, all participants had a history of diabetes, were taking diabetes medication, or had glucose intolerance (denoted by HbA1c >6.0% at screening).

3.0 STUDY DESIGN

This is a Phase II retreatment study of HIV/HCV GT-1-infected participants who have failed prior SOF-based regimens (SOF/RBV, SOF/PEG/RBV, or SOF/SIM +/- RBV) due to virologic failure. Participants will be randomized 1:1 in an open label fashion to 12 weeks of LDV/SOF with weight-based RBV or 24 weeks of LDV/SOF alone. The participants will be followed for an additional 24 weeks after completion of study treatment. There will be 20 participants in each arm, with stratification by cirrhosis status (see section 4.1.2).

The first 15 participants on ARV regimens with a HIV PI/r with tenofovir will be required to participate in the PK component in order to participate in the study. These first 15 participants on PI/r with tenofovir who enroll to the study will undergo semi-intensive PK sampling (pre-dose, hour 1 and hour 4) at weeks 0 and 4 for quantification of tenofovir in plasma. After the first 15 participants have enrolled, subsequent participants taking HIV PI/r with tenofovir may opt out of the PK evaluations but still participate in the study.

Fifteen slots will be held for participants across the study arms whose ARV regimen contains an HIV PI/r plus tenofovir for the first 3 months after the study opens to enrollment. After 3 months, these slots will no longer be reserved to allow expeditious completion of study. Up to 25 participants whose ARV regimen does <u>not</u> contain PI/r

plus tenofovir or who are not taking ARVs will be enrolled to the study during the first 3 months of study enrollment. After the first 3 months, additional participants whose ARV regimen does not contain a PI/r plus tenofovir or who are not taking ARV may be enrolled. The study may end up with fewer than 15 participants whose ARV regimens contain HIV PI/r plus tenofovir and more than 25 participants without, including participants who are not taking ARVs.

The study consists of two steps: on-HCV treatment (Step 1) and post-HCV treatment follow-up (Step 2). At study entry, participants enroll in Step 1 to complete 12 weeks of LDV/SOF with weight-based RBV (Arm A) or 24 weeks of LDV/SOF alone (Arm B). Participants, who experience HCV virologic failure, as defined in section 7.3, will be discontinued from study treatment. At treatment discontinuation, including both completion and premature treatment discontinuation, participants will enter Step 2 for a 24-week follow-up with evaluations at 4, 12, and 24 weeks after the end of treatment.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria Step 1

4.1.1 Men and Women age ≥ 18 years.

4.1.2 Documentation of Non-cirrhotic or Cirrhotic Status:

Non-cirrhotic status as documented by one of the following criteria

- Liver biopsy within 24 months prior to study entry demonstrating the absence of cirrhosis (Metavir F0-F3, Ishak 0-4, or equivalent); or
- FibroScan result of <12.5 kPa within 12 months prior to study entry; or
- HCV FibroSURE score of <0.72 and Aspartate aminotransferase to platelet ratio index (APRI) <2 within 12 months prior to study entry.

Cirrhotic status as documented by one of the following criteria:

- Liver biopsy at any time prior to study entry demonstrating cirrhosis (ie, Metavir >F3, Ishak >4, or the equivalent); or
- FibroScan showing cirrhosis with a reading of ≥12.5 kPa within 12 months prior to study entry; or
- HCV FibroSURE score of ≥0.72 and APRI ≥2 within 12 months of study entry.

NOTE A: Cirrhotic participants must be Child-Turcotte-Pugh (CTP) Class A. An online calculator is available on the A5348 protocol-specific webpage (PSWP). For participants taking atazanavir, the direct bilirubin should be used.

NOTE B: The APRI can be calculated with the following formula:
(AST [IU/L]/AST upper limit of normal ÷ platelet count [x10^9/L]) x 100.

NOTE C: If a participant is evaluated by more than one testing method, then the liver biopsy results take precedence. In the absence of biopsy results, FibroScan

criteria should be used next to determine fibrosis stage. If no biopsy or FibroScan criteria specified above can be met, then the combination of FibroSURE and APRI results can be used. The combined screening FibroSURE/APRI results are adequate for enrollment and to determine cirrhosis status if an acceptable biopsy or FibroScan are not available. If results from FibroSURE/APRI do not meet the criteria above defining the participant as “cirrhotic” or “non-cirrhotic”, the participant is considered to have an “indeterminate” liver status and Fibroscan or liver biopsy will be required prior to study entry. See Tables 4-1 and 4-2 for liver disease classification criteria.

Table 4-1: Interpretation of Serum Markers for Liver Disease Classification

Interpretation of Serum Markers from tests prior to study entry for Liver Disease Classifications		
HCV FibroSURE	APRI	Classification
<0.72	<2	Non cirrhotic
≥0.72	≥2	Cirrhotic
<0.72	≥2	An additional test required to establish the liver disease classification as presence or absence of cirrhosis. This test may be either transient elastography (FibroScan) or histology (liver biopsy). The liver disease will be classified according the result of the additional test.
≥0.72	<2	An additional test required to establish the liver disease classification as presence or absence of cirrhosis. This test may be either transient elastography (FibroScan) or histology (liver biopsy). The liver disease will be classified according the result of the additional test.
Unable to report result	Any	An additional test required to establish the liver disease classification as presence or absence of cirrhosis. This test may be either transient elastography (FibroScan) or histology (liver biopsy). The liver disease will be classified according the result of the additional test.

Interpretation of Transient Elastography for Liver Disease Classifications	
Liver Stiffness (kPa) from testing within 12 months prior to study entry	Classification
<12.5	Non-cirrhotic
≥12.5	Cirrhotic

If data from more than one classification methodology are available, classification will be determined according to the histology or transient elastography results. If both histology and transient elastography are available, classification will be determined according to the histology result.

Table 4-2: Liver Disease Classification

HCV FibroSURE/ APRI	Histology (Liver Biopsy within 2 years prior to study entry)	Transient Elastography (FibroScan) within 12 months prior to study entry	Classification
Any	Non cirrhotic	Not available	Non cirrhotic
Any	Cirrhotic (any time)	Not available	Cirrhotic
Any	Not available	<12.5	Non cirrhotic
Any	Not available	≥12.5	Cirrhotic
Any	Non cirrhotic	Any	Non cirrhotic
Any	Cirrhotic (any time)	Any	Cirrhotic

NOTE: Participants with a FibroSURE that is not reported as a numerical value (e.g., "unable to be reported") must undergo either transient elastography or liver biopsy for liver disease stage classification.

4.1.3 For participants with documented cirrhosis, liver imaging within 6 months prior to entry demonstrating absence of hepatocellular carcinoma (HCC).

NOTE: Acceptable imaging includes a negative ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) within 6 months prior to study entry. Participants who have an ultrasound with results suspicious for HCC followed by a negative CT or MRI of the liver will be eligible for the study.

4.1.4 Presence of HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (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 and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral load. Two or more HIV-1 RNA viral loads of >1,000 copies/mL, at any time prior to screening, are also acceptable as documentation of HIV infection.

4.1.5 Participants must meet one of the following criteria:

a) Not currently on ARV with CD4+ T-cell count >500 cells/mm^3 obtained within 42 days prior to study entry at any laboratory that has a CLIA certification or its equivalent.

OR

b) Not currently on ARV: elite controllers with HIV-1 RNA < 500 copies/mL on all measurements in the 48 weeks prior to study entry and CD4+ T-cell count >200 cells/mm^3 obtained within 42 days prior to study entry at any laboratory that has a CLIA certification or its equivalent.

OR

c) On a stable, protocol-approved ARV regimen, as noted below, for >8 weeks prior to entry with a CD4+ T-cell count >200 cells/mm^3 obtained within 42 days prior to study entry at any laboratory that has a CLIA certification or its equivalent and a documented plasma HIV-1 RNA level <50 copies/mL by any laboratory, obtained within 42 days prior to study entry, that has a CLIA certification or its equivalent.

NOTE: Approved ARV is limited to efavirenz, rilpivirine, raltegravir, dolutegravir, tenofovir, abacavir, 3TC/FTC, RTV-boosted atazanavir, RTV boosted darunavir (both 800 mg QD and 600 mg BID permitted).

4.1.6 For the first 15 participants taking tenofovir and a PI/r as part of their ARV regimen, willingness and intent to participate in PK component.

NOTE: In the event that 15 participants on PI/r and tenofovir have enrolled into A5348, participation in the PK evaluation will be optional for subsequent participants.

4.1.7 HCV GT-1 within 12 months prior to study entry as determined by the local laboratory.

NOTE: Inability to definitively determine genotype or a non-GT-1 will exclude the participant from study participation.

4.1.8 Prior virologic treatment failure with SOF-containing regimen (SOF/RBV, SOF/PEG/RBV, and SOF/SIM).

NOTE A: See section 6.3.3 for requirements for documentation of prior HCV treatment and response.

NOTE B: Prior virologic failure is defined as quantifiable HCV RNA at any time after receiving HCV therapy as prescribed that was not attributed to reinfection.

NOTE C: HCV reinfection is defined by (1) documentation of clearance of prior infection (as evidenced by prior positive anti-HCV Ab or HCV RNA) either spontaneously or after treatment with two negative HCV RNA a minimum of 3 months apart AND (2) positive HCV RNA after documentation of two negative HCV RNA obtained a minimum of 3 months apart *or* infection with a different HCV genotype from the prior infection.

4.1.9 Body mass index (BMI) ≥ 18 kg/m^2 within 42 days prior to study entry.

NOTE A: A BMI calculator is available at the DMC website (http://www.fstrf.org).

NOTE B: The height and weight measurement used to calculate BMI must be obtained on the same day.

4.1.10 The following laboratory values obtained within 42 days prior to study entry by any US laboratory that has a CLIA certification or its equivalent.

- HCV RNA $\geq 10^4$ IU/mL
- Hemoglobin ≥ 12.0 g/dL for male, ≥11.0 g/dL for female participants
- Platelets ≥ 50,000/mm^3
- International normalized ratio (INR) ≤1.5 x ULN unless participant has known hemophilia or is stable on an anticoagulant regimen affecting INR, in which case any INR value is acceptable
- Albumin ≥ 3.0 g/dL
- Creatinine clearance (CrCl) ≥ 60 mL/min, as calculated by the Cockcroft-Gault equation (refer to section 6.3.5 for calculator utility link)
- Aspartate aminotransferase (AST) (SGOT) < 10 x ULN
- Alanine aminotransferase (ALT) (SGOT) < 10 x ULN
- Direct bilirubin ≤ 1.5 x ULN
- Hgb A1C ≤ 8.5%

4.1.11 Screening electrocardiogram (ECG) without clinically significant abnormalities as determined by the investigator within 42 days prior to study entry.

4.1.12 Willing and able to provide written informed consent.

4.1.13 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 pregnancy test with a sensitivity of at least 25 mIU/mL performed at screening and again, within 48 hours prior to study entry.

4.1.14 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).

4.1.15 When participating in sexual activity that could lead to pregnancy, all participants must agree to use at least two reliable forms of contraceptive simultaneously while receiving protocol-specified medications, and for 6 months after stopping the medications. Such methods include:

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Tubal ligation
- Hormone-based contraceptive

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

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

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

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

4.1.17 Intention to comply with the dosing instructions for study drug administration and ability to complete the study schedule of assessments.

4.2 Exclusion Criteria Step 1

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

4.2.2 Prior exposure to a DAA other than SOF and SIM.

NOTE: Prior exposure to other HCV NS3 protease inhibitors given as part of a regimen containing only interferon/ribavirin and no other DAA agents will be allowed, as long as subsequent failure with SOF-based regimen occurred, as outlined in section 4.1.8.

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

4.2.4 Presence of active or acute AIDS-defining opportunistic infections within 42 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

4.2.5 Active, serious infection (other than HIV-1 or HCV) requiring parenteral antibiotics, antivirals, or antifungals within 42 days prior to study entry.

4.2.6 Infection with hepatitis B virus (HBV) defined as HBsAg positive within 42 days prior to study entry.

4.2.7 History of clinically significant hemoglobinopathy (e.g., sickle cell disease, thalassemia).

4.2.8 Chronic current use of systemically administered immunosuppressive agents (e.g., prednisone equivalent > 10 mg/day for more than 2 weeks).

NOTE: Participants taking 10 mg/day or less of prednisone equivalent are not excluded, but should be discussed with the team prior to enrollment.

4.2.9 History of solid organ transplantation.

4.2.10 Current or prior history of clinical hepatic decompensation (e.g., ascites, encephalopathy or variceal hemorrhage).

4.2.11 History of a gastrointestinal disorder (or postoperative condition) that could interfere with the absorption of the study drug.

4.2.12 History of significant or symptomatic pulmonary disease, cardiac disease, or porphyria that in the opinion of the investigator would interfere with the study.

4.2.13 History of difficulty with blood collection and/or poor venous access for the purposes of phlebotomy.

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, which may include active drug or alcohol use or dependence.

4.2.15 Use of any prohibited concomitant medications per the LDV/SOF product labeling, as noted on the A5348 PSWP, within 42 days prior to study entry.

4.2.16 Known hypersensitivity to RBV, SOF, LDV, their metabolites, or formulation excipients or any other contraindication to the use of RBV, SOF or LDV.

NOTE: Individuals with prior intolerance attributed to SOF will not be permitted to enroll.

4.2.17 Currently receiving zidovudine (ZDV), didanosine (ddI), stavudine (d4T) or tipranavir.

4.2.18 Acute HIV infection defined as the phase immediately following infection during which anti-HIV antibodies are undetectable.

NOTE: Inclusion of participants with early infection, defined as within the first 6 months of infection and with a positive HIV antibody, should be discussed with the A5348 protocol core team. These individuals may be considered for inclusion in the study on a case by case basis with the specific documented approval of the protocol chairs.

4.2.19 Known hepatocellular carcinoma.

4.2.20 Breastfeeding or pregnancy.

4.2.21 A male participant with a pregnant female partner.

4.2.22 Received treatment with colony stimulating agents, including but not limited to erythropoietin, within 42 days prior to study entry.

4.3 Inclusion Criteria Step 2

4.3.1 Permanent discontinuation of Step 1 study treatment.

4.3.2 Availability of date of last dose of study treatment in Step 1.

4.4 Exclusion Criteria Step 2

4.4.1 Premature study discontinuation in Step 1.

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 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 the required documents have been received. Site-specific ICF 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 participant for study entry has been identified, details will be carefully discussed with the participant. The participant (or, when necessary, the parent or legal representative if the participant is under guardianship) will be asked to read and sign the approved protocol consent form.

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

4.5.2 Randomization/Participant Registration

At entry, participants will be enrolled according to standard ACTG DMC procedures.

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.

4.6 Coenrollment Guidelines

US sites are encouraged to coenroll participants in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.”

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

5.0 STUDY TREATMENT

A5348 study treatment drugs are defined as ledipasvir (90mg)/sofosbuvir (400mg) (LDV/SOF) (brand name: Harvoni) and weight-based ribavirin (RBV).

5.1 Regimens Administration, and Duration

In this phase II retreatment study, a total of 40 participants will be randomized at entry in 1:1 open-label fashion to Arm A or Arm B (20 participants per arm), as outlined in Tables 5-1 and 5-2.

Table 5-1: A5348 Treatment Regimen

Weeks	Arm A	Arm B (no RBV)
1-12	LDV 90 mg/SOF 400 mg fixed dose tablet once daily PLUS Ribavirin, based on weight at entry For weight <75 kg: 1000 mg per day* For weight ≥75 kg: 1200mg per day*	LDV 90 mg/SOF 400 mg fixed dose tablet once daily
13-24	No treatment	LDV 90 mg/SOF 400 mg fixed dose tablet once daily

*Total daily dose of ribavirin has been divided into two doses. The dose of ribavirin will be based on participant's weight at entry. Changes in weight after entry do not require a change in dose. Doses will only be changed for toxicity management. Ribavirin will be available as ribavirin 200mg tablets.

Table 5-2: Weight-based Ribavirin Dose

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

5.1.1 Administration

Ledipasvir/sofosbuvir should be taken with morning or evening ribavirin, if assigned to a ribavirin-containing therapy (Arm A). Participants should be instructed to take all doses of study drug with food. Study drug should be taken at the same times and maintain the same time intervals every day.

If a participant forgets to take the ledipasvir/sofosbuvir at the correct time, it may be taken later in the day; however, no more than one tablet of ledipasvir/sofosbuvir should be taken on any calendar day. The participant should resume the standing dosing schedule on the next day. Study medications should not be cut or split. If participants miss a dose of ribavirin, they should take the missed dose 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. Participants should not double the next dose of either study drug in order to "make up" what had been missed.

5.1.2 Duration

Study treatment may continue for a period of 12 or 24 weeks (as assigned at study entry). Study follow-up will be for 24 weeks after treatment completion.

5.2 Study Product Formulation and Preparation

5.2.1 Formulation

Ledipasvir (90 mg) /sofosbuvir (400 mg) (brand name: Harvoni) is a fixed-dose combination tablet. It is an orange colored, diamond shaped, film-coated tablet debossed with “GSI” on one side and “7985” on the other side of the tablet. Each tablet contains ledipasvir (90 mg) /sofosbuvir (400 mg) as active ingredient. In addition to the active ingredients, ledipasvir (90 mg) /sofosbuvir (400 mg) tablet contain the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

Ribavirin will be supplied as tablets for oral administration, each containing 200 mg of ribavirin.

5.2.2 Storage

Bottle containing ledipasvir (90 mg) /sofosbuvir (400 mg) should be stored at a controlled room temperature. Controlled room temperature is defined as 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).

Ribavirin tablets should be stored at 20°C - 25°C (68°F - 77°F).

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

Gilead Sciences, Inc. will provide ledipasvir (90 mg) /sofosbuvir (400 mg) for this study; ribavirin will be provided through the study. Study products will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study products for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section *Study Product Management Responsibilities.*

ARV will not be provided through the study.

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. All unused study products in US CRSs 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 in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

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 updated ACTG Drug Interactions Database located at: http://tprc.pharm.buffalo.edu/home/di_search.

5.4.1 Required Medications

See inclusion criteria (section 4.1.5) for specifications about ARV. Changes to ARV must be discussed with the A5348 protocol core team during the study drug dosing period.

5.4.2 Prohibited Medications

For a list of prohibited medications, please refer to the A5348 PSWP, as well as the ledipasvir/sofosbuvir package insert, which is available on the A5348 PSWP.

5.4.3 Precautionary Medications

For a full list of precautionary medications, please refer to the ledipasvir/sofosbuvir package insert, which is available on the A5348 PSWP.

H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from ledipasvir/sofosbuvir at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.

Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower should only be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions.

5.4.4 Colony Stimulating Agents

Under no circumstances are potential participants to be treated with colony stimulating agents during screening to elevate hematology laboratory parameters to facilitate entry into the study. Colony stimulating agents, 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 Events

Evaluations	Screening (Within 42 days prior to entry)	Entry	STEP 1								STEP 2			HCV VF Confirmation	HIV-1 VF Confirmation	Prem. Tx/Study Discontinuation[1]
			On-Treatment (Arms A&B) Week					On-Treatment (Arm B only) Week			Post-Treatment (Arms A&B) (R=Date of Last Dose of Study Treatment) Week					
			1	2	4	8	12[1]	16	20	24[1]	R+4	R+12	R+24			
			(Within ± 3 days)		(Within ± 7 days)						(Within -5 to +7days)	(Within -5 to +14days)	(Within -7 to +14days)			
HIV-1 Documentation	X															
Cirrhosis Status Documentation	X															
Documentation of HCV Treatment	X	X														
Medical History	X	X														
Medication History	X	X														
Clinical Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Height	X															
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X			X
BMI	X															
12-Lead ECG	X															
Hematology & Chemistries	X	X	X	X	X	X	X	X	X	X	X	X	X			X

Evaluations	Screening (Within 42 days prior to entry)	Entry	STEP 1								STEP 2			HCV VF Confirmation	HIV-1 VF Confirmation	Prem. Tx/Study Discontinuation[1]
			On-Treatment (Arms A&B) Week					On-Treatment (Arm B only) Week			Post-Treatment (Arms A&B) (R=Date of Last Dose of Study Treatment) Week					
			1	2	4	8	12[1]	16	20	24[1]	R+4	R+12	R+24			
			(Within ± 3 days)		(Within ± 7 days)						(Within -5 to +7days)	(Within -5 to +14days)	(Within -7 to +14days)			
Liver Function Tests	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Hgb A1c	X															
Uric Acid		X					X			X						
Calculated CrCl	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Lipid Panel (fasting)[2]		X					X			X						X
INR	X	X					X			X						X
Urinalysis		X	X[3]	X[3]	X	X[3]	X	X[3]	X	X[3]	X[3]					
Urine for spot protein and creatinine		X	As indicated (see section 6.3.7)													
Serum Pregnancy Test[4]	X	X														
Urine Pregnancy Test			X	X	X	X	X	X	X	X	X	X	X			X
HBsAg	X															
HCV RNA Local lab	X															

Evaluations	Screening (Within 42 days prior to entry)	Entry	STEP 1								STEP 2			HCV VF Confirmation	HIV-1 VF Confirmation	Prem. Tx/Study Discontinuation[1]
			On-Treatment (Arms A&B) Week					On-Treatment (Arm B only) Week			Post-Treatment (Arms A&B) (R=Date of Last Dose of Study Treatment) Week					
			1	2	4	8	12[1]	16	20	24[1]	R+4	R+12	R+24			
			(Within ± 3 days)		(Within ± 7 days)						(Within -5 to +7days)	(Within -5 to +14days)	(Within -7 to +14days)			
HCV RNA (Real time)		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Plasma HCV Genotype Test	X													X		
HCV Resistance Testing		X												X		
Stored Plasma for HCV Studies (see section 6.3.8)		X	X	X	X		X			X				X		X
Plasma HIV-1 RNA (real-time)[5]	X	X[5]			X[5]		X[5]			X[5]	X[5]				X[5]	X[5]
Plasma HIV-1 RNA Resistance Testing															X	
CD4+/CD8+	X	X					X			X						X
Stored Whole Blood Sample for Future Genetic Testing		X														
Stored Urine		X			X		X			X	X					X

Evaluations	Screening (Within 42 days prior to entry)	Entry	STEP 1								STEP 2			HCV VF Confirmation	HIV-1 VF Confirmation	Prem. Tx/Study Discontinuation[1]
			On-Treatment (Arms A&B) Week					On-Treatment (Arm B only) Week			Post-Treatment (Arms A&B) (R=Date of Last Dose of Study Treatment) Week					
			1	2	4	8	12[1]	16	20	24[1]	R+4	R+12	R+24			
			(Within ± 3 days)		(Within ± 7 days)						(Within -5 to +7days)	(Within -5 to +14days)	(Within -7 to +14days)			
TFV PK Evaluation (pre-dose, 1hr, 4hr)[6] (FASTING)		X			X											
Dried Blood Spots for PK		X	X	X	X	X	X	X	X	X	X					
IL-28B Genotype		X														
Pregnancy Prevention Counseling	X	X			X		X				X					X
Adherence Assessments (4 day recall, pill counts)			X	X	X	X	X	X	X	X						
Study Drug Dispensing		X			X	X	X	X	X							
Medication Diary[7] (D=distribution, C=collect)		X (D)	X (C/D)	X (C/D)	X (C/D)	X (C/D)	X (C/D)	X (C/D)	X (C/D)	X (C/D)	X (C)					

NOTES

[1] Refer to Section 6.2.3 regarding registration into Step 2.

[2] Participants must be fasting for visits at entry, weeks 12, and 24, and premature discontinuation. If not fasting, they should return within 7 days of the visit to repeat the lipid panel that require fasting per section 6.3.7 and within 48 hours fasting to complete the tenofovir PK evaluation, if applicable.

[3] Urinalysis at this timepoint is required only for participants on tenofovir/ritonavir-boosted HIV protease inhibitor.

[4]Females must have a negative serum pregnancy test with a sensitivity of at least 25 mIU/mL performed at screening and within 48 hours prior to study entry.

[5]HIV RNA after screening is only required if participant is taking ARV.

[6] For participants on tenofovir and PI/r only. Participants should be in a fasting state until after the 1 hour post dose PK blood draw is obtained.

[7] Use of medication diary is recommended for the two PK visits and is optional for dried blood spot visit (see section 6.3.17).

6.2 Timing of Evaluations

6.2.1 Screening

Screening
Screening evaluations to determine eligibility must be completed within 42 days prior to entry unless otherwise specified and must occur prior to the participant starting any study medications, treatments, or interventions.

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 all screening evaluations have been completed. Entry evaluations must be performed before study treatment is started.

Participant must be fasting (i.e., no food or drink, except water for taking prescription medications, for at least 8 hours) for the lipid panel and TFV PK evaluation at entry.

Participant must begin study treatment within 48 hours after randomization.

6.2.3 Post-Entry Evaluations

Step 1: On-Treatment Evaluations
On-treatment (Step 1) visits are scheduled in reference to the date of study entry. Weeks 1 and 2 have a window of ±3 days. Weeks 4, 8, 12, 16, 20, and 24 have a window of ±7 days. Only those participants randomized to Arm B will have weeks 16, 20, and 24 on-treatment evaluations.

Step 2: Post-Treatment Evaluations
Participants will be registered to Step 2 at their last on-treatment visit. R is the date of the last dose of study treatment. Arm A participants will register to Step 2 at week 12. Arm B participants will register to Step 2 at week 24. Participants who prematurely discontinue study treatment will register to Step 2 at the premature treatment discontinuation visit.

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

- Week R+4: -5 days to +7 days
- Week R+12: -5 days and +14 days
- Week R+24: -7 days and +14 days

Study Completion Evaluations
The week R+24 visit will be completed as the participant's final study visit.

6.2.4 Event Driven Evaluations

HCV Virologic Failure/Relapse Confirmation
Participants with suspected HCV VF, as defined in section 7.3, must have a confirmation sample obtained as soon as possible, but within 2 weeks of initial notification of HCV RNA meeting criteria for HCV VF. Participants who permanently discontinue study treatment for HCV VF (see details in section 7.3) will be followed on study/off treatment in Step 2 per the SOE.

Virologic evidence of HCV relapse, defined as HCV RNA <LLOQ at end-of-treatment but HCV RNA ≥LLOQ during follow-up, will require confirmation and the sample should be obtained and the sample sent in real time to the designated laboratory as soon as possible but within 2 weeks after determination of initial observation. The results will be provided to the site investigators within 2 weeks of specimen receipt.

HIV-1 Virologic Failure (VF) Confirmation
Participants with suspected HIV-1 virologic failure, as defined in section 7.1.6, must have a confirmation sample obtained within 2 weeks after the initial sample was drawn. In addition, participants must complete the evaluations listed for HIV-1 VF Confirmation, as per section 6.1. If the HIV-1 VF confirmation visit coincides with a regularly scheduled visit, the evaluations should be combined.

Participants with confirmed HIV-1 RNA ≥200 copies/mL will have a corresponding stored sample submitted for HIV-1 resistance genotyping.

Participants confirmed to have HIV-1 VF will continue to be followed on study/off study treatment per the Schedule of Events (SOE), if an HIV-1 regimen compatible with study treatment is available. If there are no HIV-1 regimens available that are compatible with study treatment, then the participant must discontinue study treatment and will be followed on study/off study treatment per the SOE (see details in section 7.1.6).

6.2.5 Discontinuation Evaluations

Evaluations for Randomized Participants Who Do Not Start Study Treatment
Participants who do not start study treatment will be taken off study with no further evaluations required. All CRFs must be completed and keyed for the period up to and including entry.

Premature Treatment Discontinuation Evaluations
The protocol core team must be informed, as soon as possible, when a participant prematurely discontinues 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 defined in section 7.3 will also follow the Step 2 schedule in section 6.1. If applicable, additional or more frequent post-treatment toxicity follow up may be determined by the site

investigator.

Participants who prematurely discontinue study treatment (i.e., prior to completion of the last dose of LDV/SOF per the assigned dosing period) will complete the premature treatment discontinuation evaluations within 7 days of discontinuation and be registered to Step 2 (R). Participants will remain on study and complete the post-treatment visits at weeks R+4, R+12, and R+24 weeks per the SOE.

Participants who prematurely discontinue the study treatment for any reason will register for Step 2 at their Premature Treatment Discontinuation Visit.

NOTE: If LDV/SOF is discontinued, Arm A participants should discontinue RBV. Under no condition should the participant remain on RBV monotherapy.

Pregnancy
Pregnancy will result in immediate and permanent discontinuation of the study medications. Please see section 7.2 for detailed information regarding participant management. Participants will be followed on-study/off-treatment per the SOE.

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 Web site for information about what must be included in the source document: http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/sourcedocappndx.pdf

All stated evaluations are to be recorded on the CRF and keyed into the database unless otherwise specified. This includes events that meet the International Conference on Harmonisation (ICH) definitions for a serious adverse event:

- Results in death
- Life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other important medical event (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 events listed above.

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0 (November 2014), which can be found on the DAIDS RSC Web site:

http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx

6.3.1 Documentation of HIV-1

Section 4.1.4 specifies assay requirements for HIV-1 documentation. HIV-1 documentation will not be recorded on the CRF.

6.3.2 Documentation of Cirrhosis Status

Section 4.1.2 specifies requirements for documentation of cirrhosis status. Documentation will be recorded on the CRF.

6.3.3 Documentation of Prior HCV Treatment and Response

Section 4.1.8 and the table below specify requirements for documentation of prior HCV treatment and its response. This documentation will be recorded on the CRF.

Table 6-1: Prior HCV Treatment and Response

Past Treatment Response Category	Definition	Past Treatment Response Sub-category
Treatment-Intolerant	Participant discontinued prior HCV treatment due to a laboratory abnormality or intolerable side effect. Participant did not meet a virologic failure criterion.	N/A
Non-Responder	Participant did not achieve undetectable HCV RNA levels (HCV RNA ≥ LLOQ) while on HCV treatment. This was the reason for discontinuing treatment rather than an AE.	For PEG-IFN/RBV non-responders, participants should be further defined as Null or Partial Responders: Null Responders: HCV RNA <2 Log10 reduction during the first 12 weeks of treatment. Partial Responders: HCV RNA ≥2 Log10 reduction during the first 12 weeks of treatment.
Relapse/Breakthrough	Participant achieved undetectable HCV RNA levels (HCV RNA < LLOQ) during HCV treatment,	Relapse: Participant achieved undetectable HCV RNA levels (HCV RNA < LLOQ) at end of treatment but HCV RNA

Past Treatment Response Category	Definition	Past Treatment Response Sub-category
	but did not achieve a SVR. If treatment was discontinued early, it was because of breakthrough rather than an AE.	became detectable after treatment was stopped, at or before 24 weeks after treatment discontinuation. Breakthrough: Participant experienced ≥1 log increase in HCV RNA from nadir while on treatment.

6.3.4 Medical History

In addition to reporting all diagnoses within the past 42 days, the following diagnoses should be reported 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 B

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

6.3.5 Medication History

A medication history must be present, including start and stop dates. Table 6-2 below lists the medications that must be included in the history.

Table 6-2: Medication History

Medication Category	Complete History or Timeframe
HIV treatment	Within 56 days prior to entry
HCV treatment	Complete history
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

6.3.6 Clinical Assessments

Complete Physical Exam
A complete physical examination must be performed at screening and is to include at a minimum an examination of the 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 exam will also include diagnoses, signs, and symptoms and vital signs (temperature, pulse, respiratory rate, and resting blood pressure).

NOTE: Blood pressure will be measured following the current ACTG Standardization of Blood Pressure Measurement SOP.

Targeted Physical Exam
A targeted physical examination must be performed at entry and all subsequent visits, as specified in the SOE. 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 and diagnoses that the participant has experienced since the last visit.

NOTE: Blood pressure will be measured following the current ACTG Standardization of Blood Pressure Measurement SOP.

Height
Record height (in centimeters) at screening.

Weight
Record weight (in kilograms) as indicated in section 6.1.

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

BMI
BMI will be calculated at screening using standard formula. BMI will not be recorded on the CRF.

A BMI calculator is available at the DMC website (https://www.fstrf.org).

12-Lead ECG
An electrocardiogram (ECG) will be performed at screening. ECG results will not be recorded on the CRF.

NOTE: Participant should rest in a supine position for ≥ 5 minutes prior to making a recording. The investigator (or qualified designee) should review the ECG traces recorded in real time for gross abnormalities.

Signs and Symptoms
At entry, all signs and symptoms, regardless of grade, that occurred within 42 days prior to study entry must be recorded. Post-entry, only signs and symptoms Grade ≥3 and all signs and symptoms that led to a change in treatment (excluding indications for RBV dose modification) or that met ICH, EAE, or SAE guidelines, regardless of grade, must be recorded, and are defined by the protocol as reportable events that will require more detailed event reporting.

Diagnoses
After entry, record any diagnoses targeted for A5348 that are Grade ≥ 3 identified by the ACTG criteria for clinical events and other diseases, any diagnosis regardless of grade that led to a change in treatment (excluding indications for RBV dose modification), or any diagnosis that met ICH, EAE, or SAE guidelines.

Concomitant Medications
Record new or discontinued concomitant prescription and nonprescription medications.

Study Treatment Modifications
Record all study drug modifications, including initial doses, participant-initiated and/or protocol-mandated modifications, inadvertent and deliberate interruptions at each visit. Record any permanent discontinuation of treatment.

Antiretroviral Medications
Record all modifications to antiretroviral medications including initial doses, participant-initiated and/or protocol-mandated modifications, inadvertent and deliberate interruption, and permanent discontinuation.

6.3.7 Laboratory Evaluations

At screening and entry, all laboratory values must be recorded. For post-entry assessments, record all grades of creatinine and creatinine clearance and all other Grade ≥3 laboratory values. All laboratory toxicities that led to a change in treatment (excluding indications for RBV dose reduction), regardless of grade, must be recorded.

All Grade 3 or higher laboratory values, any laboratory value that led to a change in treatment (excluding indications for RBV dose modification) or that met ICH, EAE, or SAE guidelines are defined by the protocol as reportable events that will require more detailed event reporting.

The study team should be notified (actg.coreA5348@fstrf.org) of any new or worsened Grade ≥ 2 creatinine values, new or worsened Grade ≥2 proteinuria or glucosuria after week 4 of study treatment.

Fasting Instructions
Fasting is defined as nothing to eat or drink except prescription medications and water for at least 8 hours. Fasting is only required for blood draws with lipid panel and the tenofovir PK evaluation. If participants are in a non-fasting state, they can proceed with non-fasting evaluations and have a fasting lipid evaluation (if indicated) within 7 days of the visit or undergo the tenofovir PK evaluation (if indicated) within 48 hours of the visit.

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

Hemoglobin A1C: Required at screening only.

Blood Chemistries
Sodium, potassium, chloride, bicarbonate/CO_2, blood urea nitrogen (BUN), creatinine, glucose, and lipase.

Uric Acid: required at weeks 0, 12, and 24.

Liver Function Tests
Total bilirubin, direct bilirubin, indirect bilirubin, albumin, AST (SGOT), ALT (SGPT), alkaline phosphatase.

Calculated CrCl
Estimated each time that a creatinine level is determined.

To estimate calculated CrCl, use the following method of Cockcroft and Gault:
- For men: [(140 - age in years) x (body weight in kg)] ÷ (serum creatinine in mg/dL x 72).
- For women: use the same calculation as for men, then multiply the result by 0.85.

A calculator is available at the DMC website https://www.fstrf.org/ACTG/ccc.html.

Lipid Panel (fasting)
Low density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), and total cholesterol (TC).

Coagulation Marker
INR

Urinalysis
Blood, glucose, leukocyte esterase, pH, protein, urobilinogen. Reflex testing to microscopic urinalysis if dipstick result is abnormal. Please note requirement for frequency of urinalysis testing is determined by ARV regimen (PI/r/tenofovir vs. non-PI/r/tenofovir) as outlined in the SOE, section 6.1.

Record all urinalysis results including glucose and protein results on the CRF.

Urine Spot Protein & Creatinine
Spot protein and creatinine with calculation of protein/creatinine ratio is required at entry. This should be repeated in any participants who develop new proteinuria or glucosuria, an increase from entry glucosuria or proteinuria by ≥ 1+ or who develop an increase in creatinine of 0.4 from entry or CrCl < 50 (see section 7.1.3). Urine spot protein and creatinine should be conducted at each study visit through R+4, unless the preceding visit urinalysis demonstrates resolution of proteinuria and/or glucosuria or an increase in creatinine of 0.4 from entry or CrCl < 50 has resolved.

Pregnancy Test
For women with reproductive potential: a serum β-HCG documenting a negative result will be required at screening and within 48 hours prior to study entry. Serum tests should have a sensitivity of at least 25 mIU/mL.

Once a participant has enrolled with a negative documented serum pregnancy test and begins using two forms of contraceptives 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; if positive, must have immediate confirmation with serum β-HCG.

All women of reproductive potential will have a pregnancy test, as indicated in SOE. 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. See section 7.2 for detailed information regarding study management.

Serologies
HBsAg will be done during screening with results available prior to study entry. HBsAg will not be recorded on the CRF.

6.3.8 Virologic Studies

HCV RNA (screening)
The screening HCV RNA must be obtained within 42 days prior to study entry using any FDA-approved test for quantifying HCV RNA at any local laboratory that has a CLIA certification or its equivalent.

HCV RNA (on-study evaluations)
At the entry and post-entry visits, HCV RNA quantification will be performed at the designated testing laboratory) as follows:

Serum HCV RNA real-time testing will be collected, processed, and shipped to the designated testing laboratory (see A5348 laboratory processing chart [LPC] for instructions). These results will be reported within 2-3 weeks after specimen receipt.

NOTE: The study team should be notified (actg.coreA5348@fstrf.org) of detectable HCV RNA after week 4 of study treatment.

HCV Genotype
At screening, the HCV genotype and subtype result will be obtained locally from any laboratory that has a CLIA certification or its equivalent. ONLY IF IT IS NOT AVAILABLE LOCALLY should it be done at the designated testing laboratory (see A5348 LPC).

Stored plasma will be collected at the entry visit for additional testing and may be used for HCV genotype testing if confirmation of genotype is requested by the study team.

HCV genotype sample collected at the time of HCV viral failure confirmation will not be performed locally, but should be collected and shipped as per the LPC.

HCV Resistance Testing
HCV resistance testing will be performed at entry for all participants and repeated at the time of HCV virologic failure confirmation. Resistance testing at the time of virologic failure will be performed real time. Refer to the A5348 LPC for collection, storage and shipping information.

Stored Plasma for HCV Studies
Plasma samples will be collected and stored for potential HCV sequencing and other virology studies. For processing and shipping instructions, refer to the A5348 LPC.

Plasma HIV-1 RNA (real time)
A screening plasma HIV-1 RNA level must be obtained within 42 days prior to study entry, using an FDA-approved assay from any laboratory or clinic that has a CLIA certification or its equivalent. On-study HIV-1 RNA should be performed at the designated testing laboratory and is only required for participants taking ARV. Refer to the A5348 LPC for processing and shipping information.

Participants on ARV who later experience HIV-1 VF while on HIV therapy should be managed as per section 7.1.6.

Plasma HIV-1 Resistance Testing (real-time)
If there is a confirmed HIV-1 VF (HIV-1 VL ≥200 copies) in a participant while taking HCV treatment (or within 4 weeks after permanent discontinuation), a plasma specimen must be obtained at the time of the confirmation sample and, if HIV-1 VF is confirmed with an HIV-1 VL ≥200, the sample must be sent to A5348 testing lab as per the LPC for evidence of drug resistance.

6.3.9 Immunologic Studies

CD4+/CD8+ T-cells
Screening CD4+/CD8+ testing may be done by any laboratory or clinic that possesses a CLIA certification or its equivalent.

During the study, all laboratories must possess a CLIA certification or its equivalent and must be certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program.

6.3.10 Additional Stored Samples

Plasma will be collected and stored at the indicated visit (see section 6.1) for future testing including HCV and HIV resistance testing, HCV genotype confirmation if necessary, as well as future ACTG-approved research, and shipped according to the A5348 LPC. Plasma will be collected from all participants for HIV and /or HCV resistance testing, should virologic breakthrough occur. Participants will be asked to provide consent for use of stored specimens for future research.

There will be a one-time collection of whole blood for future genetic analyses for participants who consent to this sample collection.

Stored Urine
Urine will be collected and stored for evaluation of retinol binding protein, beta-2 microglobulin, and creatinine. Refer to A5348 LPC for instructions.

6.3.11 Tenofovir PK Samples

The tenofovir (TFV) PK sampling evaluations will be only required for the first 15 participants, and consenting participants thereafter, who are taking ritonavir-boosted protease inhibitor and tenofovir.

The first TFV PK evaluation will occur at entry prior to initiation of LDV/SOF. For the entry evaluation, the date and time of the last three doses of TFV and other ARVs
must be recorded on the CRF. The participant will not receive study treatment until after all of the PK samples have been obtained. The second TFV PK evaluation will occur 4 weeks after initiating LDV/SOF. For the week 4 evaluation, the date and time of the reference (current) dose and the last three doses of LDV/SOF and the last three doses of ARVs taken immediately prior to the pre-dose blood sample must be recorded on the CRF.

Weight will also be recorded on the CRF.

For these visits, participants will come in to the clinic approximately 24 hours after their previous dose of TDF, following an 8 hour fast. A blood sample will be obtained at pre-dose, participants will then take an observed dose of TDF (and LDV/SOF at week 4 only), and additional blood samples will be obtained at 1 and 4 hours post-observed dose. Participants should be fasting until after the 1-hour blood draw has been completed. After this draw, participants may eat and no specific meal is required.

If the participant is not fasting at the entry visit, all entry evaluations should be performed except for the tenofovir PK evaluation and the participant should return fasting within 48 hours and before administration of study drug for the tenofovir PK evaluation.

Participants will be instructed to keep a written record of the date and time of the last three doses of all HIV-1 and HCV drugs taken prior to the PK visit in the medication diary (see section 6.3.17), and to bring this information to the clinic.

The week 4 evaluation should be rescheduled if participants are not considered to be at steady-state due to missed doses of any ARV or DAA (for the week 4 PK visit, excluding ribavirin) within the previous 3 days.

Refer to section 10.2 for more detail on PK plan. For processing and shipping instructions, refer to the A5348 LPC.

6.3.12 Dried blood spots (DBS)

One DBS will be collected on ALL participants at required visits regardless of ARV regimen, as outlined in section 6.1 to evaluate SOF and LDV blood levels, as well as potentially to evaluate tenofovir levels and for other future research evaluations in participants who have provided consent for this. The date and time of the most recent LDV/SOF and ARV dose will be recorded on the CRF.

For processing and shipping instructions, refer to the A5348 LPC.

6.3.13 IL-28B genotype

IL-28B genotype will be conducted at entry, if no record of prior IL-28B testing is available. Testing can be conducted locally at a CLIA-certified laboratory. If not available to sites as local standard of care test, IL-28B testing may be conducted centrally, as outlined in the A5348 LPC.

6.3.14 Pregnancy Prevention Counseling

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

6.3.15 Adherence Assessment

Adherence assessment is performed for study treatment only.

This study will use a combination of three measures of adherence (1) the Adult ACTG 4-day recall, (2) pill count, and (3) LDV and SOF metabolite concentrations through collection of dried blood spots (DBS).

6.3.16 Study Drug Dispensing

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

6.3.17 Medication Diary

The medication diary will be distributed and collected as per the SOE. The diary is recommended to be used to record dosing for the three doses of HCV and HIV medications prior to the two tenofovir PK visits. They may be used as an optional tool for participants to record medication adherence throughout the study and for recall at the time of the DBS blood draws. A sample medication diary is provided for use on the DMC website (http://www.fstrf.org), but sites may choose to use a site-provided diary.

7.0 CLINICAL MANAGEMENT ISSUES

Criteria for participant management, dose interruptions, dose adjustments and discontinuation, or changes in treatment will be described only for toxicities attributable to study drugs (i.e., SOF, LDV, and RBV).

The grading system for drug toxicities is located in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, which can be found on the DAIDS RSC Web site: http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.

NOTE: The team must be notified via e-mail within 72 hours regarding toxicities that result in a change in study regimen (actg.coreA5348@fstrf.org).

7.1 Toxicity

Toxicity management is the responsibility of the site investigator who is encouraged to communicate with the core team regarding any management questions.

7.1.1 Management of Side Effects of RBV (Arm A only)

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; therefore pregnant women or breastfeeding women and men with pregnant sexual partners should not receive RBV. Women who become pregnant on study and men on study whose partners become pregnant must discontinue study treatment and will be managed per section 7.2.

RBV dosing in this study will be based on weight at study 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 7-1 It is recommended that sites contact the protocol core team with questions regarding difficult anemia management and/or if it is felt RBV discontinuation is required. Participants may continue to take LDV/SOF if RBV is temporarily or permanently discontinued.

Table 7-1: 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 period treatment	<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 7-2: Suggested RBV Dosing Intervals for Reintroduction

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 Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014. Therefore, sites are expected to use A5348-specific criteria.

7.1.2 Management of Side Effects of LDV/SOF

Dose reduction of LDV/SOF will not be allowed in the study. If LDV/SOF is stopped for toxicity, it should not be restarted and the participant should complete the treatment discontinuation visit. All participants must complete the week R+4, R+12, and R+24 visits. The week R+4, R+12, and R+24 visits will be scheduled from the date of the last dose of study treatment.

If LDV/SOF is discontinued, Arm A participants should discontinue RBV. Under no condition should the participant remain on RBV monotherapy.

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

- ALT or AST ≥10 x ULN (see section 7.1.5 for additional detail on elevated transaminases)
- Confirmed direct bilirubin 3 x ULN and > 2.0 mg/dL
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 event assessed as related to treatment with LDV/SOF

7.1.3 Specific Guidance for Creatinine Clearance (CrCl)

CrCl will be calculated throughout the study using Cockcroft-Gault method. Refer to the Cockcroft-Gault calculator located on the FSTRF web site and using the weight obtained at each visit.

7.1.3.1 If a participant experiences a CrCl decrease to <50 mL/min or an increase in creatinine of ≥ 0.4 mg/dL from entry creatinine, the following evaluations should occur:

- Within 7 days: repeat evaluation of electrolytes, creatinine, serum phosphorus, urinalysis including assessment of proteinuria and glucosuria with spot creatinine and protein assessment and calculation of protein/creatinine ratio.

- Assessment of current weight for repeat CrCl calculation.

  If calculated CrCl is confirmed to have decreased to <50 mL/min, the A5348 protocol core team should be contacted by e-mail at actg.corea5348@fstrf.org.

- Medical evaluation must include a full review of current medications, including those taken on an as-needed basis, those which are sold over the counter, and any dietary and herbal supplements. Study DAAs may be continued. Ribavirin should be dose reduced for CrCl < 50 as follows:

Table 7-3: Suggested Dose Reduction of Ribavirin

Creatinine	Ribavirin Dose
30-50	200 mg every other day alternating with 400 mg every other day
< 30	200 mg daily and consider discontinuation

- Creatinine and chemistries should be repeated as clinically indicated until resolution.

- If CrCl does not improve in the subsequent two scheduled study visits (two CrCl values still <50 mL/min) then consideration of discontinuation of all potentially nephrotoxic medications including potentially nephrotoxic ARV including tenofovir must be undertaken in consultation with the treating provider.

- Changes to the ARV regimen require notification of the A5348 protocol core team by e-mail at actg.corea5348@fstrf.org. Please refer to section 7.1.6 for guidance regarding changes in ARV.

- Continue further medical management as appropriate.

- If CrCl improves, consideration must be given to the readjustment of any dose modifications that have been made.

7.1.3.2 CrCl value <30 mL/min: This should be handled on a case by case basis. The site should notify the core team of all participants with a confirmed CrCl <30 mL/min.

7.1.4 Specific Guidance for New or Worsening Proteinuria or Glucosuria

Participant who develop new proteinuria or glucosuria (1+ or greater) or an increase in glucosuria or proteinuria of ≥1+ from baseline should have the following evaluations occur:

- Within 7 days, repeat urinalysis with spot protein and creatinine, calculation of protein/creatinine ratio, repeat serum chemistry, creatinine and phosphate.

- Medical evaluation must include a full review of current medications, including those taken on an as needed basis, those which are sold over the counter, and any dietary and herbal supplements, as well as assessments for causes of proteinuria and/or glucosuria including concomitant disease processes such as diabetes and toxicity from current medications including HCV treatment. Sites are welcome to consult with the core team with any questions or concerns regarding management actg.corea5348@fstrf.org.

If new or worsened proteinuria and/or glucosuria are confirmed, the study team should be notified. Urinalysis should be repeated as per the SOE and more frequently if clinically indicated.

7.1.5 Specific Guidance for Transaminase Elevations

If a participant experiences an ALT level ≥5 x ULN that is ≥2 x baseline, a confirmatory test must be performed within 72 hours. If the ALT is confirmed ≥5 x ULN, the management guidelines in Table 7-4 must be followed.

If a participant experiences an increase in ALT by one or more toxicity grades compared to the previous nadir (for example, ALT Grade 0 at nadir increases to Grade 1 or above, or ALT Grade 1 at nadir increases to Grade 2 or above), safety laboratory assessments and clinical evaluation of the participant should be conducted within 1 week.

Alternative management of ALT increases requires approval from the A5348 protocol core team by email at actg.corea5348@fstrf.org.

Table 7-4: Management of Confirmed ALT Levels ≥5 x ULN and ≥2 x Baseline

ALT ≥10 x ULN	Permanently discontinue study drugs. Evaluate and manage the participant as medically appropriate.
ALT ≥5 x ULN and >2 x baseline	Evaluate and manage the participant as medically appropriate. Continue study drugs and repeat liver function tests within 3 days and as clinically indicated until resolution. Perform clinical assessment within 1 week. If ALT values during follow-up are increased >2-fold from the prior values, then permanently discontinue study drugs.

7.1.6 HIV-1 Virologic Failure

Plasma HIV-1 RNA will be monitored throughout the study for participants on ARV. In this study, HIV-1 viral failure will be defined as confirmed increase in HIV-1 RNA to ≥200 copies/mL at any time after study entry, only for participants who are taking ARV.

Since “blips” in HIV-1 RNA may be observed in individuals on ARV in the absence of HIV-1 VF, any increase in plasma HIV-1 RNA ≥200 copies/mL must be confirmed with repeat testing as soon as possible (not to exceed 2 weeks). For participants with confirmed HIV-1 VF, a plasma specimen obtained at the time of confirmation will be sent to the designated central laboratory for evidence of HIV-1 drug resistance. Confirmed HIV-1 VF specimens must have repeated detection of ≥200 copies/mL for HIV-1 drug resistance testing. Results will be reported back to sites in real-time from the designated central laboratory.

Clinical management of HIV-1 VF will be handled by local site investigators according to current HIV treatment guidelines and local standard of care. The A5348 protocol core team must be contacted to notify of any changes in ARV regimen in the event of HIV-1 VF (actg.corea5348@fstrf.org).

Investigators should consult section 5.0 and the package insert.

Regarding the potential for a modified ARV regimen for HIV-1 VF: Possible modified ARV regimens should take into account the unique characteristics of the participant and the participant’s HIV treatment history as well as known and/or anticipated drug interactions with DAA or DAA+RBV therapy.

If no reasonable salvage HIV regimens compatible with continued HCV DAA or DAA+RBV therapy are deemed available for an individual participant with HIV-1 VF then the participant must discontinue HCV DAA+RBV therapy.

7.2 Pregnancy

Pregnancy will result in immediate discontinuation of the study medications in both Arm A and Arm B; for those in Arm A assigned to RBV, initiation of counseling 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 CRF will be completed. For female participants, obstetrical history will also be recorded on the CRF.

Male participants 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.

Participants who become pregnant while taking study treatment or within 6 months after discontinuing study treatment and male participants’ sexual partners who become pregnant during this time, will have their pregnancies reported to the RBV Pregnancy Registry (www.RibavirinPregnancyRegistry.com).

If a female participant or female partner of a male participant 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 a CRF at the end of the pregnancy.

The intrapartum complications and/or pregnancy outcome will be recorded on the CRFs. If applicable, pregnancies that occur on study should be reported by the site investigator prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Phone: 800-258-4263; Fax: 800-800-1052.

7.3 HCV Virologic Response-Based Stopping Criteria and Confirmation of VF/Relapse

The following on-treatment HCV virologic response-based treatment stopping criteria will be utilized for all participants:

- Confirmed increase in HCV RNA ≥LLOQ if HCV RNA previously declined to <LLOQ (detected or not detected). This will be defined as HCV breakthrough.
- Confirmed ≥1 $\log_{10}$ IUmL HCV RNA on-treatment increase from nadir.
- Confirmed HCV RNA ≥LLOQ at week 8 visit.

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 VF Confirmation in section 6.2.4).

HCV RNA measurement to confirm treatment failure or relapse after treatment will be performed in real time at the designated laboratory and the results will be provided to the site investigators 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 6.2.4.

Retreatment of HCV virologic failures will not be provided through A5348.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Premature Study Treatment Discontinuation

- Drug-related toxicity (see section 7.1 Toxicity).
- Pregnancy in a female participant or in the female partner of male participant.
- HCV failure as defined in section 7.3.
- Failure by the participant to attend three or more consecutive clinic visits.
- Seven or more missed consecutive doses of study treatment.
- Participant requests 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.

8.2 Premature Study Discontinuation

- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the Study Monitoring Committee (SMC), ACTG, institutional review board (IRB), NIAID, Office for Human Research Protections (OHRP), any other government agency as part of their duties, investigator, or industry supporter.
- Initiation of alternate non-study HCV treatment.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

A5348 is a prospective, open-label study to evaluate 12-week and 24-week regimens of LDV/SOF (Arms A and B, respectively) for the retreatment of HCV among individuals with prior treatment failures, with the addition of RBV to the 12-week regimen. It is a study to gather timely, pilot data in the retreatment of HCV in HIV-coinfected persons and to complement similar studies in HCV mono-infected persons, planned outside of the ACTG. The study will randomize the participants to the study arms, since there is clinical equipoise on the benefits and drawbacks between a shorter 12-week regimen of LDV/SOF with RBV and a 24-week regimen without RBV (see section 2.2 Rationale). The primary analysis will be conducted as a single-arm analysis for each regimen. Any comparison made between the regimens will be done as a secondary analysis. The study has not been designed to be powered for comparison between the two study regimens, and as such, any comparison needs to be interpreted with caution.

The study sample size is limited by feasibility. As a study to provide supportive data on retreatment options expeditiously in a difficult-to-treat population, the study sample size is small. Limitations inherent in most early phase studies apply. Safety and tolerability evaluations of each treatment regimen, as well as the virologic response, will inform the acceptability of each treatment regimen as a viable strategy for retreatment. Virologic outcome will be evaluated using SVR12 as the primary endpoint.

The primary analysis will be conducted as modified intent-to-treat, and all participants who meet the eligibility criteria and start study treatment will be included. The standard definition of SVR12 that is in use across the ACTG studies and, to our knowledge, the industry-sponsored studies will be used, where loss to follow-up or otherwise not evaluable for SVR12 is construed as not meeting the SVR12 response.

The study regimens have different treatment durations and, while the post-treatment follow-up time is the same for both study arms, the study durations are different in Arms A and B. Assessment of reasons for not achieving SVR12 is an important part of SVR12 and SVR24 analyses in this study, including loss to follow-up. Differential loss to follow-up in the two study arms may suggest the benefit of the shorter duration in the 12-week regimen or drawback of RBV intolerance. Either way, the SVR endpoints would capture the outcome of the regimen.

9.2 Outcome Measures

9.2.1 Primary Outcome Measures

9.2.1.1 SVR12 defined as HCV RNA < lower limit of quantification (LLOQ) (either target detected [TD] or target not detected [TND]) at 12 weeks after treatment discontinuation. The sample within the week R+12 (post-treatment) visit window, as defined in section 6.0, which is closest to the targeted time will be used. If there is no HCV RNA sample within this window, then the participant will be considered SVR12 failure, unless there are preceding and subsequent HCV RNA measurements that are both <LLOQ (either TD or TND).

9.2.1.2 Occurrence of Grade 3 or higher AE (diagnosis, sign, symptom, or laboratory abnormality), SAE according to ICH criteria, or AE reported as the reason for permanent discontinuation of study treatment, during study treatment and up to 30 days after study treatment discontinuation. (Event that is ongoing at the same grade from prior to study treatment initiation will be excluded.)

9.2.2 Secondary Outcome Measures

9.2.2.1 Renal toxicity: (a) ≥ Grade 2 creatinine clearance after study entry, or (b) new proteinuria and/or glucosuria, defined as ≥ 1+ or an increase ≥ 1+ from baseline.

9.2.2.2 SVR4 defined as HCV RNA < LLOQ (either TD or TND) at 4 weeks after treatment discontinuation. The measurement within the week R+4 visit window that is closest to the targeted time will be used. If there is no HCV RNA sample within this window, then the participant will be considered SVR4 failure, unless there are preceding and subsequent HCV RNA measurements that are <LLOQ (either TD or TND).

9.2.2.3 SVR24 defined as HCV RNA < LLOQ (either TD or TND) at 24 weeks after treatment discontinuation. Sample after 20 weeks after treatment discontinuation that is closest to the targeted time, not followed by any result ≥LLOQ, will be used.

9.2.2.4 HCV RNA <LLOQ (either TD or TND) at post-entry scheduled visits, using the visit windows as defined in section 6.

9.2.2.5 HIV-1 RNA > 50 copies/mL at all scheduled visits, using the visit windows as defined in section 6.

9.2.2.6 Change in CD4+ cell count from study entry at subsequent scheduled visits, using the visit windows as defined in section 6.

9.2.3 Exploratory Outcome Measures

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

9.2.3.2 Development of resistance mutation in SVR12 failures.

9.2.3.3 Tenofovir area under the curve (AUC) at baseline (prior to study treatment initiation) and at week 4.

9.2.3.4 SOF and LDV metabolite concentrations.

9.3 Randomization and Stratification

The study is randomized to Arm A and Arm B and stratified by the cirrhosis status. Initially, 15 slots will be reserved for participants taking a PI/r and tenofovir regimen across the two study arms. This will be lifted 3 months after the study is open to accrual, so that the accrual progress is not constrained by the PK objective on tenofovir.

The first 15 participants whose ARV regimen contains HIV PI/r plus tenofovir who enroll to the study must be willing to participate in PK sampling (pre-dose, hour 1 and hour 4) at weeks 0 and 4. After 15 such participants have contributed PK samples, participation in the tenofovir PK sampling is optional. Study accrual may conclude with fewer than 15 participants whose ARV regimen contains HIV PI/r plus tenofovir, since the reservation of 15 slots will be lifted 3 months after the study is open to accrual. There is no minimum or maximum for such participants.

9.4 Sample Size and Accrual

9.4.1 Sample Size of 20 per arm

The sample size of 20 participants per arm is determined by feasibility. The team anticipates SVR12 of 90% for both regimens. Over 70% is deemed acceptable in the study population. Precision associated with the given sample size is described here.

If the observed study proportion for SVR12 is 90% with 18 of 20 participants achieving SVR12, then the associated 90% confidence interval (CI) is (73.8%, 96.6%). Hence, the 90% CI for the true SVR12 proportion will be entirely above 70% if 18 or more of the 20 participants achieve SVR12. Table 9-1 below shows that as a single arm evaluation of 20 participants, the width of the two-sided 90% CI varies from 32% to 12%, depending on the observed proportion.

Table 9-1: Evaluation of Study Participants

Observed SVR12 Proportion	Two-Sided 90% CI*
70% (14/20)	(51.6%, 83.6%)
75% (15/20)	(56.8%, 87.3%)
80% (16/20)	(62.2%, 90.7%)
85% (17/20)	(67.8%, 93.8%)
90% (18/20)	(73.8%, 96.6%)
95% (19/20)	(80.4%, 98.9%)
100% (20/20)	(88.1%, 100%)

* Wilson Confidence Interval

No sample size adjustment is needed for loss to follow-up, because such participants are assumed to be SVR12 failures by definition.

We anticipate accrual of 5-10 participants per month to complete enrollment under six months. Therefore, a two-stage design is not feasible.

9.5 Monitoring

The study team will monitor accrual and availability of data and samples for key objectives and planned assays. In addition, the core study team will monitor routinely the renal toxicity events and HCV RNA results for evidence of virologic breakthrough. The DAIDS clinical representative will receive the standard toxicity summary report according to the schedule for phase I/II studies.

The study will also be monitored by the ACTG Hepatitis SMC. The SMC will review the study six months after the study enrolls its first participant, or when about 40% of study participants, about 16 participants have the week 16 data, whichever occurs earlier. Because Arm A treatment duration is shorter at 12 weeks, the data will include end of treatment data and potentially some SVR4 data from Arm A participants. The SMC review will occur at least annually, if additional reviews are deemed necessary, or upon

request by the SMC or the study team. The SMC review will include accrual, retention, renal toxicity events, baseline characteristics, study conduct, data/specimen collection, AE summaries, HCV virologic failures, HIV-1 RNA virologic failures, CD4+ cell count, and modifications of study treatment and ARV regimens. A formal interim efficacy review of SVR12 is not planned, because much of study follow-up will be complete before participants reach SVR12, especially in Arm A, due to the anticipated accrual rate and the small study sample size.

The details on reports, including purpose, contents, schedules and recipients, will be outlined in the Study Monitoring Plan (SMP) and reviewed by the study team and the SMC prior to study enrollment.

9.6 Analyses

As a small study to provide supportive data on SVR12, precision is limited, and analyses related to HCV virologic response will be conducted with two-sided 90% CIs. This is noting that the lower limits of these two-sided CIs are equivalent to the limits in the 95% one-sided lower CIs. Analyses related to safety will be conducted with two-sided 95% CIs to be conservative.

The primary objective will be addressed separately in Arms A and B. The proportion of participants within each study arm who achieve SVR12 will be estimated with a two-sided Wilson CI. The analysis will be conducted as modified intent-to-treat (ITT) on participants who meet the eligibility criteria and initiate study treatment. Given the SVR12 definition, a tabulation of reasons for not achieving SVR12 (e.g., detectable HCV RNA, early treatment discontinuation, loss to follow-up) will be an important supplement to the primary analysis on SVR12. The primary analysis timeline will be driven by the last participant's completion of the SVR12 visit, rather than the study completion date. Results from the primary analysis on SVR12 may be presented publicly - for example, at a conference – prior to study database finalization that includes SVR24 completion, when SVR12 data are complete.

The secondary HCV virologic measures will also be analyzed with 90% two-sided Wilson CIs around the observed proportion in each study arm.

The SVR 4, SVR12 and SVR24 differences between the two study arms will be evaluated with 90% two-sided CIs, using the Newcomb score (Wilson) methods.

For the safety analysis, the proportion of participants with events as described in section 9.2.1.2 will be summarized with 95% Wilson CIs around the observed proportions. The worst graded event per participant over time will be used. Descriptive tables summarizing the events and the number of participants experiencing the events will be provided by grade. Descriptive summaries will also be provided on the participants who discontinue the study treatment early, categorized by the reasons for discontinuation. HIV-1 RNA statuses (<50 copies/mL) and CD4+ T-cell count changes from baseline at scheduled visits will be summarized. The summary on HIV-1 and HCV virologic failures will be descriptive, and a listing will be provided with details including time of failure and participant's ARV regimen.

Given the small study sample size, evaluation of baseline predictors of SVR12 will be descriptive, and baseline characteristics (such as cirrhosis, prior treatment response, HCV genotype subtype, race, IL-28B, HCV resistance mutation, and ARV regimen) will be summarized by SVR12 status.

Renal toxicity events will be described separately, and a listing will be provided with information on the time of failure, ARV regimen, and spot protein and creatinine results.

Further details on the analyses will be provided in a separate Study Analysis Plan (SAP). See section 10 for the description of PK analyses.

10.0 PHARMACOLOGY PLAN

10.1 Pharmacology Objectives

10.1.1 Determine the impact of LDV/SOF and RTV-boosted HIV protease inhibitor coadministration on the pharmacokinetics of tenofovir.

10.1.2 Determine the association between LDV/SOF adherence and SVR12.

10.2 Pharmacology Study Design

10.2.1 Participants taking TDF and a HIV PI/r as part of their ARV will undergo two PK visits to compare tenofovir PK before and after the addition of LDV/SOF. The first visit (entry) will occur prior to initiation of LDV/SOF, and the second visit will occur 4 weeks after initiating LDV/SOF. For these visits, participants will come in to the clinic approximately 24 hours after their previous dose of TDF and following an 8 hour fast. A blood sample will be obtained at pre-dose, participants will then take an observed dose of TDF (and LDV/SOF at week 4), and additional blood samples will be obtained at 1 and 4 hours post-observed dose. The participants will remain in the fasted state until after the 1-hour post-dose sample is collected. Whole blood collected in EDTA tubes will be spun down to plasma for quantification of tenofovir in plasma using a validated LC/MS-MS method at the Colorado Antiviral Pharmacology Laboratory. Tenofovir PK will then be compared before and after the addition of LDV/SOF.

10.2.2 To determine the association between LDV/SOF adherence and SVR12, dried blood spot samples will be obtained from study participants at each on-treatment visit and one off-treatment visit for quantification of LDV and SOF metabolites. LDV and SOF metabolite concentrations will be determined using validated LC/MS-MS methods at the Colorado Antiviral Pharmacology Laboratory. The date and time of most recent LDV/SOF dose will be recorded.

10.3 Pharmacology Sample Size Considerations

In healthy volunteers, LDV/SOF increases tenofovir levels by 47% when administered as TDF/FTC/ATV/r versus TDF/FTC/ATV/r alone. LDV/SOF increases TFV between 50-64% when administered with TDF/FTC/DRV/r versus TDF/FTC/DRV/r alone [17]]. We have powered the study to detect a 40% increase in tenofovir AUC $_{0\text{-}24h}$. We assume that the coefficient of variation (CV) for tenofovir is 30% (mean ± SD of TFV AUC $_{0\text{-}24}$ of 2.29 ± 0.69 mcg*hr/mL in the TDF prescribing information), within-participant correlation is 0.5, and the AUC reported on the original scale has a log-normal distribution. Then an increase of 40% is equivalent to 0.34 on the $\log_e$ scale, and the variance of the change on the log scale is 0.087 (SD=0.30). With 11 participants, there is 90% power to detect a 40% increase as statistically significant in a within-participant analysis, in a 2-sided t-test on the log-transformed AUC with 5% type I error. We aim to collect PK samples from 15 participants to yield evaluable data from at least 11 individuals receiving this combination. However, because expeditious completion of the study is key, the study enrollment may be completed without the required number of participants on ritonavir-boosted HIV protease inhibitor plus tenofovir.

10.4 Primary and Secondary Data, Modeling, and Data Analysis

10.4.1 For Aim 1, tenofovir AUC will be determined using non-compartmental methods in Phoenix WinNonLin (Certara, Princeton, NJ). Tenofovir AUC will be compared before and after the addition of LDV/SOF using paired t-tests.

10.4.2 For Aim 2, LDV and SOF metabolite steady state concentrations (Css) will be estimated for each participant using non-linear mixed effects modeling (NONMEM, ICON, Dublin, Ireland). Logistic regression will be used to determine the association between LDV and SOF metabolite Css and SVR12 with inclusion of additional clinical or demographic covariates as appropriate (e.g., cirrhosis status).

10.5 Anticipated Outcomes

Through this study, we will determine the effect of concomitant LDV/SOF and RTV-boosted HIV PI use on the pharmacokinetics of tenofovir in HIV/HCV coinfected individuals. These data are important for establishing the safety of LDV/SOF use in persons on TDF and a RTV-boosted HIV protease inhibitor. We will also explore the relationship between LDV/SOF concentrations and likelihood of SVR. These data are essential for providing context to our clinical findings.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

Case report forms (CRF) will be provided for each participant. Participants must not be identified by name on any CRFs. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon (randomization/registration).

11.2 Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

11.2.2 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.

11.3 Clinical Site Monitoring and Record Availability

11.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, CRFs, 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.

11.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the NIAID, the OHRP, other agencies as part of their duties to ensure that research participants are protected, and the industry supporter or designee for confirmation of the study data.

11.4 Expedited Adverse Event Reporting to DAIDS

11.4.1 Adverse Event Reporting to DAIDS

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

The DAIDS Adverse Events Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be

submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

11.4.2 Reporting Requirements for this Study

- The SUSAR 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 LDV/SOF and RBV.

11.4.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, must be used and is available on the DAIDS RSC Web site at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.

11.4.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is the time of enrollment of the study participant until the study participant completes study follow-up.
- 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).

12.0 HUMAN PARTICIPANTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the participant (or parent, legal guardian, or person with power of attorney for participants who cannot consent for themselves, such as those below the legal age of consent). 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, parent, or legal guardian, and this fact will be documented in the participant's record.

12.2 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, NIAID, OHRP, other government agencies as part of their duties to ensure that research participants are protected, or the industry supporter or designee.

12.3 Study Discontinuation

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

13.0 PUBLICATION OF RESEARCH FINDINGS

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

14.0 BIOHAZARD CONTAINMENT

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

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

15.0 REFERENCES

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APPENDIX I

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT
For protocol: A5348

FINAL Version 1.0, 09/29/15: Phase II Trial of Retreatment Strategies for Difficult-to-Treat Hepatitis C Virus (HCV)-infected Individuals Who Have Failed Prior Direct Acting Antiviral (DAA)-based Regimens

SHORT TITLE FOR THE STUDY: A5348 FINAL Version 1.0, 09/29/15, 12 weeks of Ledipasvir (LDV)/Sofosbuvir (SOF) with Weight-based Ribavirin vs. 24 weeks of LDV/SOF

INTRODUCTION

You are being asked to take part in this research study because you are infected with HIV and the hepatitis C virus (HCV, a virus that affects the liver) and have been previously treated for HCV with a sofosbuvir-containing treatment that did not cure your HCV infection. This study is sponsored by the National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

People who are infected with HCV have a great chance of being cured of the infection when they are treated with sofosbuvir. However, in some instances, treatment with sofosbuvir-containing therapy does not work. It is not known if treating people with sofosbuvir again (retreatment) after it did not work the first time will work. There is an important need to understand retreatment options in those instances. This study is being done to see if two different regimens, ledipasvir with sofosbuvir and ribavirin for 12 weeks (Group A) and ledipasvir with sofosbuvir for 24 weeks (Group B) are well tolerated in HCV-infected persons where previous treatment with sofosbuvir failed. This study will also look at the safety of each regimen and how well the combination treatment of ledipasvir/sofosbuvir works in people who have cirrhosis (scarring of the liver) or HIV.

HOW MANY PEOPLE WILL BE IN THIS STUDY?

About 40 people (men and women age 18 years and older) will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for up to 48 weeks, depending on the group to which you are assigned.

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

If you decide to join this study, you will be assigned to either Group A or Group B, as shown below. Half of participants will be assigned to Group A and half will be in Group B. You will take ledipasvir/sofosbuvir (a pill taken once daily by mouth with food) and ribavirin (pills taken twice daily by mouth with food and at a dose based on your weight) if you are assigned to Group A until the end of treatment in Step 1. You will be given the medications at your study visits to take home, and you will need to store the medications in a safe place at room temperature. You will not take any ledipasvir/sofosbuvir or ribavirin during Step 2 of the study.

You will continue taking your current anti-HIV drugs if you are receiving them. If you are not currently on HIV medications and your provider does not think you need HIV medications during the study that is also acceptable.

Study Group	Study Drugs	Time on Study Drugs (STEP 1)	End of Treatment/Followup (STEP 2)
Group A	ledipasvir/sofosbuvir +ribavirin	12 weeks	No study treatment – continue study follow-up for 24 weeks
Group B	ledipasvir/sofosbuvir	24 weeks	No study treatment – continue study follow-up for 24 weeks

Everyone who enters the study will take ledipasvir/sofosbuvir (and for those in Group A, ledipasvir/sofosbuvir and ribavirin), which will be given for free by the study. Anti-HIV drugs will not be provided by the study. Note that if you stop taking ledipasvir/sofosbuvir, you must also stop taking ribavirin.

While you are in this study, you will need to be seen in the clinic about 11 times (14 times for those in Group B) during the study. The longest visit could take up to 2 hours (up to 4 hours for the two pharmacokinetic [PK] (pharmacokinetic means an evaluation of medication levels) study visits, which are only required for some participants); however, the study staff will tell you about how long each visit could be. You may need to come to the clinic if you have side effects or if you switch or take new anti-HIV drugs. 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.

You must fast for the entry, week 12, week 24 (if Group B), and early treatment/study discontinuation visits. If you are participating in the PK analysis, you will need to fast for the

week 4 visit as well. At the PK visits, you will be required to fast until after you have completed the 1 hour blood draw. (Fasting means that you cannot eat or drink anything for at least 8 hours before your visit. You may only drink water and take your prescription medications during this time. If your medications require food, the study staff will talk to you about how you should take your medications.) The study staff will remind you to fast before each of these study visits. If you do not fast before these visits, you will be asked to come back later for these tests, after fasting.

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, gender, 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.

Required Blood Tests

Your blood will be drawn from a vein in your arm and used to measure your HCV viral load (the amount of HCV in your blood) and genotype (genetic makeup of the HCV virus), to measure levels of certain hormones (hormones are chemicals in your blood), and for routine safety tests and metabolic tests (to test how your body uses the food that you eat). If you are a woman able to become pregnant, you will have a pregnancy test at the screening and entry visits. You will have blood drawn to measure your HIV viral load (the amount of HIV in your blood) and your CD4+/CD8+ cell counts (these are cells in your blood that fight infection). You will be told the results of these tests when they become available.

You will also have a test for IL-28B genotype; this is a genetic test to see if we can predict how well you will respond to HCV treatment. This marker is not currently standard of care, as it is not yet known if it is associated with better treatment response with current HCV treatments that do not contain interferon.

Some of your blood will also be stored (with no information that will identify you) and used for future HCV and HIV resistance tests required for this study. A resistance test is used to determine if the HCV/HIV viruses still respond to your medications. In addition, some of this blood will be used to understand how the drugs interact with your body and how your body responds to the drugs.

Any remaining blood will be stored for future testing required by the study.

Genetic (the message in your DNA) testing

If you agree, your blood will be drawn and used to examine different genes (pieces of your DNA). Results of testing done on these samples may not be given to you because they will be done in the future.

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

_____ YES _____ NO

Optional Tests

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

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

_____ YES _____ NO

A5348 Study Visits

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

I. Study Schedule

Evaluation or test	Screening	Entry	Post-Entry Visits			Other Visits	Early discontinuation
			STEP 1		STEP 2		
			On-treatment Visits	End of treatment	Off-treatment Visits		
Consent	✓						
Clinical assessments	✓	✓	✓	✓	✓		✓
ECG	✓						
Samples collection & laboratory testing	✓	✓	✓	✓	✓	✓	✓
Urine sample (if applicable)		✓	✓	✓	✓		
Pregnancy test (if applicable)	✓	✓	✓	✓	✓	✓	✓
Pharmacokinetic (PK) studies (if applicable)		✓	✓	✓	✓		
Pregnancy prevention counseling	✓	✓	✓	✓	✓		✓
Adherence			✓	✓			

Evaluation or test	Screening	Entry	Post-Entry Visits			Other Visits	Early discontinuation
			STEP 1		STEP 2		
			On-treat-ment Visits	End of treatment	Off-treat-ment Visits		
assessments							
Study drugs distribution and storage		✓	Every 4 weeks				
Medication Diary		✓	✓	✓	✓		

II. Description of Study Visits

Screening
After you have read and signed the consent form, you will be asked questions about your health, medical history, and medication history. You will have several tests, including blood tests, to make sure that you qualify to join the study. You will have your height and weight recorded.

Some of the blood taken will be shipped to a testing lab. Your HIV infection status will be evaluated; your HCV infection and how long you've been infected will be confirmed. Also, an electrocardiogram (ECG) will be done at this visit.

If you are a woman able to become pregnant, you will have blood taken for pregnancy testing.

Entry
When all of the results from your screening tests are available, you will come back to the clinic to have a few tests done before starting the study. You must come in fasting. If you are not fasting within the past 8 hours before this visit, you will be asked to come back fasting. Your HCV treatment status will be documented. You will be asked about your health and medication history. You will have urine and blood samples collected for routine safety tests and for some required blood tests (as listed above). For research purposes, you will have some blood drawn for a genetic test to see if we can predict how well you will respond to HCV treatment (this is called an IL-28B genotype test).

If you are a woman able to become pregnant, you will be asked to provide a blood sample for pregnancy testing.

At this visit, you will be given a medication diary and your study drugs. You will be asked to record your medications and any reactions in the medication diary. This diary will be collected. The study staff will give you enough study drugs to last four weeks; you will be

asked to come in every four weeks to receive more medications. You should take ribavirin (if applicable) and ledipasvir/sofosbuvir with food. If you are required to fast before a visit, the study staff will discuss with you how to take your medication. At each visit, you must return any remaining study drug from the previous visit. If you forget to take ledipasvir/sofosbuvir at the correct time, it may be taken later in the day; however, no more than a single daily dose (90 mg dose ledipasvir/400 mg dose of sofosbuvir) of ledipasvir/sofosbuvir should be taken on any calendar day. You should never cut or split your study medications. If you miss a dose of ribavirin, then you should take the missed dose as soon as possible with food during the same day. If an entire day has gone by, then you should skip the missed dose, and then you should go back to your normal dosing schedule. Do not double the next dose in order to "make up" what has been missed.

Pharmacokinetic Evaluation at Entry:
If you are taking part in the PK testing, and are taking an HIV ritonavir-boosted protease inhibitor and tenofovir as part of your HIV regimen, you will have an extra evaluation (PK testing) done at the entry visit. You will have blood drawn several times for PK testing, to provide a baseline measure of how the drug interacts with your body and how your body responds to the drug. You will have blood drawn at the beginning of this visit. You will be administered your HIV medications. Additional blood samples will be obtained at 1 and 4 hours after your observed dose of HIV medications.

Post-entry visits
Participants assigned to treatment Group A: You will be seen at treatment weeks 1, 2, 4, 8, and 12.

Participants assigned to treatment Group B: You will also be seen at treatment weeks 1, 2, 4, 8, 12, and every 4 weeks for an additional 12 weeks.

All participants will be seen at post-treatment weeks 4, 12, and 24 after taking the last dose of study drugs. These visits will last about 1-1 ½ hours each.

You will have urine and blood samples collected for routine safety tests and for some required blood tests (as listed above). If you are a woman able to become pregnant, you will be asked to provide a urine sample for pregnancy testing. You will have your weight measured and you will be asked about your health and any changes in your medicines since your last visit. You will be asked how well you are taking your medications. You will have blood drawn several times for PK testing. It is recommended that you use your medication diary to note any reactions after the PK testing. This diary will be collected at each study visit.

Other visits
During the study, you may have to come back to the clinic for extra visits for testing of any laboratory results that are not normal, or to follow-up on a specific side effect or symptom.

Virologic Failure Confirmation
If laboratory tests show there is evidence of virologic failure (which is detectable HCV or HIV when your levels were previously not detected or your virus has not gone down as quickly as expected), you will be asked to come back to the clinic to confirm your lab results. If virologic failure for HCV is confirmed, you will be asked to stop taking the ledipasvir/sofosbuvir and be followed in Step 2 as described above. If virologic failure for

HIV is confirmed, you will continue to be followed on study, if an HIV regimen that works well with ledipasvir/sofosbuvir is available. If there are no HIV regimens available that work well with ledipasvir/sofosbuvir, you will be asked to stop taking ledipasvir/sofosbuvir and be followed, as described above.

Early discontinuation
There are two types of discontinuation (stopping study treatment or leaving the study early) in which you will be asked to come to the clinic for an extra visit in a fasting state.

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 decides 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.

III. Description of Study Evaluations

Consent
After you read the consent form and have had a chance to ask questions about the study, you will sign the consent form if you want to continue to be tested to see if you qualify for the study.

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

Physical examination
You will have a physical exam. At screening, the study staff will check the different 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, and your height and weight will be recorded. At each following visits, the physical exam will be more limited and based on symptoms or problems that you are experiencing. You will have your weight recorded at every visit.

Medical and medication history
You will be asked questions about your health and about 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.

Electrocardiogram
You will have an electrocardiogram (ECG) done. An ECG is a test to measure the heartbeat. An ECG machine will be used to do an electrical tracing of your heart that can

show how hard it is working. You will have to lie very still for at least 5 minutes while the ECG is being done.

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. Approximately 144 mL (10 tablespoons) of blood will be drawn during any study visit. These may include: routine safety lab tests such as kidney and liver function, HIV viral load (a test that shows how much HIV is in your blood), CD4+/CD8+ counts (a test that shows how many infection-fighting cells you have in your blood), HCV viral load (a test that shows how much HCV is in your blood).

You will be asked to fast before some of the visits. This means that you should not eat or drink anything except prescription drugs and water for at least 8 hours before the visit.

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.

Stored urine
Urine will be collected for the evaluation of proteins. You will not receive the results of these studies.

Genetic testing
Blood will be drawn for testing your genes (pieces of your DNA) to understand if you naturally were born with a better or worse chance of responding to the medications. This is called an IL-28B genotype test. Some of your blood cells will also be tested to see if your responsiveness to the therapy is associated with different genes related to interferon (IFN) use. An IFN is an antiviral compound that is produced in response to many types of infections. You will not receive the results of these studies.

PK Studies
Blood will be drawn to measure the levels of the study drugs in your blood and to understand how the drugs interact with your body and how your body responds to the drugs.

Blood sample PK (for some participants only)
If you are taking tenofovir and an HIV ritonavir-boosted protease inhibitor (atazanavir or darunavir) and you give permission to participate in the PK evaluation, you will have blood collected three times at each of two visits, which will last 4 hours each. The PK samples will be used to measure the levels of the HIV medicines (first PK visit and week 4) and study drugs (week 4 only) in your blood since there is limited information available about the interaction between tenofovir, HIV protease inhibitors and the study drugs. You will not take your study medications or HIV medications that morning until you arrive at the clinic and are instructed to do so. Your visit will last 4 hours total.

You will be given a medication diary to write down when you take your last three doses of HIV and HCV medications before the PK visits.

Urinalysis
Urine samples will be collected for routine safety tests. Some urine will be stored to look at markers of kidney function and how these may change during treatment.

Pregnancy test
If you are a woman who is able to become pregnant, you will have blood taken prior to study entry. After you enter the study, you will be asked to provide urine samples for pregnancy testing.

Pregnancy prevention counseling
All participants, male and female, will be counseled on the risk of the study drugs in pregnancy and on how to prevent pregnancy.

Adherence assessments
You will be asked about how well you take your medications and the staff will count the number of pills in your medication bottles. The study staff will give you information and encouragement to help you take your medications as prescribed.

Study drugs distribution and storage
You will be given a 4-week supply of study medications at entry and additional medications will be given every 4 weeks. You will be asked to store the study medications as instructed in the medicine bottle label.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

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

- The study is cancelled.
- You start taking HCV treatment not provided by the study.
- A Study Monitoring Committee (SMC) recommends that the study be stopped early (A SMC is an outside group of experts who monitor the study).
- Your doctor thinks the study is no longer in your best interest.
- The site investigator thinks that you are at significant risk of failing to comply with the requirements of the protocol.

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

- You continue to experience HCV treatment failure.
- You or a female partner of a male participant become pregnant.
- You are breastfeeding.
- Continuing the study drugs may be harmful to you.
- You need a treatment that you may not take while on the study.
- You are not able to take the study drugs as required by the study.
- You do not have, or are not able to, have required study visits and evaluations.

If you must stop taking the study drugs earlier than indicated by the study, the study doctor will ask you to remain on the study and complete the post discontinuation visits.

NOTE: For those in Group A, if you stop taking ledipasvir/sofosbuvir , you must also stop taking ribavirin.

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

If you must permanently stop taking ledipasvir/sofosbuvir and ribavirin 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 ledipasvir/sofosbuvir and ribavirin through the study.

WHAT ARE THE RISKS OF THE STUDY?

Risks of Social Harm
Although the study site will make every effort to protect your privacy and confidentiality, it is possible that others could find out that you are participating in this study and that social harm may result (because you could become labeled as being infected with HIV and/or HCV). 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 Drugs
Drug interactions that increase the levels of medicine in your blood may increase the chances of side effects. Drug interactions that lower the levels of HIV medicines in your blood could cause drug resistance, meaning the drugs no longer work to prevent virus from reproducing. Drug interactions that lower the levels of sofosbuvir or ledipasvir in your blood may decrease your chances for a cure of hepatitis C and/or cause drug resistance.

For those persons taking HIV medicines, there is no clear risk of drug interactions between HIV medicines and sofosbuvir. Although sofosbuvir has not been studied with all HIV medicines, it has been studied with all first-line HIV medication drug classes and there are no recognized clinically significant interactions. This is also true for ledipasvir with the exception of one of the HIV medications named tenofovir. Ledipasvir increases tenofovir levels in your body. With most other HIV drug combinations this increase is not felt to lead to significant risk unless your kidneys don't work normally. However, if tenofovir and ledipasvir are used with HIV protease inhibitors that are combined with ritonavir, (which is used to increase the level of your HIV drugs in your blood stream), the potential risk of kidney toxicity may be higher. The combination of HIV protease inhibitors and ledipasvir and tenofovir has not been studied in HIV-infected patients. For this reason there will be monitoring of the kidney function for all participants in this study.

Drug resistance may prevent other medicines developed for hepatitis C from working in the future. HIV viral load will be monitored regularly to ensure that evidence of early failure of the

HIV regimen is identified quickly. In addition, multiple drug interactions studies have been completed to ensure that HIV medications can be safely dosed with sofosbuvir, and there is no evidence to suggest that giving sofosbuvir or ledipasvir and any antiretroviral allowed in this study will lead to HIV regimen failure. The risk is thought to be very low. To date only two out of over 3,000 patients have developed resistance to sofosbuvir, so this risk is also thought to be extremely low. Risk of resistance to ledipasvir is high for patients who fail therapy, with most patients developing resistance. At this time the effect of resistance to ledipasvir or similar medications is not clear, but it may increase the risk of other HCV treatments not working.

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 drug side effects please ask the medical staff at your site.

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

Ledipasvir/sofosbuvir

- Depression
- Irritability
- Sleep disturbances
- Tiredness
- Muscle pain
- Headaches
- Chills
- Nausea and vomiting
- Stomach pain
- Rash
- Anemia (low red blood cell levels). Anemia can worsen existing heart and pulmonary (lung) conditions.
- Lymphopenia (low white blood cell levels)
- Itching
- Loss of appetite
- Diarrhea
- Dizziness
- Temporary changes in liver function tests (a measure of your liver activity)

NOTE: Some of the side effects associated with ledipasvir/sofosbuvir may be seen more frequently when ledipasvir/sofosbuvir is given with ribavirin.

Ribavirin

- Anemia (low red blood cell levels). Anemia can worsen existing heart and pulmonary (lung) conditions.
- Temporary changes in blood platelet levels
- Temporary changes in liver function tests (a measure of your liver activity)

- Stomach and intestinal
  - Nausea
  - Vomiting
  - Indigestion
  - Stomach discomfort
- Skin disorders
- Upper respiratory tract inflammation, including cough and trouble breathing (dyspnea)
- Teratogenicity (risk to an unborn baby)
- Nervous system
  - Depression
  - Insomnia (inability to sleep)
  - Nervousness
  - Skin tingling
  - Drowsiness
  - Light-headedness
  - Irritability
- Hyperuricemia (excess of uric acid in blood which can lead to gout, a painful swelling of joints and may lead to kidney disease).
- Headache
- Fatigue

NOTE: There are reports indicating that HIV-infected people taking treatment for HIV and HCV have developed high lactate (an acid that can build up in the bloodstream and cause life-threatening illness) levels with worsening liver disease. It is not clear if ribavirin is the cause. This may be more common if ribavirin is taken with didanosine (ddI, Videx) for HIV infection. There may be an increased risk of inflammation of the pancreas when didanosine is taken with ribavirin. Because of these risks, didanosine use is not allowed in this study.

ARE THERE RISKS RELATED TO DELAYING HIV THERAPY?

You are not required to be on HIV medications to enter this study. If you are not on HIV medications at the time of your HCV infection and you and your doctor do not think you need to start HIV medications, we will not exclude you from the study. We also do not recommend delaying HIV medications for entry into the study if your doctor feels they are medically necessary. Although the dosing period of the HCV medications is short, a delay in necessary HIV medications could allow for progression of HIV disease, which can increase your risk of opportunistic infections and long-term after effects of HIV infection. If you have any concerns about these risks, we suggest that you discuss them with your medical provider.

ARE THERE RISKS RELATED TO PREGNANCY?

The drugs or drug combinations in this study may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a woman pregnant. Note that if you become pregnant or your partner becomes pregnant, study drugs will be stopped and you will be followed after delivery.

Because of the risk involved, you and your partner must use at least two methods of birth control that you discuss with the study staff. You must continue to use both methods until 6 months after stopping study drugs. You must choose two or more of the birth control methods listed below:

- A condom (male or female) with or without a 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. 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 or your partner may be pregnant at any time during the study, tell your study staff right away. Pregnancy will result in immediate discontinuation of the study drugs, and start of counseling on RBV's ability to cause birth defects. You will be followed on study, including male participants whose partners become pregnant, 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. Male participants whose partners become pregnant will have treatment discontinued and the same followup visit at 6 months after their partner's delivery as outlined for pregnant women. Pregnancies will be reported to the RBV Pregnancy Registry. In addition, pregnancy complications and/or pregnancies outcomes will be reported to the Antiretroviral Pregnancy Registry.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you. You may be cured of your hepatitis C infection. 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 HIV and HCV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study, you have the choice of:

- treatment with prescription drugs currently available to you
- treatment with other experimental drugs, if you qualify
- no treatment; some people may clear the HCV infection on their own over the first year of infection, although this is uncommon. Most (9 in 10) people who clear HCV infection without treatment do so in the first 12 weeks of the new 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?

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 U.S. 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.

People who may review your records include the ACTG, Office for Human Research Protection, your site's institutional review board (a committee that makes sure that your rights and safety are protected while in the study), National Institutes of Health (NIH), study staff, study monitors, and other government agencies as part of their duties, and the pharmaceutical company supporting this study. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

A description of this clinical trial will be available on www.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. [*Sites: Per US federal regulations, this language cannot be modified.*]

WHAT ARE THE COSTS TO ME?

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

Taking part in this study may lead to added costs to you and your insurance company. 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*.]

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 A5348

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

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