A5394

Safety, Tolerability, and Impact of Oral TLR8 Agonist Selgantolimod on HBsAg in Participants with Both Chronic Hepatitis B and HIV

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

Sponsored by:
National Institute of Allergy and Infectious Diseases

Industry Support Provided by:
Gilead Sciences, Inc.

IND #158394

The ACTG Hepatitis Transformative Science Group:	**Debika Bhattacharya, MD, Chair** **Arthur Kim, MD, Vice-Chair**
Protocol Chair:	**Jennifer Price, MD, PhD**
Protocol Co-Vice Chairs:	**Sharon R. Lewin, MD, PhD** **Mark S. Sulkowski, MD**
DAIDS Clinical Representative:	**Beverly L. Alston-Smith, MD**
Clinical Trials Specialist:	**Katharine J. Bergstrom, MS, CCRP**

FINAL Version 2.0
September 27, 2023

ACTG
AIDS CLINICAL TRIALS GROUP

A5394

Safety, Tolerability, and Impact of Oral TLR8 Agonist Selgantolimod on HBsAg in Participants with Both Chronic Hepatitis B and HIV

SIGNATURE PAGE

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

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

TABLE OF CONTENTS

Page

SIGNATURE PAGE 2
SITES PARTICIPATING IN THE STUDY 5
PROTOCOL TEAM ROSTER 6
STUDY MANAGEMENT 11
GLOSSARY OF TERMS 14
SCHEMA 16
1.0 HYPOTHESES AND STUDY OBJECTIVES 17
1.1 Hypotheses 17
1.2 Primary Objectives 17
1.3 Secondary Objectives 17
1.4 Exploratory Objectives 18
2.0 INTRODUCTION 19
2.1 Background 19
2.2 Rationale 21
3.0 STUDY DESIGN 24
4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS 24
4.1 Inclusion Criteria 24
4.2 Exclusion Criteria 29
4.3 Study Enrollment Procedures 30
4.4 Co-enrollment Guidelines 31
5.0 STUDY TREATMENT 32
5.1 Regimens, Administration, and Duration 32
5.2 Study Product Formulation and Storage 33
5.3 Pharmacy: Product Supply, Distribution, and Accountability 33
5.4 Concomitant Medications 34
6.0 CLINICAL AND LABORATORY EVALUATIONS 36
6.1 Schedule of Evaluations (SOE) 36
6.2 Timing of Evaluations 41
6.3 Instructions for Evaluations 43
7.0 ADVERSE EVENTS AND STUDY MONITORING 53
7.1 Definition of Adverse Events 53
7.2 Adverse Event Collection Requirements for This Protocol 53
7.3 Expedited Adverse Event (EAE) Reporting to DAIDS 54
7.4 Study Monitoring 55
8.0 CLINICAL MANAGEMENT ISSUES 55
8.1 **Nausea/Vomiting** 56
8.2 Toxicity 56
8.3 Other Diseases 58

8.4 Neutropenia 59
8.5 SARS-CoV-2 60
8.6 Pregnancy 60

9.0 CRITERIA FOR DISCONTINUATION 61
9.1 Premature Treatment Discontinuation 61
9.2 Premature Study Discontinuation 61

10.0 STATISTICAL CONSIDERATIONS 61
10.1 General Design Issues 61
10.2 Outcome Measures 62
10.3 Randomization and Stratification 64
10.4 Sample Size and Accrual 64
10.5 Data and Safety Monitoring 67
10.6 Analyses 68
10.7 Unblinding 70

11.0 PHARMACOLOGY PLAN 70
11.1 Pharmacology Objectives 72
11.2 Pharmacology Study Design 72
11.3 **P**rimary and Secondary Data, Modeling, and Data Analysis 73
11.4 Anticipated Outcomes 74

12.0 DATA COLLECTION AND MONITORING 74
12.1 Records to Be Kept 74
12.2 Role of Data Management 74
12.3 Clinical Site Monitoring and Record Availability 75
12.4 **Reporting Protocol Deviations** 75

13.0 PARTICIPANTS 75
13.1 Institutional Review Board (IRB) Review and Informed Consent 75
13.2 Participant Confidentiality 75
13.3 Study Discontinuation 76

14.0 PUBLICATION OF RESEARCH FINDINGS 76

15.0 BIOHAZARD CONTAINMENT 76

16.0 REFERENCES 77

INFORMED CONSENT FORM AND AUTHORIZATION TO DISCLOSE HEALTH INFORMATION 80

ATTACHMENT I: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES 96

ATTACHMENT II: AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION 98

SAMPLE INFORMED CONSENT FOR PREGNANCY 101

SITES PARTICIPATING IN THE STUDY

A5394 is a multi-center study open to US and non-US AIDS Clinical Trials Group (ACTG) clinical research sites (CRSs) in countries with reported cases of both chronic hepatitis B (CHB) and HIV. Refer to the Site tab on the protocol's web page on the ACTG Member Website for the list of eligible CRSs.

PROTOCOL TEAM ROSTER

Chair
Jennifer Price, MD, PhD
University of California San Francisco
HIV/AIDS CRS
513 Parnassus Avenue, S-357
San Francisco, CA 94143
Phone: 415-502-1429
E-mail: jennifer.price@ucsf.edu

Co-Vice Chairs
Sharon R. Lewin, MD, PhD
The Peter Doherty Institute for Infection and Immunity
The University of Melbourne
Level 4, 772 Elizabeth Street
Melbourne, Victoria 3000
Australia
Phone: +613-8344-3309
E-mail: Sharon.Lewin@unimelb.edu.au

Mark S. Sulkowski, MD
Johns Hopkins University
School of Medicine
1830 East Monument Street, Suite 445
Baltimore, MD 21287-0003
Phone: 410-614-4172
E-mail: msulkowski@jhmi.edu

DAIDS Clinical Representative
Beverly L. Alston-Smith, MD
CCRB/TRP/DAIDS/NIAID/NIH/DHHS
Chief, Complications and Co-Infections Research Branch
Therapeutics Research Program
5601 Fishers Lane, Room 9F50
Rockville, MD 20852
Phone: 301-453-3773
Email: balston@niaid.nih.gov

Clinical Trials Specialist
Katharine J. Bergstrom, MS, CCRP
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.,
A DLH Holdings Company
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3000
E-mail: katharine.bergstrom@dlhcorp.com

Statisticians
Minhee Kang, PhD
Statistical and Data Analysis Center
Harvard School of Public Health
651 Huntington Avenue
FXB Building, Room 503
Boston, MA 02115-6017
Phone: 617-432-2819
E-mail: mkang@sdac.harvard.edu

Roy Matining, MS
Statistical and Data Analysis Center
Harvard School of Public Health
651 Huntington Avenue
Building 2, Room 437B
Boston, MA 02115-6017
Phone: 617-432-3025
E-mail: rmatining@sdac.harvard.edu

Data Manager**s**
Stephanie R. Caruso, MBA
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900, ext. 7322
E-mail: scaruso@frontierscience.org

Data Managers (Cont'd)
Shannon Sloan
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900, ext. 7252
E-mail: sloan@frontierscience.org

DAIDS Pharmacist
Cynthia Parker, PharmD, RPh
Pharmaceutical Affairs Branch
DAIDS, NIAID, NIH
5601 Fishers Lane, 9D37
Rockville, MD 20852
Phone: 301-761-7199
E-mail: cindy.parker@nih.gov

Immunologist
Adam Gehring, PhD
Toronto General Hospital Research Institute
Princess Margaret Cancer Research Tower
Room 10-356
101 College Street
Toronto, M5G1L7
Ontario
Canada
Phone: 416-634-7095
E-mail: adam.gehring@uhnresearch.ca

HBV Virologists
Raymond T. Chung, MD
Massachusetts General Hospital (MGH) CRS
55 Fruit Street
Boston, MA 02114
Phone: 617-724-7562
E-mail: rtchung@partners.org

Alex Greninger, MD, PhD, MPhil, MS
University of Washington
Retrovirus Laboratory
300 9th Avenue, RM725
Seattle, WA 98104
Phone: 415-439-3448
E-mail: agrening@uw.edu

HIV Virologist
Rajesh Gandhi, MD
Harvard Medical School
GRB 504, Infectious Disease
55 Fruit Street
Boston, MA 02114
Phone: 617-726-3811
E-mail: rgandhi@mgh.harvard.edu

Pharmacologists
Peter Anderson, PharmD
University of Colorado Hospital CRS
University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences
12850 East Montview Boulevard, Room 4101
Aurora, CO 80045
Phone: 303-724-6128
E-mail: peter.anderson@cuanschutz.edu

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

Ophthalmologist
Jennifer E. Thorne, MD, PhD
The Wilmer Eye Institute
Johns Hopkins School of Medicine
600 North Wolfe Street, Woods Building, Rm 470
Baltimore, MD 21287
Phone: 410-955-2966
E-mail: jthorne@jhmi.edu

Investigators
Jennifer Audsley, PhD, BAppSc
The Peter Doherty Institute for Infection and Immunity
The University of Melbourne
Level 4, 792 Elizabeth Street
Melbourne, Victoria 3000,
Australia
Phone: +613-834-433-266
E-mail: jennifer.audsley@unimelb.edu.au

Investigators (Cont'd)
Anchalee Avihingsanon, MD, PhD
Thai Red Cross AIDS Research Center
Treatment (TRC-ARC Treatment) CRS
104 Rajdamri Road
Patumwan, Bangkok 10330
Thailand
Phone: 66-2-6523040 x107
E-mail: anchalee.a@hivnat.org

Claudia Hawkins, MD, MPH, DTM&H
Northwestern University CRS
645 North Michigan
Suite 900
Chicago, IL 60611
Phone: 312-695-4993
E-mail: c-hawkins@northwestern.edu

Marion G. Peters, MD
Northwestern University CRS
645 North Michigan, Suite 900
Chicago, IL 60611
Phone: 415-345-9036
E-mail: marion.peters@ucsf.edu

Chloe L. Thio, MD
Johns Hopkins University CRS
Division of Infectious Diseases
1503 East Jefferson Street
Baltimore, MD 21231
Phone: 410-614-6088
E-mail: cthio@jhmi.edu

Michael J. Vinikoor, MD
University of Alabama
THT 215-1530 3rd Avenue S.
Birmingham, AL 35294-0006
Phone: 847-902-5400
E-mail: michaelvinikoor@uabmc.edu

Investigators (Cont'd)
Tanyaporn Wansom, MD
Thai Red Cross AIDS Research Centre
(TRC-ARC) CRS
Unit 46151, AFRIMS
APO, AP
Bangkok 96546
Thailand
Phone: +66-9-536-53917
E-mail: tanyaporn.wansom@gmail.com

Field Representative
Ian S. Mugisa, BDS, MSD
Joint Clinical Research Center
(JCRC)/Kampala CRS
P.O. Box 10005
Plot 101, Lubowa Estates, off Entebbe Road
Kampala 256
Uganda
Phone: 256-701911225
E-mail: mugisaian@yahoo.co.uk

Source Document Specialist
Josie Marshall, BS
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.,
A DLH Holdings Company
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 303-724-0803
E-mail: josie.marshall@dlhcorp.com

Laboratory Technologists
Cheryl Jennings, BS
Rush University Medical Center
Clinical Retrovirology Research
Laboratory
859 Jelke Building
1750 West Harrison Street
Chicago, IL 60612
Phone: **312-942-5954**
E-mail**: cheryl_jennings@rush.edu**

Laboratory Technologists (Cont'd)
Sasiwimol Ubolyam, PhD
Thai Red Cross AIDS Research Center
Treatment (TRC-ARC Treatment) CRS
104 Rajdamri Road
Patumwan, Bangkok 10330
Thailand
Phone: 662-256-4648 x111
E-mail: sasiwimol.u@hivnat.org

Community Scientific Subcommittee (CSS) Representative
Moses Nsubuga
Joint Clinical Research Center (JCRC)/Kampala CRS
PO Box: 10005
Kampala, Uganda
Phone: 256-772551000
E-mail: embassols@yahoo.co.uk

International Site Specialist
Anshika Verma, BA
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.,
A DLH Holdings Company
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3022
E-mail: anshika.verma@dlhcorp.com

Industry Representatives
Frida Abramov, DMSc, PA-C
Senior Director, Clinical Development
Gilead Sciences, Inc.
333 Lakeside Drive, Building 300
Foster City, CA 94404
Phone: **917-742-8557**
E-mail: **Frida.Abramov@gilead.com**

Art Guzman, BS
Clinical Trial Man**ager**
Gilead Sciences, Inc.
3**00** Lakeside Drive, Building 300
Foster City, CA 94404
Phone: 650-5**77-6477**
E-mail: **Art.Guzman@gilead.com**

Laboratory Data Manager**s**
Christopher Dolina, BS
Frontier Science & Technology Research Foundation
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 x7**215**
E-mail: **cdolina@frontierscience.org**

Philip Marzinek, BS
Frontier Science & Technology Research Foundation
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 x7399
E-mail: marzinek@frontierscience.org

Laboratory Specialists
Ceora Beijer, BS
ACTG Laboratory Center at UCLA
675 Charles E Young Drive South
MRL #4-774
Los Angeles, CA 90095
Phone: **424-946-5709**
E-mail: cbeijer@milabcentral.org

Emma Duffy
ACTG Laboratory Center at UCLA
675 Charles E Young Drive South
MRL #4-629
Los Angeles, CA 90095
Phone: 617-407-8713
E-mail: eduffy@milabcentral.org

Kathie Ferbas, PhD
ACTG Laboratory Center at UCLA
675 Charles E Young Drive South
MRL #4-629
Los Angeles, CA 90095
Phone: 310-780-3639
E-mail: kferbas@milabcentral.org

Laboratory Specialists (Cont'd)
Jade Paris, BS
ACTG Laboratory Center at UCLA
10990 Wilshire Boulevard
Unit 260
Los Angeles, CA 90024
Phone: 210-544-6937
E-mail: jparis@milabcentral.org

STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5394@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5394@fstrf.org. A response should generally be received within 24 hours (Monday through Friday).

Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5394 e-mail group. Include the protocol number in the e-mail subject line.

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

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

- Send an e-mail message to actg.cmcA5394@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions related to immunologic laboratory tests, contact the Protocol Immunologist. Send an e-mail message to actg.teamA5394@fstrf.org (ATTENTION: Adam Gehring).

For questions related to virologic laboratory tests, contact the Protocol HBV Virologists or Protocol HIV Virologist. Send an e-mail message to actg.teamA5394@fstrf.org (ATTENTION: Raymond Chung and Alex Greninger or Rajesh Gandhi, respectively).

For questions related to pharmacologic laboratory tests, contact the Protocol Pharmacologists. Send an e-mail message to actg.teamA5394@fstrf.org (ATTENTION: **Peter Anderson and** Charles Venuto).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the data managers. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the Frontier Science website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact Stephanie Caruso **and Shannon Sloan** directly.
- For other questions, send an e-mail message to actg.teamA5394@fstrf.org (ATTENTION: Stephanie Caruso **and Shannon Sloan**).
- 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 or call the DMC Randomization Desk at 716-834-0900, extension 7301.

DMC Portal and Medidata Rave Problems
Contact DMC User Support.

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

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

- Send an e-mail message to actg.teamA5394@fstrf.org (ATTENTION: Katharine Bergstrom).

Copies of the Protocol
To request a hard copy of the protocol, send an e-mail message to ACTGNCC@dlhcorp.com. Electronic copies can be downloaded from the ACTG website at https://www.actgnetwork.org.

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

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

Protocol Activation
For questions related to protocol activation at US sites, contact the Clinical Trials Specialist.

- Send an e-mail message to actg.teamA5394@fstrf.org (ATTENTION: Katharine Bergstrom).

For questions related to protocol activation at non-US sites, contact Anshika Verma, the International Site Specialist.

- Send an e-mail message to anshika.verma@dlhcorp.com.

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call Cynthia Parker, Protocol Pharmacist, at 301-761-7199, or send an e-mail message to cindy.parker@nih.gov.

Study Product Orders
Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741 between 8 AM and 5 PM Eastern Time (ET). Outside of this timeframe, sites may use other contact information found in the CRPMC Online Site Management and Ordering System (COSMOS).

IND (Investigational New Drug) Number or Questions
The IND number **is** available on the protocol-specific web page (PSWP). For any questions related to the IND submission, contact the DAIDS RSC at Regulatory@tech-res.com or call 301-897-1706.

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

Telephone Calls
Sites are responsible for documenting telephone calls made to A5394 team members.

- Send an e-mail message to actg.teamA5394@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 TERMS

AE	adverse event
anti-HBe	anti-hepatitis B e-antigen
anti-HBs	hepatitis B virus surface antibody
anti-HDV	hepatitis D virus antibody
ART	antiretroviral therapy
ARV	antiretroviral
cccDNA	covalently closed circular DNA
CHB	chronic hepatitis B
CLIA	Clinical Laboratory Improvement Amendments
CMC	Clinical Management Committee
CrCl	creatinine clearance
DBS	dried blood spot
DOT	directly observed therapy
ECG	electrocardiogram
ETR	etravirine
ETV	entecavir
FSH	follicle-stimulating hormone
FTC	emtricitabine
GCLP	Good Clinical Laboratory Practices
HAV IgM	hepatitis A virus immunoglobulin M
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B e-antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBV RNA	hepatitis B virus RNA
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV IgM	hepatitis E virus immunoglobulin M
IFNγ	interferon-γ
IGRA	**i**nterferon-gamma release assay
IL	interleukin
IL-1RA	IL-1 receptor antagonist
INR	international normalized ratio
IoR	**Investigator of Record**
IPDA	intact proviral DNA assay

IQA	Immunology Quality Assurance
LPC	**Laboratory Processing Chart**
MAIT cells	mucosal-associated invariant T cells
mDCs	myeloid dendritic cells
MOPS	Manual of Procedures
NA	nucleos(t)ide analogue
NK cells	natural killer cells
NRTI	nucleoside reverse transcriptase inhibitor
OAV	optimized antiviral
OCSO	**Office of Clinical Site Oversight**
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PK	pharmacokinetic
PWH	people with HIV
POC	point of care
PPD	purified protein derivative
PSWP	protocol-specific web page
PT	prothrombin time
qHBcrAg	quantitative hepatitis B core related antigen
qHBeAg	quantitative hepatitis B e-antigen
qHBsAg	quantitative HBsAg
RSR	**Remote Source Review**
SLGN	Selgantolimod
SOE	Schedule of Evaluations
TAF	tenofovir alafenamide
TAF/FTC	tenofovir alafenamide + emtricitabine
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TDF/3TC	tenofovir disoproxil fumarate + lamivudine
TDF/FTC	tenofovir disoproxil fumarate + emtricitabine
TILDA	tat-rev induced limiting dilution assay
TLR	toll-like receptor
TNFα	tumor necrosis factor-α
SIV	simian immunodeficiency virus
VCTE	vibration controlled transient elastography
3TC	lamivudine

SCHEMA

A5394
Safety, Tolerability, and Impact of Oral TLR8 Agonist Selgantolimod on HBsAg in Participants with **B**oth Chronic Hepatitis B and HIV

DESIGN	A5394 is a phase II, randomized, double-blind, placebo-controlled clinical trial to assess the safety, tolerability, and efficacy of 24 weeks of treatment with Selgantolimod (SLGN). Intensive **pharmacokinetic (**PK**)** sampling will be conducted in 12 participants.
DURATION	Participants will be on study for **up to** 48 weeks (24-week treatment phase and 24-week post-treatment follow-up).
SAMPLE SIZE	The total sample size will be 48 participants (36 **SLGN** and 12 placebo). Up to 6 additional participants may be enrolled if replacements are needed for key analyses.
POPULATION	Participants with both (1) HIV and chronic hepatitis B (CHB) on suppressive effective antiviral therapy for HIV (ART) and HBV for ≥5 years immediately prior to study entry and (2) screening quantitative hepatitis B surface antigen (qHBsAg) >1000 IU/mL, and without evidence of advanced liver fibrosis or cirrhosis. Enrollment of women (female sex assigned at birth) is encouraged, **with** an enrollment goal of at least 14 women. The study is expected to enroll participants in North America, South America, Africa, and Asia. **T**he first **12** months **of** enrollment will be capped at 24 participants at US sites and 24 participants at non-US sites. After **12 months**, enrollment will be open to all sites without regional caps.
STRATIFICATION	Randomization will be stratified by **hepatitis B e-antigen (**HBeAg**)** status at screening: 24 participants with positive HBeAg and 24 participants with negative HBeAg.
REGIMEN	Selgantolimod (SLGN) 3 milligrams (Arm A) or matching placebo (Arm B) by mouth once weekly for 24 weeks via directly observed therapy (DOT). Participants will be randomized 3:1 to the active treatment arm.

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 Administration of the oral toll-like receptor (TLR) 8 agonist **Selgantolimod (**SLGN**)** will be safe and well-tolerated in participants with both **chronic hepatitis B (**CHB**)** and HIV on suppressive antiviral therapy for both viruses.

1.1.2 TLR8 stimulation with SLGN will reduce hepatitis B surface antigen (HBsAg) titers in the blood of participants with both CHB and HIV on suppressive antiviral therapy for both viruses.

1.2 Primary Objectives

1.2.1 To assess the safety and tolerability of treatment with SLGN administered once weekly by mouth for 24 weeks.

1.2.2 To determine the proportion of participants with ≥1 $\log_{10}$ IU/mL decline in quantitative HBsAg (qHBsAg) after SLGN treatment at Week 24.

1.3 Secondary Objectives

1.3.1 To determine the proportion of participants with ≥1 $\log_{10}$ IU/mL decline in qHBsAg at any time during the study after SLGN treatment initiation.

1.3.2 To determine the proportion of participants with ≥0.5 log10 IU/mL decline in qHBsAg after SLGN treatment at Week 24.

1.3.3 To determine the proportion of participants with ≥0.5 log10 IU/mL decline in qHBsAg at any time during the study after SLGN treatment initiation.

1.3.4 To evaluate the proportion of participants who achieve HBsAg loss after SLGN initiation and who sustain HBsAg loss during follow-up.

1.3.5 To evaluate changes in qHBsAg levels at Weeks 4, 12, 24, 36, and 48 after SLGN initiation and, separately, among the placebo recipients.

1.3.6 To determine the proportion of **hepatitis B e-antigen (**HBeAg**)** positive participants at baseline who lose HBeAg at any time during the study, by study arm.

1.3.7 To determine the proportion of **anti-hepatitis B e-antigen (**anti-HBe**)** negative participants at baseline who develop anti-HBe at any time during the study, by study arm.

1.3.8 To determine the proportion of hepatitis B surface antibody (anti-HBs) negative participants at baseline who develop anti-HBs at any time during the study, by study arm.

1.4 Exploratory Objectives

1.4.1 To define the pharmacokinetic (PK) profile and PK-pharmacodynamic (PD) associations of SLGN in people with both HIV and CHB taking suppressive antiviral therapy for both viruses.

1.4.2 To explore if SLGN and antiretroviral (ARV) PK are altered when administered together.

1.4.3 To evaluate participants' adherence by using several tools, including self-report, directly observed therapy (DOT), and drug concentrations.

1.4.4 To compare quantitative changes in experimental measures of HBV antiviral efficacy (including HBV RNA, hepatitis B core related antigen [HBcrAg], qHBeAg, and low positive HBsAg measured with a high sensitivity qHBsAg assay [LLOQ of 0.05 IU/mL]) and measure changes in large, medium, and small HBsAg isoforms from baseline during and after treatment.

1.4.5 To determine the immunological effects of SLGN on circulating immune signaling by performing single cell RNA sequencing using peripheral blood mononuclear cells (PBMCs) and evaluating HIV-specific T-cell responses.

1.4.6 To determine the effects on circulating immune cells, including cellular phenotypes and T and B-cell responses.

1.4.7 To determine whether administration of SLGN will affect levels of circulating cytokines, including TNF-alpha, IL-12, IL18, IP-10, ISG15, IL-21, Fas Ligand, and TRAIL.

1.4.8 To evaluate levels of circulating cytokines, including IFN-gamma, IL-12p40, IL-1RA, and CD163 at entry, 24 hours post-first study drug dose, Weeks 4, 12, 24, 36, and 48, by study arm.

1.4.9 To determine whether administration of SLGN will perturb HIV latency as measured by an increase in HIV transcription.

1.4.10 To determine whether administration of SLGN will decrease the size of the latent reservoir, as measured by the change in amount of cell-associated unspliced HIV RNA, HIV DNA, and replication-competent and/or intact virus at Weeks 2, 4, 24, and 48.

2.0 INTRODUCTION

2.1 Background

Globally, 257 million people are living with CHB, including 2.7 million people with HIV (PWH) and CHB. CHB is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) [Global Hepatitis Report 2017; Stanaway 2016]. The majority of individuals exposed to HBV as infants develop CHB, whereas most adults exposed to CHB resolve the infection due to a robust immune response. Despite resolution of the infection, viral covalently closed circular DNA (cccDNA) persists within the nuclei of hepatocytes and can serve as a reservoir for viral reactivation. Virologic/complete sterilizing cure requires loss of all cccDNA within the hepatocyte and is not presently achievable.

Functional cure, defined as loss of HBsAg and HBV DNA with or without anti-HBs seroconversion, occurs in ~1% of untreated HBV monoinfected patients annually [Yeo 2019]. Treatment with nucleos(t)ide analogues (NA) can suppress viral replication, but similar to untreated patients, functional cure only occurs in ~1% of NA-treated HBV monoinfected patients annually [Yeo 2019]. In patients with HIV and HBV, loss of HBsAg is higher especially in the first year of effective antiviral therapy for HIV (ART) and HBV (reviewed in [Audsley and Sasadeusz 2020]). PEG-IFN suppresses HBV DNA via multiple mechanisms including stimulating innate immune responses. While rates of HBsAg loss are higher with PEG-IFN administered weekly for 48 weeks compared to NA therapy, functional cure remains rare [Terrault 2018].

A global effort is underway to develop more effective HBV therapies resulting in functional cure without the need for life-long antiviral therapy [Lok 2017; Revill 2019]. In addition to alleviating the cost of life-long treatment and the associated burdens of ongoing adherence and disease monitoring among people living with CHB, finite therapy with HBsAg loss may further reduce risk of HCC below what is achieved with long-term HBV DNA suppressive therapy [Anderson 2019]. People with both HIV and CHB are excluded from HBV cure trials but have much to gain from functional cure of CHB. Coinfection with HIV and CHB is associated with accelerated fibrosis progression and increased risk of HCC and liver-related mortality [Singh 2017], as well as worse HIV-related disease and all-cause mortality. The incidence of adverse liver outcomes in PWH and CHB remains high despite antiviral therapy that suppresses both viruses [Klein 2016]. In a study of 120 participants with both HIV and CHB on antiviral therapy that suppresses both viruses, who underwent liver biopsy, 37% had significant fibrosis [Sterling 2019]. Finally, in people with both HIV and CHB, because effective antiviral therapy for HIV (ART) and HBV includes agents active against HIV as well as HBV (including tenofovir disoproxil fumarate [TDF], tenofovir alafenamide [TAF], emtricitabine [FTC], or lamivudine [3TC]), NA therapy is always continued lifelong. These medications have associated toxicity, and there is high interest in identifying new approaches for management of HIV that do not include these agents.

Immune control of HBV occurs in most people with adult-acquired HBV infection, and involves both host innate and adaptive immune responses. Toll-like receptors (TLRs)

have a critical role in the host response to viruses by initiating intracellular signaling pathways to induce antiviral mediators such as interferons, cellular immune mediators, and antiviral cytokines. Recent studies show that the activation of TLR-mediated signaling pathways results in a suppression of HBV replication in vitro and in vivo, and agonism of both TLR7 and TLR8 have both been explored in the treatment of people with CHB infection on antiviral therapy [Ma 2018]. TLR7 agonists appeared to be effective in driving clearance of HBV in animal models, and the TLR7 agonist vesatolimod increased HBV-specific T-cell responses in people with HBV on NA, but did not reduce HBsAg levels in vivo [Boni 2018; Janssen 2018]. Therefore, vesatolimod is no longer being explored as an option for HBV cure and there has been an increased interest in the role of TLR8 agonists.

TLR8 is expressed on intracellular vesicular membranes of monocytes/macrophages and myeloid dendritic cells (mDCs) and is involved in recognition of nucleic acids. SLGN is a potent, selective, oral, small-molecule TLR8 agonist, which is in clinical development for HBV treatment. In vitro, SLGN induced cellular immune mediators interleukin (IL)-12 and IL-18, as well as the antiviral cytokines tumor necrosis factor-α (TNFα) and interferon-γ (IFNγ) in human PBMCs [Daffis 2017]. SLGN also activated natural killer (NK) cells and mucosal associated invariant T (MAIT) cells and lowered PD-1 expression by HBV-specific CD8+ cells [Daffis 2018]. In HBV-infected primary human hepatocytes, SLGN induced cytokines that decrease HBV DNA, HBV RNA, and HBsAg levels [Niu 2017]. In vivo, once-weekly dosing of oral SLGN induced dose-dependent increases in serum IL-12p40 and IL-1 receptor antagonist (IL-1RA) in cynomolgus monkeys and induced functional cure in the woodchuck model of chronic HBV infection [Daffis 2017; Daffis **2021**].

SLGN has been investigated in people without HIV and people with CHB infection. In people without HIV, oral SLGN induced a dose-dependent and transient increase in immunomodulatory and antiviral cytokines (IL-12p70, TNFα, and IFNγ) in serum and activated peripheral MAIT cells, NK cells, and mDCs [Grant 2018; Reyes 2020]. SLGN was further evaluated in a phase 1b study of non-cirrhotic participants with HIV and without suppressed HBV DNA. Participants received up to 4 doses of SLGN, which was generally safe with treatment-emergent headache, nausea, and dizziness but no Grade 3 or 4 adverse events (AEs) or drug discontinuation. SLGN induced rapid, dose-dependent increases in serum IL-12p40 and IL-1RA, with peak concentrations occurring approximately 4 hours post-dose [**Chen 2020**]. In this short duration study, no significant changes were observed for HBsAg, HBV DNA, hepatitis B core-related antigen, quantitative HBeAg, or HBV RNA.

SLGN 1.5 mg and 3 mg doses are being evaluated in two ongoing phase 2, multicenter, randomized, double-blind, placebo-controlled studies in virally suppressed (GS-US-389-2024) and viremic CHB participants not currently on optimized antiviral (OAV) treatment (GS-US-389-2025). The Study GS-US-389-2024 interim Week 48 analysis demonstrated that SLGN administered weekly as 1.5 mg or 3 mg doses for 24 weeks was generally well-tolerated. Overall, the 5 most commonly reported AEs were nausea (37.5%), upper respiratory tract infection (25.0%), headache (25.0%), vomiting (18.8%), and fatigue (18.8%).

There was no Grade 3 or 4 treatment-emergent AE considered related to study drug. One participant in the 1.5 mg group and no participants in the 3 mg group discontinued SLGN dosing early due to an AE. The Study GS-US-389-2025 preliminary Week 24 analysis demonstrated that SLGN administered weekly as 1.5 mg or 3 mg doses for 24 weeks was generally well-tolerated. Overall, the 5 most commonly reported AEs were nausea (20.9%), headache (14.9%), vomiting (13.4%), fatigue (11.9%), and dizziness (9.0%). A Grade 3 AE (rhinorrhea) was reported for 1 subject (treatment group omitted to avoid subject level unblinding). One subject (treatment group omitted to avoid subject level unblinding) was discontinued due to the AEs of abdominal pain upper and vomiting.

In the Study GS-US-389-2024, a total of 1 subject (HBeAg-negative in the SLGN 1.5 mg dose group) met the primary endpoint of ≥1 log10 IU/mL decline from baseline in qHBsAg at Week 24. There were no clinically meaningful changes from baseline in mean serum qHBsAg observed across treatment groups. A total of 2 HBeAg-negative subjects achieved HBsAg loss during the study. A total of 3 HBeAg-positive subjects (2 subjects in the SLGN 3 mg dose group and 1 subject in the SLGN 1.5 mg dose group) achieved HBeAg loss during the study, and 1 of those (SLGN 3 mg dose group) also achieved HBeAb seroconversion at Week 48. No subjects in the placebo group achieved HBsAg or HBeAg loss or seroconversion during the study. Dose-dependent increases in serum cytokines, including IL-1RA and IL-12p40, in the SLGN treatment groups were observed with no tachyphylaxis observed with weekly dosing through Week 24.

Although safety data of TLR8 agonists in PWH are not available, TLR7 and TLR9 agonists are being evaluated in latency reversal strategies in PWH without CHB. Fifteen virologically suppressed PWH on ART received the TLR9 agonist lefitolimod 60 mg subcutaneously twice weekly for 4 weeks in an open-label phase 1b/2a single arm trial [Vibholm 2017]. The most frequent drug-related AE was injection site reaction (23 reported events), followed by neutropenia (11), fatigue (7), and malaise (4). Three cases of neutropenia were Grade 2 and one case was Grade 1. All other drug-related AEs were Grade 1. All AEs resolved spontaneously. In a phase 1b, randomized, placebo-controlled trial, 17 PWH virologically suppressed on ART received 10 doses of the TLR7 agonist vesatolimod [SenGupta 2020]. Vesatolimod was generally well tolerated with no discontinuations due to AEs. In a separate dose escalation study of vesatolimod in 36 PWH virologically suppressed on ART, the most common study-drug related AEs were transient flu-like symptoms, and most lab abnormalities were Grade 1 or 2 [Riddler 2019].

2.2 Rationale

This study will evaluate 3 mg SLGN dosing among virally suppressed individuals with both HIV and CHB. Given adherence is an important determinant of drug efficacy, and self-report traditionally over-represents true medication adherence, once weekly SLGN dosing will occur via DOT.

TLR8 agonists have a potential role of suppressing HBsAg by inducing immunomodulatory and antiviral cytokines, as described in HBV monoinfection. This

study will generate the data necessary to advocate for further use of SLGN in PWH and CHB as part of a strategy for HBV functional cure.

The team anticipates 8% of participants in the active arm will achieve the primary outcome of ≥1 log_{10} IU/mL decline in HBsAg levels at Week 24. Of note, participants with CHB in this study are likely to have adult-acquired HBV that did not resolve due to HIV-associated immune dysfunction and therefore may be particularly responsive to TLR8 agonism. The estimated annual rate of HBsAg loss among CHB-monoinfected individuals is 1% [Yeo 2019]. Notably, patients with lower qHBsAg have a higher likelihood of losing HBsAg, and qHBsAg declines are most pronounced within the first year of antiviral therapy, with levels remaining stable after that time [Vibholm 2017]. Reported annual rates of HBsAg loss among individuals with HIV and CHB on nucleos(t)ide treatment range from 0.6-6% per year, with the highest rates of clearance in the first few years of nucleos(t)ide treatment in the setting of immune restoration [Boyd 2015; Matthews 2013; Plaza 2013; Psevdos 2010; Strassl 2014; Zoutendijk 2012]. In a study of 47 participants with both HIV and CHB, all qHBsAg declines of ≤1 log_{10} IU/mL or loss of HBsAg occurred prior to Week 48 after starting tenofovir [Matthews 2013]. Among 32 participants with qHBsAg levels available at 48 weeks after starting tenofovir, none experienced a ≥1 log_{10} IU/mL **decline** in qHBsAg [Audsley 2020]. Given that the A5394 study population will include participants on antiviral therapy for at least 5 years who have baseline qHBsAg >1000 IU/mL, the team anticipates qHBsAg will be relatively stable without intervention and therefore has selected a null rate of 0.5%. A placebo arm will be included to evaluate that no one will achieve ≥1 log_{10} IU/mL decline in qHBsAg in the absence of SLGN. The placebo arm will also serve as a reference group for safety assessments, analyses of exploratory markers, and exploration of potential drug-drug interactions between ARVs and SLGN.

Selection of the weekly administration of 3 mg of SLGN is based on the safety, tolerability, and PD data from the phase 1b study (GS-US-389-2022) and the phase 2 study (GS-US-389-2024) in CHB participants for up to 24 weeks. SLGN 3 mg administered up to 24 weeks was generally well-tolerated and safe in both the phase 1b and phase 2 studies. Additionally, the 3 mg dose has resulted in quantifiable and consistent increases in PD biomarkers, including IL-12p40 and IL-1RA, and tachyphylaxis has not been observed with weekly dosing. SLGN 3 mg will be dosed in a fasted state based on the result from the first-in-human study GS-US-389-2021 **which** showed **similar PK parameters in the fed and fasted state but significant impact of fed versus fasting on the pharmacodynamic effect of SLGN. The fed state led to less TLR8 engagement, including lower** IL-12p40 and IL-1RA serum**,** compared with fasted state dosing.

Investigation of the effects of SLGN on the HIV reservoir will also be explored. TLR8 agonists may also potentially perturb the HIV reservoir through either reversal of latency or enhancing immune mediated clearance of infected cells that present virus antigen. In PWH on suppressive ART, virus can persist in long lived forms as latent infection in resting and proliferating CD4+ T cells. One strategy being investigated to eliminate latent HIV is the activation of latent virus with the goal of inducing virus-mediated cytolysis and/or

immune mediated clearance [Rasmussen 2016; Zerbato 2019]. Activation of latent HIV will not lead to further rounds of infection if this is done while on suppressive ART. In addition to other agents such as histone deacetylase inhibitors and protein kinase C agonists, TLR7 can activate HIV latency in vitro [Tsai 2017] and can also activate simian immunodeficiency virus (SIV) infection in non-human primates on antiviral therapy in vivo in some [Lim 2018] but not all studies [Borducchi 2016; Borducchi 2018]. Similar to TLR7 agonists, TLR9 agonists appear to have some activity as latency reversing agents in vivo in individuals with HIV on antiviral therapy [Vibholm 2017]. Recent work in vitro has shown that TLR8 agonists are also latency reversing agents [Meås 2020; Schlaepfer 2011] and they potently synergize with prostratin to activate latent HIV [Rochat 2017]. TLR8 agonists also activate CD4+ T cells but in addition have broader activity in activating innate immune function, including mDCs, monocytes**,** and neutrophils. To date, there have been no non-human primate or human trials of a TLR8 agonist, but we hypothesize that latency reversal will be induced and this could potentially result in a decline in latently infected cells.

CHB infection is more common in men than women due to differential immune responses to the infection. During chronic infection, women may also be more likely to clear HBsAg. In a recent NA-ACCORD study, 86.6% of 3,573 people with both HIV and CHB were male [Lo Re 2019]. Similarly, in the TREAT Asia HIV Observational Database, women with HIV were significantly less likely to also have HBV (adjusted odds ratio = 0.66) [Chen 2016]. Understanding the biological impact of sex on HBV outcomes is important. Accordingly, the study will specifically focus on enrollment of women, and we have set an enrollment goal of at least 14 women. Sex will be defined by sex assigned at birth.

The study is expected to enroll PWH receiving care in North America, South America, Africa, and Asia. For the first **12** months after the study opens to enrollment, enrollment will be limited to 24 participants at US sites and 24 participants at non-US sites. After **12** months, enrollment will be open to all sites without regional caps. With international site participation, minority populations will be well represented.

Novel HBV markers of antiviral efficacy will be assessed, including quantitative hepatitis B core related antigen (HBcrAg), quantitative HBeAg, HBV RNA, HBsAg measured with a high sensitivity qHBsAg assay (LLOQ of 0.05 IU/mL), and the measurement of changes in large, medium, and small HBsAg isoforms. Effects on circulating immune cells, including cellular phenotypes and T and B-cell responses will be evaluated, and single cell RNA sequencing will be used to understand gene expression changes in PBMCs.

Novel HIV assays will include the intact proviral DNA assay (IPDA) which requires at least 5 million CD4+ T cells and detects the proportion of intact DNA [Bruner 2019]. In addition, virus transcription will be assessed by quantification of cell-associated unspliced HIV RNA as previously described [Rasmussen 2018]. Standard assessments of the reservoir will be performed, including total HIV DNA and integrated HIV DNA [Rasmussen 2018], as will an assessment of the inducible virus reservoir using the tat-rev induced limiting dilution assay (TILDA) [Procopio 2015].

There are no clinical data available on SLGN treatment in pregnant women. Nonclinical studies in rabbits showed no adverse effect on fertility, but did show a possible risk of teratogenicity/fetotoxicity during embryo-fetal development. Therefore, the use of highly effective contraception will be required for participation in this study. Nonclinical studies showed no genotoxicity. Nonclinical studies demonstrated low induction potential with once-weekly dosing of SLGN. Based on these data, no reduction in the exposure of hormonal contraception is expected. It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure of the male participant's seminal fluid and poses a potential risk to an embryo/fetus. Refer to the latest version of the Investigator's Brochure for additional information.
Participants age ≥18 years and ≤70 years will be enrolled based on the Investigator's Brochure.

3.0 STUDY DESIGN

A5394 is a phase II, randomized, double-blind, placebo-controlled clinical trial to assess the safety, tolerability, and efficacy of 24 weeks of treatment with SLGN.

Forty-eight (48) PWH and CHB (24 HBeAg+, 24 HBeAg-) on suppressive, effective antiviral therapy for HIV (ART) and HBV will be randomized to active treatment with SLGN or matching placebo once weekly by mouth for 24 weeks. Random assignment of three active **to** one placebo will be stratified by HBeAg status (see Schema). All participants will be followed for 48 weeks (24-week treatment phase and 24-week post-treatment follow-up). All treatment will be administered by DOT (in person and remotely).

Twelve participants enrolled in the study **and randomized to either the SLGN arm or matching placebo arm** will undergo intensive PK assessment.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 HIV-1**,** documented by:

- **A**ny licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry
  AND
- **C**onfirmed by **one of the following:**
  - **A** second antibody test **from different manufacturers or based on different principles and epitopes (combination antigen-antibody-based rapid tests may be used)**
  - HIV-1 antigen
  - HIV-1 RNA viral load**, or**
  - **A** licensed Western blot

NOTE: The term "licensed" refers to a US FDA-approved kit

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

4.1.2 Effective antiviral therapy for **both** HIV (ART) and HBV **for ≥5 years immediately prior to study entry,** that includes TDF, TAF, TDF/FTC, TDF/3TC (tenofovir disoproxil fumarate plus lamivudine), TAF/FTC, or entecavir (ETV). ART is defined as including a minimum of two anti-HIV antivirals.

NOTE A: Switches are allowed as long as the regimen contains TDF, TAF, or ETV and as long as the participant has maintained HIV and HBV suppression for at least 12 months immediately prior to study entry.

NOTE B: Interruptions are permitted; however, in the 12 months prior to study entry, an interruption in therapy of up to **2** weeks on one occasion only is permitted, as long as the interruption occurred at least 24 weeks prior to study entry.

4.1.3 CD4+ cell count ≥350 cells/mm^3 obtained within **60** days prior to study entry at any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, or at any **N**etwork-approved non-US laboratory that is DAIDS Immunology Quality Assurance (IQA) certified.

4.1.4 HIV-1 RNA <50 copies/mL measured on at least two occasions at least 12 weeks apart, with no documented value >200 copies/mL, over the 12 months prior to study entry**. The latest measure must be obtained within 60 days prior to study entry from** any US laboratory that has CLIA certification or its equivalent, or at any **N**etwork-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs (non-US sites). The **earlier** measure **can** be **extracted from routine medical records**.

4.1.5 Positive or negative HBeAg result obtained within **60** days prior to study entry **from any US laboratory that has CLIA certification or its equivalent, or at any Network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs (non-US sites)**.

4.1.6 Negative **hepatitis D virus antibody (**anti-HDV**)** result obtained **as measured by Network-approved central laboratory** within **60** days prior to study entry.

4.1.7 Current CHB infection, defined as HBsAg positive in the blood on at least 2 occasions. The earliest positive HBsAg must be obtained at least 24 months prior to study entry and the latest within **60** days prior to study entry **with no documented negative HBsAg in between. If HBsAg at least 24 months prior to study entry is not available, a history of CHB documented in the medical records is acceptable.**

4.1.8 HBV DNA level <50 IU/mL measured on at least two occasions at least 12 weeks apart, with no documented value ≥50 IU/mL, over the 12 months prior to study entry**. The latest measure must be obtained within 60 days prior to study entry from** any US laboratory that has CLIA certification or its equivalent, or at any **N**etwork-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs **(non-US sites)**. The **earlier** measure **can** be **extracted from routine medical records**.

4.1.9 Quantitative HBsAg >1000 IU/mL measured within **60** days prior to study entry **as measured by Network-approved central laboratory**.

4.1.10 Hepatitis C virus (HCV) antibody negative result within **60** days prior to study entry, or if the participant is HCV antibody positive, an undetectable HCV RNA result within **60** days prior to study entry by any US laboratory that has a CLIA certification or its equivalent, or at any **N**etwork-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

4.1.11 The following laboratory values obtained within **60** days prior to study entry by any US laboratory that has a CLIA certification or its equivalent, or at any **N**etwork-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

- Aspartate aminotransferase (AST) (SGOT) ≤3 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) (SGPT) ≤3 x ULN
- Total bilirubin ≤1.5 x ULN or, for participants with Gilbert's syndrome, direct bilirubin ≤ULN
- Serum albumin ≥3.4g/dL
- Hemoglobin ≥12 g/dL for men and ≥10 g/dL for women based on sex assigned at birth
- Platelet count ≥150,000/mm^3
- International normalized ratio (INR) **≤**1.1
- Creatinine clearance (CrCl) >60 mL/min
- Hemoglobin A1c ≤9.0%

4.1.12 Abdominal imaging obtained within 24 weeks prior to study entry showing no evidence of HCC.

NOTE: Results of clinical ultrasounds or CT/MRI of abdomen with contrast performed within 24 weeks of study enrollment should be used if available. If an ultrasound or CT/MRI of abdomen with contrast is not available within the pre-enrollment window, an ultrasound procedure should be performed during the screening window.

4.1.13 FIB-4 ≤2.67 within **60** days prior to study entry.

NOTE: A FIB-4 value is calculated using a participant's age, AST and ALT levels, and platelet count. A calculator can be found on the PSWP.

4.1.14 For participants of reproductive potential who can become pregnant (defined as a female-born participant following the initiation of puberty [Tanner stage 2] until becoming postmenopausal unless permanently sterile or has medically documented ovarian failure), a negative serum or urine pregnancy test (urine test must have a sensitivity of <25 mIU/mL) **at screening and** within 2 days prior to study entry by any US clinic or laboratory that has a CLIA certification or its equivalent, or is a US clinic with a CLIA Certificate of Waiver using a point of care (POC)/CLIA-waived test, or at any **N**etwork-approved non-US laboratory or clinic that operates in accordance with GCLP and participates in appropriate EQA programs.

NOTE A: Participants are considered to be in a postmenopausal state when they are ≥54 years of age with cessation of previously occurring menses for ≥12 months without an alternative cause. In addition, participants <54 years of age with amenorrhea of ≥12 months may also be considered postmenopausal if their follicle-stimulating hormone (FSH) level is in the postmenopausal range established by the reporting laboratory and they are not using hormonal contraception or hormonal replacement therapy.

NOTE B: Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a participant of any age. Documentation is required.

4.1.15 Interferon-gamma release assay (IGRA) **conducted at any US clinic or laboratory that has a CLIA certification or its equivalent or any non-US DAIDS-approved laboratory or clinic that operates in accordance with GCLP and participates in appropriate EQA programs** or **purified protein derivative (**PPD**)** for tuberculosis (TB) with negative results within 90 days prior to study entry, OR documented evidence of completed tuberculosis therapy.

NOTE: IGRA does not need to be repeated at screening.

4.1.16 If participating in sexual activity that could lead to pregnancy, participants who can become pregnant must have started using contraception as listed below at

least 45 days prior to study entry and must agree to use two forms of contraception until 7 days after the last dose of study product.

NOTE: If participating in sexual activity that could lead to pregnancy, participants who can become pregnant must agree either to complete abstinence from intercourse of reproductive potential (abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle), or consistent and correct use of one of the following methods of birth control:

- Hormonal or nonhormonal intrauterine device (IUD)
- Subdermal contraceptive implant
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Participants who wish to use a hormonally-based method not listed above must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Oral contraceptives (either combined or progesterone only)
- Injectable progesterone
- Transdermal contraceptive patch
- Contraceptive vaginal ring
- Male condom
- Female condom
- Cervical cap, diaphragm, or sponge with spermicide

4.1.17 Fertile male participants with sexual partners who can become pregnant must agree to use condoms during study treatment and until 7 days after the last dose of study product when participating in sexual activity that could lead to pregnancy.

NOTE A: If the partner of childbearing potential is not pregnant, additional contraception should also be considered.

NOTE B: A male-born participant is considered fertile after the initiation of puberty, unless the participant is permanently sterile by bilateral orchidectomy or medical documentation.

4.1.18 Participants must agree to refrain from egg donation and in vitro fertilization during study treatment and until 7 days after the last dose of study product.

4.1.19 Participants must agree to refrain from sperm donation during study treatment and until 7 days after the last dose of study product.

4.1.20 Participants age ≥18 years and ≤70 years at study entry.

4.1.21 Participants must agree to stay on an effective antiviral therapy for HIV (ART) and HBV throughout the study.

4.1.22 Ability and willingness to comply with study procedures, including technology-based directly observed **study product** dosing.

4.1.23 Ability and willingness of participant to provide informed consent.

4.2 Exclusion Criteria

4.2.1 Receipt of treatment for HCV within 24 weeks prior to study entry.

4.2.2 Evidence of advanced fibrosis or cirrhosis (Metavir ≥F3 or equivalent) as diagnosed by one of the following:

- Liver biopsy within 24 months prior to study entry
- Vibration controlled transient elastography (VCTE) (FibroScan) of >8.5 kPa within 12 months prior to study entry
- FibroSure® score of >0.58 within 12 months prior to study entry
- FIB-4 score of >2.67 within 12 months prior to study entry

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

4.2.4 History of HCC or cholangiocarcinoma.

4.2.5 Malignancy within 5 years prior to study entry.

NOTE: A history of non-melanoma skin cancer (e.g., basal cell carcinoma or squamous cell skin cancer) is not exclusionary.

4.2.6 History of solid organ transplantation.

4.2.7 Presence of any active or acute AIDS-defining opportunistic infections within **60** days prior to study entry. A list of AIDS-defining opportunistic infections is located on the PSWP.

4.2.8 History of **or active** uveitis or posterior synechiae.

4.2.9 Breastfeeding **or pregnancy**.

4.2.10 **Acute illness** within 7 days prior to study entry.

4.2.11 Receipt of an**y** vaccine within 14 days prior to study entry.

4.2.12 Receipt of potent CYP3A inhibitors and inducers, including atazanavir, ritonavir, cobicistat, efavirenz, etravirine (ETR), or nevirapine within 2 weeks prior to study entry.

4.2.13 Current receipt **and/or anticipated need during the study** of prohibited medications listed in Table 5.4.2-1.

4.2.14 Known allergy/sensitivity or any hypersensitivity to components of study drug or its formulation.

4.2.15 Active substance use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.16 Acute or serious illness requiring systemic treatment and/or hospitalization within **60** days prior to study entry.

4.2.17 Unwillingness to consent to genetic testing.

4.2.18 Screening electrocardiogram (ECG) with clinically significant abnormalities or with QTcF interval (QT corrected using Fridericia's formula) >450 msec for males or >470 msec for females.

4.2.19 Receipt of PEG-IFN within 4 weeks prior to study entry.

4.2.20 Enrollment in or discontinuation of an investigational product or non-approved drug within 4 weeks or 5 half-lives of last dosing, whichever is longer, prior to study entry.

4.3 Study Enrollment Procedures

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

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration

process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approvals **as well as meeting any additional study-specific requirements as determined by the protocol team**, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific ICF(s) WILL NOT be reviewed or approved by the DAIDS PRO. Sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

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

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

Participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify. An ACTG Screening Checklist must be entered through the DMC Study Enrollment System.

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.

4.3.2 Protocol Activation

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

4.3.3 Randomization

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

4.4 Co-enrollment Guidelines

- US sites are encouraged to co-enroll participants in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently

Unspecified Analyses." Co-enrollment in A5128 does not require permission from the A5394 protocol chairs.

- Non-US sites are encouraged to co-enroll participants in A5243, "Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses." Co-enrollment in A5243 does not require permission from the A5394 protocol chairs.
- For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the protocol team via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment is defined as Selgantolimod or matching Placebo for Selgantolimod.

Required background ART and HBV regimens will not be provided by the study. CRS pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations. Refer to the product information summary provided in this section and to the Investigator's Brochure (IB) for further information regarding study product.

5.1 Regimens, Administration, and Duration

5.1.1 Regimens

Participants will be randomized 3:1 to one of the following treatment arms:

Arm A: Selgantolimod 3 mg once weekly for 24 weeks.

Arm B: Matching Placebo for Selgantolimod once weekly for 24 weeks.

5.1.2 Administration

Selgantolimod 3 mg: Administered by DOT as two 1.5 mg tablets orally once weekly on an empty stomach.

Matching Placebo for Selgantolimod: Administered by DOT as two matching placebo tablets **orally** once weekly on an empty stomach.

The Selgantolimod or Placebo for Selgantolimod **tablets** should be taken on the same day at the same time each week.

Both Selgantolimod and matching Placebo for Selgantolimod tablets must be administered in a fasted state. Participants should not eat or drink anything for at least 8 hours before **the** dose **is administered** and must continue fasting (no food or drink) for an additional 4 hours after dose administration. Fasting will be self-reported by the participant. Water is allowed up to 1 hour before dosing and 2 hours

after dosing**;** however, participants may administer the dose orally with water as needed.

Participants should take other medications, including ARV treatment, no earlier than 2 hours after administration of Selgantolimod or Placebo for Selgantolimod. If medications are recommended to be dosed with food, administer dose at least 4 hours after Selgantolimod or Placebo for Selgantolimod dosing.

If the participant vomits the dose, the dose for that week will be skipped and the participant should resume with the following week's dose.

Participants who do not administer Selgantolimod or Placebo for Selgantolimod on their scheduled day of weekly dosing may administer the missed dose up to 3 days after their scheduled day of dosing. The participant will then resume weekly dosing of Selgantolimod or Placebo for Selgantolimod on their regularly scheduled day of the week. If >3 days after the missed dose, the dose for that week should be skipped and the participant should resume with the following week's dose on their regularly scheduled day of the week.

5.1.3 Duration

Participants will remain on study treatment for 24 weeks.

5.2 Study Product Formulation and Storage

5.2.1 Formulation

Selgantolimod 1.5 mg tablets and matching Placebo for Selgantolimod tablets are round, plain-faced, film-coated white tablets.

5.2.2 Storage

Selgantolimod and matching Placebo for Selgantolimod tablets are to be stored below 30°C (86°F).

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

Selgantolimod and matching Placebo for Selgantolimod are manufactured and provided by Gilead Sciences and are available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study product for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

5.3.2 Study Product Accountability

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

5.4 Concomitant Medications

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

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

5.4.1 Required Medications

Required medications should be continued throughout study participation. These include TDF, TAF, TDF/FTC, TDF/3TC, TAF/FTC, or ETV. These medications are not provided through the study.

5.4.2 Prohibited Medications

Drug interaction data with SLGN are evolving. Prohibited agents are shown in Table 5.4.2-1. Medications not listed in Table 5.4.2-1 should be reviewed prior to randomization and throughout study treatment. See the A5394 PSWP for any additional information on prohibited and precautionary medications with SLGN.

If there is reason for use of a prohibited medication due to a concurrent condition, study product will be discontinued and the participant will be monitored through study completion. The site must notify the Clinical Management Committee (CMC) via e-mail at actg.cmca5394@fstrf.org.

Table 5.4.2-1: Drug Classes and Disallowed Agents

Drug Class	Agents Disallowed
Antibiotics	Clarithromycin, erythromycin rifabutin, rifampin, rifapentine, telithromycin, troleandomycin
Anticonvulsants	Carbamazepine, eslicarbazepine,

Drug Class	Agents Disallowed
	oxcarbazepine, phenobarbital, phenytoin
Antidepressants	Nefazodone
Antifungals	Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
Antiretrovirals	Atazanavir, cobicistat, efavirenz, etravirine, nevirapine, ritonavir
Cardiac Medications	Mi**b**efradil
Diuretics	Conivaptan
Gastrointestinal Motility Agents	Cisapride, metoclopramide, domperidone, mosapride citrate, pruc**a**lopride, itopride hydrochloride, levosulpride
Herbal/Natual Supplements	St. John's Wort, Echinacea, Milk thistle (silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Immunosuppressants*	Cyclosporine
Other	Avasimi**b**e, enzalutamide, idelalisib, lumacaftor, **m**itotane

*Short-term use of prednisone as a steroid burst (≤1 week of use) is permitted.

Data from the drug-drug interaction study indicate that cytochrome P450 (CYP)3A plays a major role in SLGN metabolism and, therefore, the administration of potent CYP3A inhibitors/inducers is not permitted in this study. Additionally, participants will be required to refrain from consumption of grapefruit juice, grapefruits, Seville oranges, and Seville orange juice 72 hours prior to the first dose of SLGN and through 7 days after the last dose of study product.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations (SOE)

Table 6.1-1: Schedule of Evaluations

Evaluation	Screening (within **60** days before Entry)	Entry (≥24 hours to **60** days after screening)	Post-Entry Evaluations Weeks										In the Event of Liver Enzyme Elevation (see section 8.2.2)	Premature Treatment/Study Disc.
			24 hours post-first study product dose	2	4	8	12	16	20	24	28	36	48	
				±3 day window							±2 week window			
Documentation of HIV-1	X													
Documentation of CHB	X													
Medical History	X	X												
Medication History (see Table 6.3.4-1)	X	X												
Clinical Assessments (see section 6.3.5)	X	X		X	X	X	X	X	X	X	X	X	X	**X**	X
Hematology	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistries	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Liver Function Tests	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X		X	X	X	X	X	X	X	X	X	X	X	X

Evaluation	Screening (within **60** days before Entry)	Entry (≥24 hours to **60** days after screening)	Post-Entry Evaluations Weeks										In the Event of Liver Enzyme Elevation (see section 8.2.2)	Premature Treatment/Study Disc.
			24 hours post-first study product dose	2	4	8	12	16	20	24	28	36	48	
				±3 day window							±2 week window			
Serum or Urine Pregnancy Test (see section 6.3.6)	X	**X**			X	X	X	X	X	X					X
Urinalysis		**X**		X	X	X	X	X	X	X	X	X	X		X
Hemoglobin A1c (HbA1c)	**X**														
IGRA or PPD Testing (see section 4.1.15)	X														
Fibrosis Measure	X														
CD4+	X	X			X		X			X		X	X		X
Anti-HDV	X														
Anti-HCV	X														
HBsAg Quantitative	X	X			X		X			X		X	X		X
HBsAg **Qualitative and** Anti-HBs	X	X			X		X			X		X	X	X	X
HBeAg **and** Anti-HBe	X	X			X		X			X		X	X	X	X

Evaluation	Screening (within **60** days before Entry)	Entry (≥24 hours to **60** days after screening)	Post-Entry Evaluations Weeks										In the Event of Liver Enzyme Elevation (see section 8.2.2)	Premature Treatment/Study Disc.
			24 hours post-first study product dose	2	4	8	12	16	20	24	28	36	48	
				±3 day window							±2 week window			
Quantitative HBeAg		X			X		X			X		X	X		X
Quantitative HBcrAg		X			X		X			X		X	X		X
Serum Biomarkers		X	X		X		X			X		X	X		X
Plasma PD Biomarkers		X	X		X		X			X		X	X		X
HBV RNA		**X**			**X**		**X**			**X**		**X**	**X**		**X**
HCV RNA (only if anti-HCV is positive)	X														
HIV-1 RNA	X	X		X	X		**X**			X			X		X
HBV DNA	X	X		X	X		**X**			X		X	X	X	X
HIV Genotype and Drug Resistance				**As needed (see section 6.3.9)**											
HBV Genotype and Drug Resistance				**As needed (see section 6.3.9)**											
Stored Plasma/PBMCs		X		X	X	X	X	X	X	X			X		X
Stored Serum		X		X	X	X	X	X	X	X			X		X

Evaluation	Screening (within **60** days before Entry)	Entry (≥24 hours to **60** days after screening)	Post-Entry Evaluations Weeks										In the Event of Liver Enzyme Elevation (see section 8.2.2)	Premature Treatment/Study Disc.
			24 hours post-first study product dose	2	4	8	12	16	20	24	28	36	48	
				±3 day window							±2 week window			
Whole Blood Gene Expression Biomarkers		X	X				X			X			X		X
TLR8 SNP (see section 6.3.9)		X													
HCV RNA														X	
HDV RNA														X	
HAV IgM														X	
HEV IgM														X	
Cell-associated HIV unspliced RNA and HIV DNA		X		X	X					X			X		
IPDA and TILDA (see section 6.3.12)		X								X			X		
DBS Collection (see section 6.3.13)		X		X	X	X	X	X	X	X	X	X	X		X
Intensive PK (see section 6.3.14)		X	X												
Sparse (Timed) Plasma PK (see section 6.3.15)		X	X	X	X	X	X	X	X	X				X	

Evaluation	Screening (within **60** days before Entry)	Entry (≥24 hours to **60** days after screening)	Post-Entry Evaluations Weeks										In the Event of Liver Enzyme Elevation (see section 8.2.2)	Premature Treatment/Study Disc.
			24 hours post-first study product dose	2	4	8	12	16	20	24	28	36	48	
				±3 day window							±2 week window			
Directly Observed Therapy (see section 6.3.16 for timing of dosing)		X		X	X	X	X	X	X					
Antiviral Therapy Adherence Assessments		X		X	X	X	X	X	X	X	X	X	X	X
Ophthalmologic Examinations (see section 6.3.18)	X									X				X
12-Lead ECG	X						X			X				
Ultrasound (see section 6.3.20)	X									X				

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant's starting study medications.

Screening evaluations to determine eligibility must be completed within **60** days prior to study entry unless otherwise specified. 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 to **60** days after screening evaluations unless otherwise specified. Participants must begin treatment within 1 day after randomization. Note that on the day of study entry, all participants will need to be available for multiple blood collections up to 4 hours post-**study product** dose. The 12 participants who will undergo intensive PK sampling will need to be available for multiple blood collections up to 12 hours post-**study product** dose and again at 24 hours post-dose. All **other** participants who undergo sparse PK at entry will need to be available for blood collections at 0.5, 4, and 24 hours post-dose.

6.2.3 Post-Entry Evaluations

<u>On-Treatment Evaluations</u>
On-treatment evaluations will be performed until Week 24, when treatment ends. On-treatment evaluations have ±3 day windows. With the exception of Weeks 4, 12, and 24, blood draws will be performed 6-24 hours post-weekly study product dosing. At Weeks 4 **and** 12, all study labs will be performed before study product administration, except for the **s**parse PK samples, one of which will be drawn within **0.25 to** 3.5 hours after study product administration and a second 4 hours after study product administration. Samples for PD biomarkers will be obtained before study product administration and 4 hours after study product administration.

<u>Post-Treatment Evaluations</u>
Post-treatment evaluations will be performed as shown in the SOE.

<u>Study Completion Evaluations</u>
Week 48 will be the final scheduled visit on study.

<u>Alternative Completion of Post-Entry Evaluations</u>
For visits that cannot be completed in person or if limited face-to-face contact is desired, evaluations may be conducted remotely (technology-assisted via

telephone, video call, etc.) for elements of the SOE that do not require an in-person visit. The technology-assisted evaluations may include: 1) review of signs and symptoms, diagnoses, and concomitant medications, 2) HBV antiviral therapy (nucleoside reverse transcriptase inhibitor [NRTI]) adherence assessment, and 3) study product DOT. In addition to the remote technology-assisted contact, the participant should be scheduled for an in-person blood and urine sample collection for all pertinent evaluations, along with the completion of a targeted physical examination, per the SOE. Technology-assisted evaluations should be timed around the **s**parse PK draws (e.g., if a single **s**parse PK sample is to be collected between 6-24 hours post-dose, the technology-assisted evaluation which includes **study product** DOT should occur 6 to 24 hours prior to the in-person evaluation). If the participant is unable or prefers not to come to the site for a visit, priority safety labs are permitted to be done at a local lab or as part of the standard of care. The priority safety labs include: chemistry, hematology, and liver function tests. Non-safety evaluations may be done remotely (technology-assisted), with the participant coming into the site only to have blood/urine collected for PK evaluations and completion of a targeted physical examination, per the SOE.

Refer to the Manual of Procedures (MOPS), located on the protocol-specific web page (PSWP), for additional guidance on conducting technology-assisted study evaluations.

6.2.4 Discontinuation Evaluations

Evaluations for Randomized Participants Who Do Not Start Study Treatment
All eCRFs must be keyed for the period up to and including the study entry visit. No further evaluations or follow-up are required for these participants. Up to 6 participants will be replaced.

Premature Treatment Discontinuation
Participants who prematurely and permanently discontinue study treatment will have discontinuation evaluations performed per the SOE. These evaluations should be completed within 1 week after treatment was discontinued. If the premature study treatment discontinuation evaluation visit falls within another visit window, the visits can be combined. Participants should continue to attend all study visits and receive study evaluations per the SOE.

NOTE: If study treatment is held due to a laboratory-confirmed SARS-CoV-2 infection, scheduled study visits should be conducted remotely (technology-assisted) until the participant has met CDC guidance for discontinuation of isolation found **on the CDC website**. Individual institutional policies supersede CDC guidance, in the event of discordant recommendations. If a participant discontinues treatment due to SARS-CoV-2 infection, a premature treatment discontinuation visit will be conducted. Refer to section 8.5 for clinical management guidance.

Premature Study Discontinuation
Participants who prematurely discontinue from the study for any reason should have the study discontinuation evaluations performed as noted in the SOE prior to being taken off study.

6.3 Instructions for Evaluations

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

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

The protocol team and/or study monitoring entity (e.g., Study Monitoring Committee [SMC]) may determine that additional source data associated with procedures or evaluations performed per protocol should be entered into eCRFs so that the data can be used for analysis or to otherwise assist with interpretation of study findings. In such cases, sites will be officially instructed to enter the additional data into eCRFs from available source documentation.

6.3.1 Documentation of HIV-1

Section 4.1.1 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the eCRF.

HIV-1, 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 one of the following:**
  - **A second antibody test from different manufacturers or based on different principles and epitopes (combination antigen-antibody-based rapid tests may be used)**
  - **HIV-1 antigen**
  - **HIV-1 RNA viral load, or**
  - **A licensed Western blot**

NOTE: The term “licensed” refers to a US FDA-approved kit

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

6.3.2 Documentation of CHB

CHB infection is defined as HBsAg positive in the blood on at least **two** occasions, **or if not available, historical chart documentation of CHB** per section 4.1.7. Historical HBsAg test result obtained at least 24 months prior to study entry should be documented, but not recorded on the eCRF**. If HBsAg test 24 months prior to study entry is not available, historical chart documentation of CHB should be documented, but not recorded on the eCRF. If available, HBV diagnosis date and HBV genotype will be recorded on the eCRF.**

6.3.3 Medical History

The medical history must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within **60** days prior to study entry. In addition, the following diagnoses should be recorded regardless of when the diagnosis was made:

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B
- COVID-19

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

6.3.4 Medication History

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

Table 6.3.4-1: Medication History

Medication Category	Timeframe
Over the counter and prescription acid reducing agents	Within 7 days prior to study entry
Antiretroviral therapy[1]	Within 5 years prior to study entry
Hepatitis B treatment history	Within 5 years prior to study entry
Immune-based therapy	Within 1 year prior to study entry
Blinded study treatment	Within 1 year prior to study entry
HIV-1-related vaccines	Within 1 year prior to study entry
COVID-19 vaccines	Complete
Prescription drugs for treatment of opportunistic infections	Within 60 days prior to study entry
Prescription drugs for prophylaxis of opportunistic infections	Within 60 days prior to study entry
Prescription drugs (other)	Within 60 days prior to study entry
Alternative therapies	Current use
Dietary supplements	Current use
Sex-hormone medications or sex-hormone analogues or antagonists[2]	Last 12 months except as noted below

[1] Establish that the participant has been receiving TDF, TAF, TDF/FTC, TDF/3TC, TAF/FTC, or ETV for at least the 5 years prior to study entry.

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

6.3.5 Clinical Assessments

Complete Physical Examination

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

Targeted Physical Examination

A targeted physical examination will be performed as part of the Clinical Assessments at each scheduled visit. It should include vital signs (weight, temperature, pulse, respiration rate, and blood pressure) and is to be driven by any previously identified or new AE that the participant has experienced since the last visit.

Height
Height is required to be recorded at screening only.

Tobacco Use
Current use of tobacco **and electronic cigarettes** including the number of cigarettes smoked per day is required to be recorded at study entry only. Current use is defined as within the 30 days prior to study entry. The questionnaire will be available in the Forms Management Utility.

Concomitant Medications
Post-entry, record all new and discontinued concomitant medications including dietary and herbal supplements, and prescription and over-the-counter medications taken since the last visit. Record vaccinations received, including the COVID-19 vaccination, since the last study visit.

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

6.3.6 Laboratory Evaluations

At screening and study entry all laboratory values must be recorded and keyed, regardless of grade. For post-entry assessments, record all laboratory values for AST, ALT, total bilirubin, albumin, INR, GGT, white blood cell count, and platelets regardless of grade; record abnormal laboratory findings per section 7.2.

If the participant is unable or prefers not to come to the site for a visit, priority safety labs may to be done at a local lab or as part of the standard of care. The priority safety labs include: chemistry, hematology, and liver function tests. Non-safety evaluations may be done remotely (technology-assisted), with the participant coming to the site only to have blood/urine collected for PK evaluations, and completion of a targeted physical examination, per the SOE.

Hematology
Hemoglobin, hematocrit, white blood cell count (WBC), WBC differential (absolute count or percentages), platelets.

Serum Chemistries
Sodium, potassium, chloride, bicarbonate, calcium, phosphate, creatinine, creatinine clearance, blood urea nitrogen (BUN), albumin.

Liver Function Tests (LFTs)
Total bilirubin, direct bilirubin, AST [SGOT], ALT [SGPT], GGT, alkaline phosphatase.

Coagulation
Prothrombin time (PT**)**, INR.

Serum or Urine Pregnancy Test
A pregnancy test is required **at screening and** within **2 days prior to** study entry for participants with reproductive potential who were identified as female at birth: Serum or urine β-HCG (urine test must have a sensitivity of <25 mIU/mL).
Record pregnancy and pregnancy outcome per section 8.0.

The inclusion of participants of reproductive potential requires the use of highly effective contraceptive measures with a failure rate of <1% per year. These participants must have a negative serum or urine pregnancy test ≤2 days prior to study entry as part of screening. While a participant is on treatment and through 7 days after the last dose of study product, a pregnancy test must be performed **per the SOE** to rule out pregnancy. This is applicable also for participants of childbearing potential with infrequent or irregular periods. Post-treatment, whether or not a participant with a delayed period is required to come in for an unscheduled visit for a pregnancy test or wait for their next follow-up visit is per investigator discretion.

Post-entry, see section 8.6 for collection requirements for pregnancy.

Urinalysis
Urinalysis will be performed by reagent strip plus microscopy **for urine protein, glucose, nitrate, leucocytes, and erythrocytes**. A microscopic test will only be required if the results of the reagent strip exceed the normal results.

Hemoglobin A1c (H**b**A1c)
H**b**A1c for metabolic studies will be obtained per the SOE.

IGRA or PPD Testing
IGRA or PPD per the SOE and processed in real time. IGRA testing is not required if there is documentation of appropriate full course of tuberculosis preventive therapy (TPT). Latent TB test results are not entered on the eCRF.

6.3.7 Fibrosis Measure

At Screening, the tests required to calculate FIB-4 will be recorded (i.e., age, AST, ALT, and platelet count). For screening purposes, a FIB-4 Calculator can be found on the following website: https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4.

If available, liver biopsy results obtained within 24 months **prior to** study entry, VCTE (FibroScan) results available within 12 months **prior to** study entry, and/or FibroSure results available within 12 months **prior to** study entry will be recorded.

See section 4.2.2 regarding documentation of liver fibrosis stage.

6.3.8 Immunologic Studies

CD4+
Screening absolute CD4+ count and percentages must be performed within **60** days prior to study entry at a laboratory that possesses a CLIA certification or equivalent (US sites) or IQA certification (non-US sites).

For study entry and post-entry evaluations, all laboratories must possess a CLIA certification or equivalent (US sites) or IQA certification (non-US sites).

Hepatitis D Virus Antibody (anti-HDV)
Anti-HDV status will be assessed within **60** days prior to study entry **as part of screening from a laboratory that possesses a CLIA certification or equivalent (US sites) or at any Network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs**.

Hepatitis C Virus Antibody (anti-HCV)
Obtain anti-HCV within **60** days prior to study entry **as part of screening from a laboratory that possesses a CLIA certification or equivalent (US sites) or at any Network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs**.

Quantitative HBsAg (qHBsAg)
Obtain qHBsAg as part of screening **and then on study per the SOE. Testing must be performed by a Network-approved central laboratory**.

Hepatitis B Surface Antigen (HBsAg) Qualitative **and** Hepatitis B Surface Antibody (anti-HBs)
Obtain HBsAg qualitative **and** anti-HBs as part of screening from a laboratory that possesses a CLIA certification or equivalent (US sites) or at any **N**etwork-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs. **Obtain HBsAg qualitative and anti-HBs on study per the SOE; testing must be performed by a Network-approved central laboratory.**

Hepatitis B e-Antigen (HBeAg) and Hepatitis B e-Antibody (anti-HBe)
Obtain HBeAg and anti-HBe as part of screening from a laboratory that possesses a CLIA certification or equivalent (US sites) or at any Network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs. Obtain HBeAg and anti-HBe on study per the SOE; testing must be performed by a Network-approved central laboratory.

Quantitative HBeAg (qHBeAg)
Obtain qHBeAg at study entry and post-entry, per the SOE.

Quantitative HBcrAg (qHBcrAg)
Obtain qHBcrAg at study entry and post-entry, per the SOE.

Serum Biomarkers
Serum biomarkers will be collected at the following time points: study entry (pre-dose), 4 hours post-first dose, 24 hours post-first dose, 4 hours post-dose at Weeks 4 **and** 12, and any time during the visit at Weeks **24,** 36**,** and 48 as indicated in the SOE.

Plasma PD Biomarkers
Plasma PD biomarkers will be collected at the following time points: study entry (pre-dose), 4 hours post-first dose, 24 hours post-first dose, 4 hours post-dose at Weeks 4 and 12, and any time during the visit at Weeks 24, 36, and 48 as indicated in the SOE.

6.3.9 Virologic Studies

HBV RNA
Obtain stored sample for HBV RNA at study entry and post-entry, per the SOE. Refer to the Laboratory Processing Chart (LPC) for instructions.

HCV RNA
HCV RNA will be performed only if anti-HCV is positive within 60 days prior to study entry as part of screening from a laboratory that possesses a CLIA certification or equivalent (US sites) or at any Network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

HIV-1 RNA
Samples will be collected per the SOE. See section 4.1.4.

HBV DNA
HBV DNA must be measured on at least 2 occasions over the 12 months prior to study entry with the latest one performed within **60** days prior to study entry by a laboratory that possesses a CLIA certification or equivalent, or at any **N**etwork-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs. Samples will also be collected at study entry and post-entry, per the SOE.

HIV Genotype and Drug Resistance
HIV genotype and drug resistance testing will be performed in the event of elevated HIV RNA (>500 copies/mL) as indicated in the SOE.

HBV Genotype and Drug Resistance
HBV genotype and drug resistance testing will be performed in the event of elevated HBV DNA (>500 IU/mL) as indicated in the SOE.

Stored Plasma/PBMCs
Plasma and PBMCs will be collected and stored for virologic, immunologic, and latency studies per the SOE. Samples will be collected pre-dose at Weeks 4 **and** 12. At the other visits, samples can be collected at any time.

Only sites certified by the IQA Cryopreservation PT Program at the Duke Human Vaccine Institute are required to collect PBMCs.

Stored Serum
Serum will be collected and stored for virologic, immunologic, and latency studies per the SOE. Samples will be collected pre-dose at Weeks 4 and 12. At the other visits, samples may be collected at any time.

Whole Blood Gene Expression Biomarkers
Samples will be collected for whole blood gene expression biomarker testing at study entry and post-entry, per the SOE. Samples will be collected at the following time points at study entry: pre-dose, 4 hours post-dose, and 24 hours post-dose. At post-entry visits, as indicated in the SOE, samples will be collected pre-dose and 4 hours post-dose.

TLR8 SNP
A sample will be collected for TLR8 SNP genotyping **once** at any time during the study, including at any unscheduled visit.

6.3.10 Other Hepatitis Investigations **in the Event of Liver Enzyme Elevation**

The following samples must be tested by a laboratory that possesses a CLIA certification or equivalent (US sites) or at any Network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

HCV RNA
In case of liver enzyme elevation, obtain HCV RNA per section 8.2.2.2.

HDV RNA
In case of liver enzyme elevation, obtain HDV RNA per section 8.2.2.2.

HAV IgM
In case of liver enzyme elevation, obtain hepatitis A virus immunoglobulin M (HAV IgM) per section 8.2.2.2.

HEV IgM
In case of liver enzyme elevation, obtain hepatitis E virus immunoglobulin M (HEV IgM) per section 8.2.2.2.

6.3.11 Cell-associated HIV Unspliced RNA and HIV DNA

Samples for cell-associated HIV unspliced RNA and HIV DNA testing will be collected per the SOE.

6.3.12 IPDA and TILDA

Samples for IPDA and TILDA testing will be collected per the SOE. Testing of samples will occur pending the results of the cell-associated HIV unspliced RNA and HIV DNA testing.

6.3.13 Dried Blood Spots (DBS)

DBS will be prepared at the time points indicated in the SOE and stored for PK analysis. DBS obtained at study entry must be obtained prior to study product administration.

6.3.14 Intensive PK

Intensive PK sampling will only be conducted in 12 participants who agree to take part in the intensive PK portion of the study. Samples for intensive PK will be collected at the following time points relative to the first administration of study product: pre-dose, 15 minutes, 30 minutes, 1 hour, 1 hour and 30 minutes, 2 hours, 3 hours, 4 hours, 5 hours, 8 hours, 12 hours, and 24 hours post-dose. Participants are required to remain at the clinic for the first 12 hours, and then must return for the 24 hour assessment. Participants may stay overnight to complete all of the required collections.

6.3.15 Sparse (Timed) Plasma PK

Sparse (timed) PK samples will be collected at the visits indicated per the SOE. Participants who have intensive PK samples collected, as outlined in section 6.3.1**4**, do not need to have sparse samples collected at the study entry visit. Those not undergoing intensive PK sampling at the study entry visit will have sparse samples collected at 0.5, 4, and 24 hours post-first witnessed **study product** administration. At Weeks 4 **and** 12, when **study product** DOT is performed in person, two **s**parse PK samples will be obtained: the first **s**parse PK sample will be collected within **0.25 to** 3.5 hours following study product administration and the second will be obtained when PD biomarkers are obtained at 4 hours post-dose. At Weeks 2, 8, 16, and 20, a single sample will be obtained between 6 and 24 hours post-**study product** dose. **At Week 24, a sample will be obtained at any time during the visit.**

6.3.16 Directly Observed Therapy (DOT)

Study product adherence will be assessed via DOT.
Study product will be taken orally for 24 weeks. Doses should be taken once per week at approximately the same time on the same day each week. All study product doses will be administered in a fasted state. Dosing should be done at the clinic at study entry, Weeks 4 **and 12**, if possible. For the other study visits, dosing must be done 6-24 hours before the clinic visit and observation should be done via technology-assisted DOT before the clinic visit (although in-person DOT is allowed).

Record the time of each dose.

Refer to the MOPS, located on the PSWP, for additional guidance.

6.3.17 Antiviral Therapy Adherence Assessments

Monitor adherence to effective antiviral therapy for HIV (ART) and HBV. Adherence is self-reported. The adherence assessment form is posted on the DMC Portal in the Forms Management Utility.

6.3.18 Ophthalmologic Examinations

An ophthalmologic evaluation will be performed at screening. A second documented exam will be performed between Weeks 24 and 48, and at premature treatment discontinuation. These exams include vision, slit lamp, and fundoscopy performed by an ophthalmologist. Symptom-directed ophthalmology examinations will be performed at any time until end of study. Results of the exam will only be recorded if uveitis is diagnosed.

6.3.19 12-lead Electrocardiogram (ECG)

12-lead ECG will be performed at screening and per the SOE. ECG Mean Heart Rate, aggregate PR Interval, aggregate QRS Duration, aggregate RR interval, and QTc results will be recorded.

6.3.20 Ultrasound

If abdominal imaging has not been performed within 24 weeks prior to study entry, an ultrasound will be performed at screening (within **60** days prior to study entry). An additional ultrasound will be performed at the Week 24 visit with a **±**12-week window.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

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

7.2 Adverse Event Collection Requirements for This Protocol

All AEs must be recorded on the eCRFs if any of the following criteria have been met.

- Grade ≥2 AEs
- All AEs that led to a change in study treatment/intervention regardless of grade
- All AEs meeting SAE definition or EAE reporting requirement

Grade ≥3 AEs, including laboratory events, must be recorded on the eCRFs within 3 **working** days of the event. AEs of lower grade may be reported on the eCRFs according to the standard reporting timeline.

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

All **AEs** that are reported must have their severity graded. To grade **AEs**, sites must refer to the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Serious Adverse Events (SAEs)
An SAE is defined as any untoward medical occurrence that results in any of the following outcomes:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

AESI (**AEs** of Special Interest)
An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further

investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

AESIs include the following:

- Grade ≥2 uveitis

For all AESIs, the Clinical Management Committee (CMC) should be notified within **72** hours via e-mail at actg.cmca5394@fstrf.org. AESIs must be recorded on the eCRFs within 3 **working** days of the event.

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

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

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.
For questions about expedited reporting, please contact the DAIDS RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com.

7.3.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The study agents for which expedited reporting are required are Selgantolimod or Placebo for Selgantolimod. In addition to the SAE Reporting Category identified above, other AEs that must be reported in an expedited manner are all events of hepatic decompensation and all events of uveitis. See sections 8.2.3 and 8.3.1.

7.3.3 Grading Severity of Events

The DAIDS AE Grading Table, corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

The expedited AE reporting period for this study is as per the DAIDS EAE Manual. After the protocol-defined EAE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the DAIDS EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.4 Study Monitoring

A5394 Core Team members (including study chairs, DAIDS clinical representative, and statisticians) will monitor the conduct and safety of the study via regular summaries of accrual, AEs, study conduct (including premature treatment discontinuations and premature study discontinuations), data completeness, and specimen collection, as appropriate. The Core Team will review the safety criteria as outlined in section 10.5 approximately monthly while study treatment is being administered to any participant.

The DAIDS clinical representative will review and assess select EAE reports for potential impact on the study participant safety and protocol conduct per DAIDS policies, guidance documents, and standard operating procedures (SOPs), as applicable. Additionally, the DAIDS clinical representative will review aggregated AE summaries prepared every 3 months by the Statistical and Data Analysis Center (SDAC). The study will undergo interim review at least annually by an ACTG-appointed SMC. The first planned interim review will occur when the study Week 24 data are available from the first 10 participants or 1 year after the enrollment of the first study participant, whichever occurs first. An interim review may also be convened if a concern is identified by the DAIDS clinical representative, the study chairs, or study statistician in consultation with the team. See section 10.5 for statistical and other considerations related to interim monitoring related to the safety criteria.

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

8.0 CLINICAL MANAGEMENT ISSUES

The recommendations and toxicity management guidelines within this section should be seen as guidelines. The treating physician should exercise clinical judgment regarding best clinical management, based on the symptoms and condition of the individual participant.

Criteria for participant management, dose interruption, and discontinuation are mandated only for toxicities related to study product. Toxicities due to drugs in the antiviral regimen should be managed according to standard clinical practice, with the goal of maintaining continuous therapy, if possible.

The grading system for drug toxicities is located in the DAIDS AE Grading Table.

NOTE A: The CMC must be notified within 24 hours by e-mail at actg.cmca5394@fstrf.org regarding any Grade 3 or 4 reactions that are deemed at least possibly related to study treatment.

NOTE B: For toxicities that cause DISCONTINUATION of study product, future doses of study product should not be given to the participant. Whereas, for toxicities that cause WITHHOLDING of study product, there is potential for continued/future doses to be given once the toxicity(ies) in question have been further investigated by the site investigator and the Core Team.

8.1 Nausea/Vomiting

If needed, prophylactic use of an antiemetic (such as ondansetron or prochlorperazine) for nausea and/or vomiting is allowed 1 hour before or 2 hours after Selgantolimod or Placebo for Selgantolimod dosing.

8.2 Toxicity

8.2.1 Grade**s** 3 and 4 Toxicity

For a Grade 3 or 4 laboratory AE that occurs following receipt of study product that is not specifically discussed below, and that is judged by the site investigator to be, at least possibly, study product-related, the CMC must be notified within 24 hours by e-mail at actg.cmca5394@fstrf.org. Study product should be withheld until repeat laboratory tests (performed at least once weekly or more frequently if clinically indicated) demonstrate that the laboratory abnormality returns to Grade ≤2. Once the laboratory abnormality returns to Grade ≤2, the study product can be restarted or dose reduced by 50% after discussion with the CMC **and at the discretion of the Investigator of Record (IoR)**.

The participant should be followed closely and if the AE does not return to Grade ≤2 within 2 weeks, the CMC should again be notified within 24 hours by e-mail at actg.cmca5394@fstrf.org.

For participants who experience a Grade 3 or 4 AE that is judged not related to the study product by the investigator, continued study treatment is at the discretion of the site investigator in consultation with the CMC.

8.2.2 Transaminase Elevation

NOTE: The guidance for Grades 2-4 ALT or AST elevation is further subdivided by ALT ULN sections. Investigators should note the distinction between DAIDS grade levels and ALT ULN designations.
Refer to the MOPS for AST/ALT toxicity management.

8.2.2.1 Grade 1 (1.25 to <2.5 x ULN)

Monitor liver function tests per the SOE.

8.2.2.2 **ALT or AST Elevation** (2.5 to ≥10 x ULN)

The CMC should be notified within 48 hours via e-mail at actg.cmca5394@fstrf.org.

ALT or AST >2.5 x ULN but <3 x ULN

- **If ALT and AST are ≤2 at baseline monitor liver function tests per the SOE.**
- If ALT or AST >2x baseline (study entry) and ALT or AST ≥2.5 to <3 x ULN, repeat ALT and AST **with**in 72 hours (via non-scheduled visits if necessary).
- If confirmatory ALT or AST ≥3 x ULN, follow guidance for elevation of ALT or AST ≥3 x ULN.
- If confirmatory ALT or AST <3 x ULN, then follow the study SOE. If there is a greater than 2-week window from confirmed elevated ALT or AST to next evaluation, please consult the CMC at actg.cmca5394@fstrf.org for further guidance on timing of subsequent ALT and AST assessments.
- Continue study product **at the discretion of the IoR**.

ALT or AST ≥3.0 x ULN but <5 x ULN

- Repeat ALT and AST within **72 hours (via non-scheduled visits if necessary) and obtain hepatitis investigations: HBV DNA, HBeAg, anti-HBe, HBsAg, anti-HBs, HCV RNA, HDV RNA, HAV IgM, and HEV IgM.**
- **Obtain ALT/AST/total bilirubin/direct bilirubin/albumin/INR twice weekly until ALT and AST plateau/decline, and then weekly until ALT and AST return to <3 x ULN. Continue to monitor per the SOE.**
- **Continue study product at the discretion of the IoR.**

ALT or AST ≥5 x ULN but <10 x ULN

- **Repeat ALT and AST within 72** hours (via non-scheduled visits if necessary) and obtain hepatitis investigations: HBV DNA, HBeAg, anti-HBe, HBsAg, anti-HBs, HCV RNA, HDV RNA, HAV IgM, and HEV IgM.
- Obtain ALT/AST/total bilirubin/direct bilirubin/albumin/INR twice weekly until ALT and AST plateau/decline, and then weekly until ALT and AST returns to **<3 x ULN**. Continue to monitor per the SOE.
- Continue study product **at the discretion of the IoR if the elevations are not considered drug-related. If needed, consult with the CMC**.

ALT or AST ≥10 x ULN

- ALT ≥10 x ULN is considered a dose-limiting ALT flare.
- Repeat ALT and AST within **72** hours (via non-scheduled visits if necessary) and obtain **hepatitis investigations:** HBV DNA, HBeAg, anti-HBe, HBsAg, anti-HBs, HCV RNA, HDV RNA, HAV IgM, and HEV IgM.
- Obtain ALT/AST/total bilirubin/direct bilirubin/albumin/INR twice weekly until ALT and AST plateau/decline, and then weekly until ALT and AST return to **<3 x ULN**. Continue to monitor per the SOE.
- Hold further doses of study product until ALT returns to **<3 x ULN** or lower levels. Once lab abnormality returns to **<3 x ULN** or lower, study product can be restarted or dose reduced by 50% after discussion with the CMC.

ALT ≥3 x ULN if normal at baseline or ALT ≥3 x baseline or ALT ≥300 IU/mL (whichever occurs first) and direct bilirubin ≥2 x ULN

- Hold further doses of study product.
- Obtain ALT/AST/total bilirubin/direct bilirubin/albumin/INR twice weekly until ALT, AST, and direct bilirubin plateau/decline, and then weekly until ALT and AST return to **<3 x ULN**. Continue to monitor per the SOE.
- Study product can be restarted only if a self-limited non-drug etiology is identified **and in consultation with the CMC**.

8.2.3 Hepatic Decompensation

If hepatic decompensation (i.e., development of jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy) or elevation of INR to ≥1.5 occurs, notify the CMC immediately via e-mail at actg.cmca5394@fstrf.org and refer the participant immediately to a transplant hepatologist. Discontinue the study product.

8.3 Other Diseases

8.3.1 Suspected Ocular Toxicity

New or worsening eye symptoms
A high index of suspicion for ocular toxicity or treatment-related uveitis should be maintained in participants who present with new or worsening eye or visual symptoms.

The CMC must be notified within 24 hours of all suspected cases of uveitis by e-mail at actg.cmca5394@fstrf.org.

For any suspected SLGN ocular toxicity, WITHHOLD further doses of study product until diagnostic evaluation has been completed and etiology of the signs

and symptoms has been determined. Report all ophthalmologist-diagnosed uveitis to DAERS in an expedited timeframe.

For participants who have new or worsening ocular signs or symptoms, ophthalmologic evaluation should be obtained within 24 hours. Signs and symptoms include eye pain, redness, irritation, swelling of the eye and conjunctiva, as well as changes in vision.

All grades, signs, and symptoms related to the eye other than uveitis (as diagnosed by an ophthalmologist) should be managed in accordance with standard clinical care in conjunction with an ophthalmologist.

If grading criteria for a particular ocular diagnosis or sign/symptom is not specifically listed in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected Version 2.1, July 2017, refer to the Estimating Severity Grade section for the "Clinical Adverse Events Not Otherwise Identified in the DAIDS AE Grading Table" grading scale.

Uveitis
Study product should be **permanently** discontinued if the participant is diagnosed with uveitis (sometimes termed iritis or iridocyclitis) during ophthalmologic exam while on treatment. **Contact the CMC within 24 hours via e-mail at actg.cmca5394@fstrf.org. Treat in consultation with an ophthalmologist.**

8.3.2 Arrhythmia, including heart block or QTc prolongation

If a clinically significant ECG measurement (defined as a change from screening QTcF value of >60 ms, an absolute QTcF value of ≥500 ms, second- or third-degree heart block, or pronounced QRS widening) occurs and is confirmed, **permanently** discontinue study product.

8.4 Neutropenia

8.4.1 Grade 1 – ANC of 800 to 1000/mm^3

NO CHANGE in SLGN dose. Participants may continue study procedures and study product unless clinically contraindicated.

8.4.2 Grade 2 or higher – ANC less than or equal to 799/mm^3

- Participant should return to the study center within 7 days for retest and result confirmation.
- If Grade 2 or higher neutropenia is confirmed, study product should be withheld until retest results available. Participant should have weekly repeat laboratory testing until neutrophils improve to Grade <2.

- When neutrophils improve to Grade <2 and with CMC approval, study product may be restarted per the original treatment schedule.
- Participants may continue study procedures unless clinically contraindicated.

8.4.3 Grade 3 – ANC of 400 to 599/mm^3

- DISCONTINUE further doses of study product.
- Contact the CMC within 24 hours via e-mail at actg.cmca5394@fstrf.org.
- Consult a hematologist.
- Participants may continue study procedures unless clinically contraindicated.

8.4.4 Grade 4 – ANC of <400 cells/mm^3

- DISCONTINUE further doses of study product.
- Contact the CMC within 24 hours via e-mail at actg.cmca5394@fstrf.org.
- Consult a hematologist.
- Participants may continue study procedures unless clinically contraindicated.

8.5 SARS-CoV-2

Upon documentation of laboratory-confirmed SARS-CoV-2 infection, as determined by a test (antigen or nucleic acid) from any respiratory tract specimen (e.g., oropharyngeal, NP, nasal swab, or saliva), immediately withhold study product and contact the CMC via e-mail at actg.cmca5394@fstrf.org. After resolution and discussion with the CMC, participant may continue study treatment if approved by the CMC **and at the discretion of the IoR**. This will be decided on a case-by-case basis. Otherwise, discontinue study product permanently.

8.6 Pregnancy

Pregnancy and pregnancy outcome will be recorded on the eCRFs. Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. At sites in the US, telephone: 800-258-4263; Fax: 800-800-1052. For sites outside the US, telephone: 910-679-1598; Fax: 44-1628-789-666 or 910-256-0637.

Nonclinical studies in rabbits showed no adverse effect on fertility but did show a possible risk of teratogenicity/fetotoxicity during embryo-fetal development. Participants who become pregnant must discontinue study product **and** will be encouraged to remain on study. The outcome and the AEs for the participant and infant will be recorded on an outcome eCRF. Report abnormal pregnancy outcomes to DAIDS in an expedited timeframe.

Pregnancy Outcomes and Reporting

If a 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 the participant regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy.

Participants whose partner has become pregnant from start of study to 7 days after the last study product dose must also report the pregnancy to the investigator and discontinue study product immediately.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Premature Treatment Discontinuation

- Drug-related **or other study-specified toxicity** (see sections 8.2 and 8.3).
- Requirement for prohibited concomitant medications (see section 5.4).
- Pregnancy.
- Participants whose sexual partner has become pregnant.
- Request by participant to terminate treatment.
- Clinical reasons believed life-threatening by the physician, even if not addressed in the Toxicity section of the protocol.
- Discontinuation of antiviral therapy for HIV or HBV.
- Study treatment disruptions of up to 2 doses are allowed. More than two missed doses will be handled on a case-by-case basis after discussion with the CMC (actg.cmca5394@fstrf.org).
- **HBV DNA ≥500 IU/mL at two consecutive visits and the participant is adherent to nucleos(t)ide analog reverse transcriptase inhibitor therapy.**

9.2 Premature Study Discontinuation

- Request by the participant to withdraw.
- Request of the primary care provider if they think the study is no longer in the best interest of the participant.
- At the discretion of the IRB/EC, FDA, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5394 is a phase II, double-blinded, placebo-controlled trial. The study aims to assess safety and decline in qHBsAg with the administration of oral TLR8 agonist Selgantolimod in people with CHB and HIV-1 who have been receiving effective antiviral therapy for HIV (ART) and HBV for ≥5 years and have qHBsAg level >1000 (3 $\log_{10}$) IU/mL at screening. Forty-eight study participants will be randomized 3:1 to receive SLGN (36 active and 12 placebo), and randomization will be stratified by HBeAg status. One-half of the study participants will be HBeAg positive (n=24) at screening, and the other half will be HBeAg negative (n=24). Enrollment of women (female sex at birth) is encouraged, with an enrollment goal of at least 14 women. The participants will be followed until Week 48.

The primary outcome of the study is achieving at least 1 log_{10} IU/mL decline in qHBsAg from baseline at the end of treatment (Week 24). The probability of achieving a decline ≥1 log_{10} IU/mL in the study population is deemed to be very low (<1%), and it is expected that none of the 12 placebo participants will achieve such decline. The primary analysis of qHBsAg decline will be conducted as a single-arm evaluation in the active SLGN arm and pooled across screening HBeAg statuses (**n**=36). **If the premature study discontinuation prior to collection of any post-baseline sample for qHBsAg analysis is related to the study treatment, then the outcome will be assigned as failure to achieve at least 1 log10 IU/mL decline in qHBsAg from baseline at the end of treatment (Week 24).** The placebo arm will serve as a reference group for safety assessments and the analyses of exploratory markers. A comparison of the qHBsAg decline between the active and placebo arms will require a large-scale study that is not deemed to be appropriate at this exploratory stage.

A5394 is an exploratory study to evaluate the effect of SLGN in qHBsAg decline, which can lead to HBsAg loss deemed to be a functional cure of HBV. As such, the type I error is relaxed to 2-sided 10% (equivalent to 1-sided 5%) for the primary analysis of qHBsAg decline, and any positive finding will be tested further in future trials. However, the power is set high so that a promising result would not be missed.

The primary analysis on qHBsAg will include all participants who initiate the active treatment. If the Week 24 qHBsAg is not available, then the preceding available measurement will be carried forward. If there are participants who discontinue the study for reasons clearly unrelated to the study treatment (e.g., participant moved away, participant cannot get to the clinic, participant cannot be located) prior to collection of samples for qHBsAg analysis, then the missing post-baseline qHBsAg will be considered missing completely at random. Up to six additional participants may be enrolled to ensure sufficient power for the primary analysis on qHBsAg.

The primary outcomes by Week 24 may be evaluated prior to the completion of the study**, whose** timeline **would** be driven by the last participant's completion of the primary outcome visit. Results from the primary analysis on qHBsAg may be presented publicly, for example at a conference, when the data related to such analysis are complete.

10.2 Outcome Measures

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

10.2.1 Primary Outcome Measures

10.2.1.1 [Objective 1.2.1 on safety] Grade ≥2 AEs reported out to scheduled Week 24 visit.

10.2.1.2 [Objective 1.2.1 on tolerability] Premature discontinuation of treatment due to AEs.

10.2.1.3 [Objective 1.2.2] Quantitative HBsAg (qHBsAg) decline ≥1 log_{10} from baseline at Week 24.

10.2.2 Secondary Outcome Measures

10.2.2.1 [Objective 1.3.1] Quantitative HBsAg (qHBsAg) decline ≥1 log_{10} from baseline at any time during the study.

10.2.2.2 [Objective 1.3.2] Quantitative HBsAg (qHBsAg) decline ≥0.5 log10 from baseline at Week 24.

10.2.2.3 [Objective 1.3.3] Quantitative HBsAg (qHBsAg) decline ≥0.5 log_{10} from baseline at any time during the study.

10.2.2.4 [Objective 1.3.4] HBsAg loss determined by the qualitative HBsAg assay at any time during the study.

10.2.2.5 [Objective 1.3.5] qHBsAg change from baseline at Weeks 4, 12, 24, 36, and 48.

10.2.2.6 [Objective 1.3.6] HBeAg loss at any time during the study among the HBeAg positive participants at baseline.

10.2.2.7 [Objective 1.3.7] Anti-HBe gain at any time during the study among the anti-HBe negative participants at baseline.

10.2.2.8 [Objective 1.3.8] Anti-HBs gain at any time during the study among the anti-HBs negative participants at baseline.

10.2.2.9 [Safety] Detection of HIV RNA >50 copies/mL at Weeks 2, 4, 24, and 48.

10.2.2.10 [Safety] Detection of HBV DNA >50 IU/mL at Weeks 2, 4, 24, and 48.

10.2.3 Other Outcome Measures

The time points for the changes in the exploratory measures below will be determined at a later time. They will be specified in a separate analysis plan prior to the analysis. The measurements related to the objective on the pharmacokinetics are addressed in section 11.0 (Pharmacology Plan).

10.2.3.1 Adherence to the background HBV regimen, measured by the proportion of the prescribed pills taken by the participant using self-reported questionnaire.

10.2.3.2 HBV RNA change from baseline.

10.2.3.3 HBcrAg change from baseline.

10.2.3.4 qHBeAg change from baseline.

10.2.3.5 qHBsAg change from baseline measured with a high sensitivity qHBsAg assay in the subset of samples with low positive HBsAg (threshold to be determined prior to the analysis).

10.2.3.6 Changes from baseline in the presence of large, medium, and small HBsAg isoforms.

10.2.3.7 Changes from baseline in HBV-specific T-cell and B-cell responses.

10.2.3.8 Changes from baseline in circulating immune signals using single cell RNA sequencing.

10.2.3.9 Changes from baseline at Weeks 4, 12, 24, 36, and 48 in circulating cytokines.

10.2.3.10 Changes from baseline in cell-associated unspliced HIV RNA at Weeks 2, 4, 24, and 48.

10.2.3.11 Changes from baseline in cell-associated HIV DNA and/or ratio of cell-associated unspliced HIV RNA to HIV DNA at Weeks 2, 4, 24, and 48.

10.2.3.12 Changes from baseline in replication-competent and/or intact virus, as measured by assays such as IPDA (intact proviral DNA assay) and TILDA (Tat/Rev Induced Limiting Dilution Assay) at Weeks 2, 4, 24, and 48.

10.3 Randomization and Stratification

Participants will be randomized in a 3:1 ratio to SLGN treatment and placebo. Randomization will use permuted blocks. Half of the study participants will be HBeAg positive and the other half will be HBeAg negative, and randomization will be stratified by HBeAg status (positive or negative).

10.4 Sample Size and Accrual

The primary outcome is qHBsAg decline of at least 1 $\log_{10}$ from baseline at Week 24. The primary analysis on this decline will pool across the HBeAg statuses and will be conducted as a single-arm evaluation in the active SLGN arm only. The team anticipates 8% to achieve the primary outcome in the active arm and aims to rule out 0.5% (see section 2.2 Rationale). With 36 participants who initiate treatment in the active SLGN arm, there is 89% power to conclude that the proportion is greater than the null rate of

0.5% when the true proportion is 8% in a one-sided exact binomial test with a targeted significance level of 5%, using the normal approximation approach for power calculation (PASS 15 Version 15.0.4). Table 10.4-1 shows the study power under various true proportions. If the true proportion is lower at 6%, then the study power is still good but lower at 82%. The study will be considered a success regarding this outcome measure, if there are 2 or more out of 36 treated participants who achieve the primary outcome.

Table 10.4-1: Study Power for the Underlying Proportion with ≥1 $\log_{10}$ Decline in qHBsAg

True Proportion Meeting the Outcome	Power
6%	82%
8%	89%
10%	93%
12%	96%

Table 10.4-2 below shows two-sided 90% CIs for various potential observed proportions in a sample of 36 participants. With a sample size of 36 participants, the two-sided 90% exact (Clopper-Pearson) confidence interval for the true proportion will be entirely above 0.5% if two or more out of 36 participants achieve ≥1 $\log_{10}$ decline in qHBsAg. The width of the CI indicates precision around the proportion estimate.

Table 10.4-2: CIs for Various Potential Observed Proportions with ≥1 $\log_{10}$ Decline in qHBsAg

Observed Proportion with ≥1 $\log_{10}$ Decline	Two-sided 90% CI
2.8% (1/36)	(0.1%, 12.5%)
5.6% (2/36)	(1.0%, 16.5%)
8.3% (3/36)	(2.3%, 20.2%)
11.1% (4/36)	(3.9%, 23.7%)

Table 10.4-3 presents the probabilities of observing various numbers of participants with the primary outcome on qHBsAg decline under various true proportions. As an example, if the true underlying proportion of achieving qHBsAg decline ≥1 $\log_{10}$ is 8% (as assumed above), then there is a 79% probability of observing 2 or more participants with such declines in 36 participants. Given that 8% is considered success, 79% represents the probability of correctly concluding study success with 2 or more participants achieving such declines. However, if the true underlying proportion is as low as the study null rate of 0.5%, then there is a very low 1% probability of observing 2 or more participants with such declines among 36 participants. Given that we wish to exclude 0.5%, 1% represents the probability of falsely concluding study success with 2 or more participants achieving declines ≥1 $\log_{10}$.

Table 10.4-3: Probability of Observing ≥1 $\log_{10}$ Decline in qHBsAg in N=36 Participants

Number of Participants with qHBsAg Decline ≥1 $\log_{10}$ out of 36 Participants	True Proportion of qHBsAg Decline ≥1 $\log_{10}$	Probability of Observing the Number of Participants with qHBsAg Decline ≥1 $\log_{10}$
1 or more	0.005	17%
	0.010	30%
	0.020	52%
	0.040	77%
	0.060	89%
	0.080	95%
	0.100	98%
	0.120	99%
2 or more	0.005	1%
	0.010	5%
	0.020	16%
	0.040	42%
	0.060	64%
	0.080	79%
	0.100	89%
	0.120	94%
3 or more	0.005	<1%
	0.010	<1%
	0.020	3%
	0.040	17%
	0.060	37%
	0.080	56%
	0.100	71%
	0.120	82%

For the analysis of continuous exploratory biomarker measurements, Table 10.4-4 provides statistical power for various magnitudes of differences between the active and placebo arms that may be detected in a 2-sided t-test with a type I error of 5%. The difference is given as a multiple of inter-subject standard deviation (SD) of the change from baseline at a given time. With 36 active and 12 placebo participants, there is 84% power to detect a difference of 1 SD of the change from baseline, as an example.

Table 10.4-4: Power to Detect Differences in a Continuous Measure between Active and Placebo Arms

Active Arm Difference from Placebo (in SD)	Power
0.8 SD	65%
1.0 SD	84%
1.2 SD	94%

Accrual of about **four** participants per month is expected **among the US sites**. Completion of enrollment would depend on the timing of the approval at each site. Enrollment is anticipated to be completed in about **6** months after most sites have completed the approval processes. In consideration of participants who discontinue the study without data for the primary outcome for reasons clearly not related to study treatment as determined by the Core Team, additional participant(s) may be enrolled to maintain sufficient power for the primary qHBsAg analysis. Reasons for discontinuation unrelated to study treatment may include: participant moved away, participant cannot get to the clinic, participant cannot be located. Up to 6 additional participants may be enrolled, if the enrollment is still open, for inclusion in the primary analysis on qHBsAg. Enrollment completion **timeline** may be extended if additional enrollments occur.

10.5 Data and Safety Monitoring

10.5.1 Interim Monitoring Guidelines

If any of the following safety criteria are not met at any time while the study treatment is ongoing for any of the study participants, then an AE data review by the Study Monitoring Committee (SMC) will be triggered. If a trigger occurs while the study is enrolling, then enrollment into the study will be temporarily suspended. The team and the site are blinded to treatment assignment, but the SMC can become unblinded to the treatment assignment. The worst AE outcome from each participant would be considered for the safety criteria below, and the participants will be monitored continually.

a) ≤2 participants experience Grade 3 AE that is deemed related to the study product as judged by the Core Team who will take into account the site's attribution.
b) ≤1 participant experience a Grade 4 AE related to the study product as judged by the Core Team who will take into account the site's attribution.
c) None of the participants with death attributed to the study product as judged by the Core Team and/or the site.

To assess the operational characteristics of the proposed safety criteria in 36 participants receiving active treatment, assumptions are needed for the true proportions of participants with events in the above three mutually exclusive event categories (worst event in Grade 3, worst event in Grade 4, death). We want a low probability of passing the safety criteria when the true AE rates are unacceptably high. On the other hand, we want a high probability of passing the safety criteria to proceed when the true AE rates are acceptably low. The Table below presents the probabilities of passing the safety criteria, using multinomial distributions. As an example, if the true proportion with Grade 3 AEs is as high as 15%, and the proportions are 10% for Grade 4 events and 1% for deaths, then there is a very low probability of <1% of passing the safety criteria. Assuming that these are unacceptable proportions, there is a very low probability of incorrectly passing the safety criteria. On the other hand, if the true proportion with Grade 3 AEs is as low as 1%, the true proportion with

Grade 4 adverse events is also low at 1%, and the true proportion of deaths is as low as 0.1%, then there is a high probability of 91% of passing the safety criteria to proceed with the study. Assuming that these are acceptable adverse event proportions, there is a high probability of correctly passing the criteria.

Table 10.5.1-1: Probabilities of Passing Safety Criteria Based on 36 Participants

True Proportion of Grade 3 AE	True Proportion of Grade 4 AE	True Proportion of Death	Probability of Passing Safety Criteria
0.15	0.10	0.010	<1%
	0.05	0.010	2%
0.10	0.05	0.010	8%
		0.005	10%
0.05	0.02	0.005	51%
0.03	0.01	0.005	72%
0.01	0.01	0.005	79%
		0.003	85%
		0.001	91%

Following the above guideline on criteria, the SMC will review all AE data and the AE attribution to the study treatment. The SMC will review the relationships of the event(s) to study treatment as assessed by the blinded Core Team and recommend how the study should proceed with respect to resuming enrollment and continuing study treatment. SMC reviews may also be requested by the study team or the SMC at any time while the study is ongoing.

10.5.2 Analysis Plan

The safety report to the Core Team will include the frequency summary of AEs by class and grade. In addition, the report will include a list of AEs included in the safety criteria by a masked participant ID, with the site assessment of relationship to the study product. The report to the Core Team will be pooled across the treatment arms and without information about the treatment assignment. Any deaths will also be included. The safety report to the SMC will include the summary by treatment arm. If deemed necessary and requested, the treatment assignment of participants with AEs will be provided to the SMC.

10.6 Analyses

For all confidence intervals (CIs) around proportions, the Clopper-Pearson exact method for binomial data will be used.

10.6.1 Primary Analyses

The primary objective on the qHBsAg will be addressed by estimating the proportion of participants who achieve ≥1 $\log_{10}$ decline in the SLGN arm. All

enrolled participants who received any SLGN treatment will be included in the primary analysis. Missing data from participants who discontinue the study too early to contribute to this primary analysis will be considered missing completely at random, if discontinuation was not related to the study treatment as determined by the team. If the discontinuation was deemed to be related to the study treatment, then the outcome will be assigned as a failure to achieve ≥1 $\log_{10}$ decline. A two-sided 90% CI will be calculated around the estimated proportion. If this CI is entirely above 0.5%, then it will be concluded that there is evidence that the underlying proportion is greater than 0.5%, the assumed rate without treatment with SLGN. The qHBsAg declines in the placebo arm will also be reported to ascertain the assumption that there will be none who achieve ≥1 $\log_{10}$ decline.

For the primary safety analysis, the AEs occurring after initiation of study treatment through the treatment completion at scheduled Week 24 visit will be summarized by arm. All participants who initiated study treatment will be included for the primary safety analysis. The proportion of study participants with AEs will be estimated with a two-sided 95% CI around the estimate. As a secondary analysis, all reported AEs (which include events that occur after the time frame defined for the primary safety analysis) will be summarized. A two-sided 95% CI will be provided for the proportion of study participants with AEs.

For the assessment on tolerability, a proportion of participants on SLGN who discontinue prematurely due to AEs will be provided with a two-sided 95% CI. The number is expected to be very small, if any, and a descriptive listing of premature discontinuations of treatment due to AEs will be provided. AEs leading to discontinuations will be described.

10.6.2 Secondary Analyses

Because the study sample size is small and the numbers of participants achieving the secondary outcomes are anticipated to be small, simple summary statistics are proposed for the secondary analyses in the study. They are exploratory analyses to be confirmed in future, larger trials.

For the analysis on qHBsAg decline ≥1 $\log_{10}$ at any time during the study, participants who received any SLGN treatment with any follow-up with a post-baseline qHBsAg result will **be** included. The estimated proportion will be provided with a two-sided 90% CI. The analysis will be conducted in a similar manner for the HBsAg loss. The assumption that there will be none who achieve the loss in the placebo arm will be checked and reported.

For the analysis on the qHBsAg change from baseline as a continuous variable, the changes over time on the available data will be summarized by arm with median and other descriptive statistics, including lower and upper quartiles, mean, standard deviation, minimum, and maximum.

For the analysis on the loss of HBeAg, the participants who had positive HBeAg at baseline with any post-baseline HBeAg result will be included in the proportion analysis. For the analysis on the development of anti-HBe, the participants who had negative anti-HBe at study baseline will be included in the proportion analysis. For the analysis on the development of anti-HBs, the participants who had negative anti-HBs at study baseline will be included in the proportion analysis. These analyses will be conducted by arm, because it is possible for these events to occur in the placebo arm. These proportions will be provided with two-sided 90% CIs.

For the secondary analyses on the continuous biomarker measurements, the changes from baseline at the scheduled times will be summarized by study arm. Comparisons between study arms will be made at each time using nonparametric statistical tests (e.g., Wilcoxon rank-sum tests).

10.7 Unblinding

Planned Unblinding
Participants will be unblinded at completion of the study. The study will follow ACTG SOP-123 Unblinding Participants.

Unplanned Unblinding
The decision to unblind the study arms of an ongoing study is made by the team in conjunction with the relevant Scientific Committee and the Executive Committee. This can occur based on a recommendation from the SMC or the results of another trial. (See DAIDS SOP “Termination of a Trial or a Single Treatment Arm.”)

Unblinding is conducted through the DMC, which sends treatment assignments to the sites soon after the unblinding decision. Every effort should be made by the sites to contact participants who have completed follow-up.

11.0 PHARMACOLOGY PLAN

SLGN PK in People With and Without CHB: The pharmacokinetics of SLGN have been characterized in healthy volunteers, and in HBV virally suppressed (HBV DNA ≤20 IU/mL) and viremic (HBV DNA ≥2000 IU/mL) individuals. Among individuals with CHB infection, exposures of SLGN appear to be 50-100% higher compared to healthy volunteers. The pharmacokinetics of SLGN have not been assessed in PWH and CHB infection.

In a single ascending dose study (0.5 to 5 mg) in volunteers without HIV or CHB, the median SLGN $t_{1/2}$ was similar between 1.5 mg, 3 mg, and 5 mg dose groups (4.28, 4.91, and 5.05 hours, respectively). Among the 3 mg dose group, the observed mean (% coefficient of variation) C_{max} was 165.3 (56%) pg/mL; the AUC_{last} and AUC_{inf} were 494.9 (11%) and 507.5 (10%) pg*h/mL, respectively. Table 11.0-1 summarizes the pharmacokinetics of SLGN among HBV virally suppressed and viremic cohorts receiving SLGN 3 mg weekly for **2** or **4** weeks (PK sampling at Day 8). According to the

Investigator's Brochure for SLGN, although the mean AUC_{inf} was lower numerically for the virally suppressed cohort receiving two weekly doses compared to the virally suppressed cohort receiving four weekly doses, the PK differences between cohorts was not considered significant. Table 11.0-2 summarizes the pharmacokinetics of SLGN among HBV virally suppressed individuals receiving SLGN 3 mg weekly for 24 weeks at Day 1 and Week 24.

Table 11.0-1: SLGN Plasma Pharmacokinetic Parameters Among People with HBV who were Virally Suppressed or Viremic and Who Received 3 mg Weekly Dosage for 2 or 4 Weeks [a]

SLGN PK Parameter at Day 8	Mean (%CV)		
	Suppressed, 2 weekly doses (n=7)	Viremic, 2 weekly doses (n=8)	Suppressed, 4 weekly doses (n=8)
C_{max} (pg/mL)	234.8 (68.3)	433.4 (79.1)	621.0 (71.0)
T_{max} (h)[b]	0.50 (0.50, 0.50)	0.50 (0.50, 1.50)	0.50 (0.50, 0.50)
AUC_{last} (pg*h/mL)	434.0 (44.0)	899.9 (61.2)	967.4 (61.1)
AUC_{inf} (pg*h/mL)	444.5 (43.5)	918.8 (60.9)	986.4 (60.8)
CL/F (L/h)	8410.0 (60.2)	4887.6 (81.4)	4004.3 (48.3)
$t_{1/2}$ (h)[b]	5.32 (4.60, 6.05)	4.98 (4.60, 5.95)	5.76 (4.69, 6.00)

[a] Gilead Study GS-US-389-2022
[b] Median (Quartile 1, Quartile 3)

Table 11.0-2: SLGN Plasma Pharmacokinetic Parameters at Day 1 and Week 23 Among People with HBV who were Virally Suppressed and Who Received 3 mg Weekly Dosage for 24 Weeks[a]

SLGN PK Parameter	Day 1 (n=7)	Week 23 (n=6)
C_{max} (pg/mL)	150.7 (63.1)	171.4 (85.7)
T_{max} (h)[b]	0.55 (0.50, 1.00)	0.52 (0.50, 1.00)
AUC_{last} (pg*h/mL)	364.7 (33.1)	399.0 (50.9)
AUC_{inf} (pg*h/mL)	378.5 (32.3)	412.1 (51.2)
CL/F (L/h)	8947.9 (42.9)	9815.6 (68.3)
$t_{1/2}$ (h)[b]	4.79 (3.27, 5.26)	4.62 (4.38, 6.18)

[a] Gilead Study GS-US-389-2024
[b] Median (Quartile 1, Quartile 3)

Factors Affecting SLGN Pharmacokinetics: Administration of SLGN with food (moderate-fat breakfast) leads to minimal increases in SLGN AUC_{last} (23% ↑), AUC_{inf} (18% ↑), and C_{max} (8% ↑) compared with administration of SLGN in the fasted state.

In vitro, SLGN is a substrate for CYP1A2, CYP2C9, CYP2C19, CYP3A4, and UGT2B7. SLGN was not an inhibitor or inducer of CYP enzymes or an inhibitor of UGT in vitro. SLGN was not a P-gp or BCRP substrate in vitro, but may inhibit intestinal P-gp or BCRP. Smoking leads to minimal decreases in SLGN AUC_{inf} (23% ↓) and C_{max} (26% ↓). Drug-drug interaction studies indicate that CYP3A plays a major role in the elimination of SLGN. When administered with voriconazole (CYP3A inhibitor), SLGN AUC_{inf} and C_{max}

increase 3.4-fold and 8-fold, respectively. When administered with rifampin (CYP3A inducer), SLGN AUC_{inf} and C_{max} decrease by 53% and 50%, respectively. UGT also plays a minor role in the elimination of SLGN: when administered with probenecid (UGT inhibitor), SLGN AUC_{inf} and C_{max} increase by 44% and 13%, respectively. With ciprofloxacin, a less potent CYP3A inhibitor, SLGN $AUC_{0\text{-}inf}$ and C_{max} are increased by 40% and 77%, respectively. Collectively, these data suggest SLGN should not be administered with potent CYP3A inhibitors or inducers, but UGT inhibitors (e.g., probenecid) and less potent CYP3A inhibitors (e.g., ciprofloxacin) can be administered with SLGN without dose modification.

SLGN Pharmacodynamics: Following treatment with SLGN, IL-12p40 and IL-1RA serum concentrations increase, with peak concentrations occurring approximately 4 hours post-dose and return to approximate baseline levels 24 hours post-dose. There have been no observations to suggest a diminution in the magnitude of changes in these biomarker responses following multiple weekly doses. However, increases in IL-12p40 and IL-1RA concentrations are reduced by >50% following fed-state treatment compared with fasted-state treatment. Smoking does not have a relevant impact on IL-12p40 and IL-1RA serum concentrations.

11.1 Pharmacology Objectives

11.1.1 To define the pharmacokinetic profile and pharmacokinetic-dynamic associations of SLGN in people with both HIV and CHB taking suppressive antiviral therapy for both viruses (see exploratory Objective 1.4.1).

11.1.2 To explore if SLGN and ARV pharmacokinetics are altered when administered together.

11.1.3 To evaluate participants' adherence by using several tools, including self-report, DOT, and drug concentrations (see exploratory Objective 1.4.3).

11.2 Pharmacology Study Design

Intensive PK Sampling at Entry: For 12 participants enrolled, intensive PK sampling over 24 hours will be conducted at study entry (see section 6.3) for initial estimation of SLGN pharmacokinetic parameters via non-compartmental analysis in PWH and CHB. Among the 12 participants with intensive PK data collected, it is expected that there will be approximately 9 participants randomized to active treatment and 3 participants randomized to placebo. Study participants will fast (nothing but water) for 8 hours prior to the start of the intensive PK visit. On the day of the intensive PK sampling visit, study participants are to withhold administration of their ARVs at home and instead, bring their ARVs for an observed in-clinic dose administration. **Study product** will be administered with water in the fasted state. ARVs that can be taken in the fasted state will be administered 2 hours post-**study product** dose. Intensive PK blood samples will be collected pre-dose, and at the following time points after an in-clinic dose: 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, 12, and 24 hours. The exact sample times will be reported on the eCRF. The time of prior ARV dose will be reported. Participants will continue to fast for 4

hours following witnessed drug administration. Following the 4 hour blood draw, participants can eat and drink as usual. ARVs with a food requirement will be taken with food 4 hours after **study product** dosing.

Sparse PK Sampling at Entry: Participants that do not undergo intensive PK sampling at entry will have sparse samples obtained at 0.5, 4, and 24 hours post-SLGN administration.

Sparse PK Sampling at Weeks 2, 8, 16**,** 20**, and 24**: A single sparse sample will be obtained between 6-24 hours post SLGN dose.

Sparse PK Sampling at Weeks 4 **and** 12: SLGN dosing is performed in person at these visits. Two sparse PK samples will be obtained. The first sparse PK sample will be obtained within **0.25 to** 3.5 hours of SLGN dosing and the second sparse PK sample will be obtained at 4 hours post-dose.

11.3 **P**rimary and Secondary Data, Modeling, and Data Analysis

See the A5394 Lab Processing Chart for instructions on PK sample collection, processing, and shipment.

Non-Compartmental SLGN PK Analysis: From intensive PK samples, the following PK parameters will be observed or calculated via non-compartmental analysis:

- C_{max} is defined as the maximum concentration observed during the dosing interval.
- T_{max} is defined as the time at which C_{max} occurs.
- AUC_{24}, the area under the concentration-time curve over 24 hours, will be calculated either using the linear or log-linear trapezoidal rule. If drug is not detectable or is below the assay limit of quantitation, $AUC_{0\text{-}t}$ will be calculated using the last measurable concentration.
- $AUC_{0\text{-}inf}$, the area under the concentration-time curve from time 0 extrapolated to infinite time, will be calculated either using the linear or log-linear trapezoidal rule.
- Apparent clearance (CL/F) will be calculated as dose divided by $AUC_{0\text{-}inf}$.
- Apparent terminal elimination half-life ($t_{1/2}$) can be estimated using $\frac{\ln(2)}{K_e}$, where K_e is the first-order rate constant and is obtained from the lambda z parameter calculated by standard pharmacokinetic software packages.

SLGN Population PK Modeling: The SLGN PK parameter estimates derived from non-compartmental analysis will be used as prior initial estimates when constructing a population pharmacokinetic model of SLGN via nonlinear mixed effects modeling. Both sparse and intensive PK sampling data will be leveraged for model development. Covariates such as sex, race/ethnicity, smoking status, HBeAg status, qHBsAg, concomitant ARVs, and other factors to be defined in the PK analysis plan, will be considered as potential covariates in population pharmacokinetic models of SLGN.

SLGN PK/PD Analysis: To examine the association of SLGN exposure with biomarkers related to HBV treatment outcomes and other PD biomarkers to be defined in the PK

analysis plan, participant-specific estimates (from the population PK models) of SLGN clearance (or another PK parameter) will be used as independent variables in models of PD biomarker response as the dependent variable. Drug exposure parameter estimates may also be used as independent variables in models for the occurrence of selected toxicities. Further details will be provided in the PK SAP.

To address pharmacology Objective 11.1.2, if there are a sufficient number of participants on a particular ARV or there is a need to provide clinical context to study findings, we may explore the potential for drug interactions between SLGN and ARVs. To evaluate the effect of ARVs on SLGN PK, the ARV will be tested as a covariate in our population PK model if there are enough participants receiving different ARV regimens. If the ARV reduces the objective function by 3.84 this is analogous to a $p<0.05$ in a Chi square test. We will also descriptively compare SLGN pharmacokinetics in participants with both HIV and CHB to those with HBV mono-infection reported from prior studies. To evaluate the effect of SLGN on ARVs, we have two data sources, 1) Intensive ARV PK in the placebo group, and 2) The pre-dose sample at the intensive PK visit (before **study product** is administered).

To address pharmacology Objective 11.1.3, adherence (measured by self-report, DOT, and/or drug concentrations) may be used as predictor variable(s) in evaluations of associations with treatment response.

11.4 Anticipated Outcomes

We anticipate that participants with HIV and CHB who are taking effective antiviral therapy for HIV (ART) and HBV, as well as SLGN, will have similar PK of SLGN and PK-PD associations, compared to historical data in individuals with CHB but without HIV.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form (eCRF) screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization.

12.2 Role of Data Management

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

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

12.3 Clinical Site Monitoring and Record Availability

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity [FDA 2021]. The site **must** make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. **The Data Management Center will configure Medidata Remote Source Review (RSR) and make it available to all sites. We encourage Sites to use the DMC-provided Medidata RSR platform, but other p**otential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal**, and** direct access to Electronic Medical Record (EMR). Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

12.4 **Reporting Protocol Deviations**

The site principal investigator and staff are responsible for identifying and reporting deviations. If protocol deviations are identified, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be reported to the IRB/EC per their guidelines.

Refer to the MOPS for the definition of protocol deviation and instructions for completing the study protocol deviation eCRF.

13.0 PARTICIPANTS

13.1 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 EC responsible for oversight of the study. A signed consent form will be obtained from the participant. 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, and this fact will be documented in the participant's record.

13.2 Participant Confidentiality

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

13.3 Study Discontinuation

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

14.0 PUBLICATION OF RESEARCH FINDINGS

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

15.0 BIOHAZARD CONTAINMENT

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

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

16.0 REFERENCES

Anderson RT, Choi HSJ, Lenz O, Peters M, Jenseen HLA, Miller V, Hansen BE. Association between HBsAg loss and long-term clinical outcome in chronic hepatitis B: a systematic review and meta-analysis. [Abstract]. EASL 2019; Vienna, Austria, April 10-14, 2019.

Audsley J, Avihingsanon A, Littlejohn M, et al. Long-term TDF-inclusive ART and progressive rates of HBsAg loss in HIV-HBV co-infection - lessons for functional HBV cure? J Acquir Immune Defic Syndr 2020;84:527-33.

Audsley J, Sasadeusz J. Challenges and opportunities for hepatitis B cure in the setting of HIV--hepatitis B virus co-infection. Curr Op HIV AIDS 2020;15:193-9.

Boni C, Vecchi A, Rossi M, et al. TLR7 agonist increases responses of hepatitis B virus-specific T cells and natural killer cells in patients with chronic hepatitis B treated with nucleos(t)ide analogues. Gastroenterology 2018;154:1764-77.e7. doi: 10.1053/j.gastro.2018.01.030.

Borducchi EN, Cabral C, Stephenson KE, et al. Ad26/MVA therapeutic vaccination with TLR7 stimulation in SIV-infected rhesus monkeys. Nature 2016;540:284-7.

Borducchi EN, Liu J, Nkolola JP, et al. Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys. Nature 2018;563:360-4.

Boyd A, Gozlan J, Miailhes P, et al. Rates and determinants of hepatitis B 'e' antigen and hepatitis B surface antigen seroclearance during long-term follow-up of patients coinfected with HIV and hepatitis B virus. AIDS 2015;29:1963-73.

Bruner KM, Wang Z, Simonetti FR, et al. A quantitative approach for measuring the reservoir of latent HIV-1 proviruses. Nature 2019;566:120-5.

Chen DY, C. M, Tan SK, et al. Characterization of cytokine response to toll-like receptor 8 agonist selgantolimod in viremic and virally suppressed chronic hepatitis B patients [Poster 0721]. American Association for the Study of Liver Diseases (AASLD): The Liver Meeting Digital Experience; 13-16 November, 2020.

Chen M, Wong WW, Law MG, et al. Hepatitis B and C co-infection in HIV patients from the TREAT Asia HIV Observational Database: analysis of risk factors and survival. PLoS One 2016;11:e0150512.

Daffis S, Balsitis S, Chamberlain J, et al. Toll-like receptor 8 agonist GS-9688 induces sustained efficacy in the woodchuck model of chronic hepatitis B. Hepatology **2021;73:53-67**. PMID: 32246499.

Daffis S, Morar M, Pattabiraman D, Voitenleitner C, Fletcher S, Javanbakht H. Cytokine-dependent activation of MAIT cells by the TLR8 agonist GS-9688 but not the TLR7 agonist GS-9620. J Hepatol 2018;68(Suppl 1):S800.

Daffis S, Ramakrishnan D, Niu C, et al. In vitro and in vivo characterization of the selective toll-like receptor 8 agonist GS-9688. J Hepatol 2017;66(Suppl 1):S694.

FDA. FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards. March 2020; Updated on January 27, 2021. Accessed at: https://www.fda.gov/media/136238/download.

Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

Grant E, Joshi A, Ayithan N, et al. Pharmacodynamic response to oral administration of the selective toll-like receptor 8 agonist GS-9688 in healthy volunteers. Hepatology 2018;68:270A.

Janssen HLA, Brunetto MR, Kim YJ, et al. Safety, efficacy and pharmacodynamics of vesatolimod (GS-9620) in virally suppressed patients with chronic hepatitis B. J Hepatol 2018;68:431-40.

Klein MB, Althoff KN, Jing Y, et al. Risk of end-stage liver disease in HIV-viral hepatitis coinfected persons in North America from the early to modern antiretroviral therapy eras. Clin Infect Dis 2016;63:1160-7.

Lim SY, Osuna CE, Hraber PT, et al. TLR7 agonists induce transient viremia and reduce the viral reservoir in SIV-infected rhesus macaques on antiretroviral therapy. Sci Transl Med 2018;10(439):eaao4521.

Lo Re V, 3rd, Newcomb CW, Carbonari DM, et al. Determinants of liver complications among HIV/hepatitis B virus-coinfected patients. J Acquir Immune Defic Syndr 2019;82:71-80.

Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: from discovery to regulatory approval. Hepatology 2017;66:1296-313.

Ma Z, Cao Q, Xiong Y, Zhang E, Lu M. Interaction between hepatitis B virus and toll-like receptors: current status and potential therapeutic use for chronic hepatitis B. Vaccines (Basel) 2018;6:6.

Matthews GV, Ali RJ, Avihingsanon A, et al. Quantitative HBsAg and HBeAg predict hepatitis B seroconversion after initiation of HAART in HIV-HBV coinfected individuals. PLoS One 2013;8:e61297.

Meås HZ, Haug M, Beckwith MS, et al. Sensing of HIV-1 by TLR8 activates human T cells and reverses latency. Nat Commun 2020;11:147.

Niu C, Daffis S, Mackman RL, Delaney WE, Fletcher SP. Cytokines Induced by GS-9688, a Toll-Like Receptor 8 Agonist, Inhibit HBV RNA, DNA and Antigen Levels in Primary Human Hepatocytes. [Abstract 915]. Hepatology 2017;66:489A.

Plaza Z, Aguilera A, Mena A, et al. Influence of HIV infection on response to tenofovir in patients with chronic hepatitis B. AIDS 2013;27:2219-24.

Procopio FA, Fromentin R, Kulpa DA, et al. A novel assay to measure the magnitude of the inducible viral reservoir in HIV-infected individuals. EBioMedicine 2015;2:874-83.

Psevdos Jr G, Kim JH, Suh JS, Sharp VL. Predictors of loss of hepatitis B surface antigen in HIV-infected patients. World J Gastroenterol 2010;16:1093-6.

Rasmussen TA, Lewin SR. Shocking HIV out of hiding: where are we with clinical trials of latency reversing agents? Curr Opin HIV AIDS 2016;11:394-401.

Rasmussen TA, McMahon JH, Chang JJ, et al. The effect of antiretroviral intensification with dolutegravir on residual virus replication in HIV-infected individuals: a randomised, placebo-controlled, double-blind trial. Lancet HIV 2018;5:e221-e30.

Revill PA, Chisari FV, Block JM, et al. A global scientific strategy to cure hepatitis B. Lancet Gastroenterol Hepatol 2019;4:545-58.

Reyes M, Lutz JD, Lau AH, et al. Safety, pharmacokinetics and pharmacodynamics of selgantolimod, an oral toll-like receptor 8 agonist: a **p**hase Ia study in healthy subjects. Antivir Ther 2020;25:171-80.

Riddler SA, Para M, Benson CA, et al. Vesatolimod (GS-9620) is safe and pharmacodynamically active in hiv-infected individuals. 10th IAS Conference on HIV Science (IAS 2019), July 21-24, 2019; Mexico City, Mexico.

Rochat MA, Schlaepfer E, Speck RF. Promising role of toll-like receptor 8 agonist in concert with prostratin for activation of silent HIV. J Virol 2017;91:e02084-16.

Schlaepfer E, Speck RF. TLR8 activates HIV from latently infected cells of myeloid-monocytic origin directly via the MAPK pathway and from latently infected CD4+ T cells indirectly via TNF-alpha. J Immunol 2011;186:4314-24.

SenGupta D, Ramgopal M, Brinson C, et al. Safety and analytic treatment interruption outcomes of vesatolimod in HIV controllers. [Abstract 40]. CROI 2020, March 8-11, 2020; Boston, Massachusetts.

Singh KP, Crane M, Audsley J, Avihingsanon A, Sasadeusz J, Lewin SR. HIV-hepatitis B virus coinfection: epidemiology, pathogenesis, and treatment. AIDS 2017;31:2035-52.

Stanaway JD, Flaxman AD, Naghavi M, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet 2016;388:2081-8.

Sterling RK, Wahed AS, King WC, et al. Spectrum of liver disease in hepatitis B virus (HBV) patients co-infected with human immunodeficiency virus (HIV): results of the HBV-HIV Cohort Study. Am J Gastroenterol 2019;114:746-57.

Strassl R, Reiberger T, Honsig C, et al. Viral determinants predicting hepatitis B surface antigen (HBsAg) seroclearance in HIV-/HBV-coinfected patients. J Viral Hepat 2014;21:508-16.

Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-99.

Tsai A, Irrinki A, Kaur J, et al. Toll-like receptor 7 agonist GS-9620 induces HIV expression and HIV-specific immunity in cells from HIV-infected individuals on suppressive antiretroviral therapy. J Virol 2017;91:e02166-16.

Vibholm L, Schleimann MH, Hojen JF, et al. Short-course toll-like receptor 9 agonist treatment impacts innate immunity and plasma viremia in individuals with human immunodeficiency virus infection. Clin Infect Dis 2017;64:1686-95.

Yeo YH, Ho HJ, Yang HI, et al. Factors associated with rates of HBsAg seroclearance in adults with chronic HBV infection: a systematic review and meta-analysis. Gastroenterology 2019;156:635-46.

Zerbato JM, Purves HV, Lewin SR, Rasmussen TA. Between a shock and a hard place: challenges and developments in HIV latency reversal. Curr Opin Virol 2019;38:1-9.

Zoutendijk R, Zaaijer HL, de Vries-Sluijs TE, et al. Hepatitis B surface antigen declines and clearance during long-term tenofovir therapy in patients coinfected with HBV and HIV. J Infect Dis 2012;206:974-80.

INFORMED CONSENT FORM AND AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

Sponsor / Study Title:	**National Institute of Allergy and Infectious Diseases / "Safety, Tolerability, and Impact of Oral TLR8 Agonist Selgantolimod on HBsAg in Participants with Both Chronic Hepatitis B and HIV"**
Protocol Number:	**A5394**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

SHORT TITLE FOR THE STUDY: Selgantolimod in CHB and HIV

SUMMARY

PURPOSE

The purpose of this study is to see if the experimental drug Selgantolimod (SLGN) is safe and tolerable for people who have chronic hepatitis B (CHB) and HIV, and whether it reduces the amount of hepatitis B virus in people with CHB and HIV. SLGN has been studied in people with and without CHB. This drug has not been approved for treatment of CHB.

STUDY TREATMENT

SLGN and placebo for SLGN (which will both be referred to as "study product") will be provided by the study. A placebo is an inactive substance like a sugar pill. You have a 75% chance of getting assigned to receive SLGN and a 25% chance of receiving placebo for SLGN. SLGN and placebo for SLGN are both pills to be taken by mouth.

You will take study product once a week for the first 6 months of the study. You will take study product under direct observation. This means that you will either take it in the clinic, in front of clinic staff, or live on camera, using a smartphone or computer with an internet connection. After you stop taking the study product, you will remain on study for another 6 months for follow-up evaluations.

To enter and remain in this study, you must be taking one of the following:

- Tenofovir disoproxil fumarate (TDF)
- Tenofovir alafenamide (TAF), tenofovir disoproxil fumarate + emtricitabine (TDF/FTC)

- Tenofovir disoproxil fumarate + lamivudine (TDF/3TC)
- Tenofovir alafenamide + emtricitabine (TAF/FTC)
- Entecavir (ETV)

These medications will not be provided by the study.

NUMBER OF PARTICIPANTS

There will be 48 people across 2 groups.

LENGTH OF STUDY

The study will last about 12 months. There will be about 11 study visits.

REQUIRED ACTIVITIES

Blood and urine collections

- At all visits, some blood will be collected from one of your veins.
- At all visits, you will be asked to provide a urine sample.

Special procedures

- You will have 3 electrocardiograms (ECGs), which are pictures of the electrical action of your heart.
- You will have at least 2 eye exams.

Directly observed therapy

You will take the study product under direct observation (in front of study staff in the clinic) or live on camera using a smartphone or computer with an internet connection. Directly observed therapy (DOT) is used to make sure that you take the study product as instructed.

RISKS

The following are possible risks of the study product:

- Nausea or vomiting
- Painful, red, watery eyes or blurry vision
- Headache
- Tiredness
- Dizziness
- Infection of the nose, sinus, or throat

BENEFITS

If you take part in this study, there will not be a direct health benefit to you. Information learned from this study may help others who have hepatitis B and HIV.

OTHER CHOICES

Instead of being in this study, you have the option of continuing with your current treatment or starting a new treatment under the care of your regular doctor or other health care provider.

INTRODUCTION

You are being asked to take part in this research study because you have CHB and HIV, are taking HIV antiretroviral therapy, and do not have advanced liver disease or damage. This study is sponsored by the National Institutes of Health (NIH). The study doctor in charge of this study at this site is listed on the first page of this informed consent form. 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 and date this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Chronic hepatitis B (CHB) is caused by the hepatitis B virus (HBV). CHB can cause cirrhosis (a disease that scars the liver) and liver cancer. Although there are currently therapies that are effective in reducing the amount of HBV for long periods of time, people with CHB still need life-long therapy.

The purpose of this study is to see how safe and tolerable SLGN is, and how well it reduces the amount of hepatitis B virus in people with CHB and HIV. Results from this study could help evaluate whether SLGN can lower the amount of hepatitis B virus in blood and prevent illness in people with CHB and HIV, without the need for life-long therapy. SLGN has not been tested in people with HIV.

This is a research study that is designed to answer scientific questions about SLGN, a new, experimental drug that has not been approved by the United States Food and Drug Administration (FDA). Only people that want to participate in this study will be a part of the study. No matter what your decision is, any other care that you get at this clinic will not change.

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

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

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

If you agree to be in this study, you will be asked to sign and date this informed consent form. Before signing and dating it, ask your study nurse or doctor to explain anything that you do not

fully understand. After you have signed and dated the form, you will be asked some questions and will undergo some tests to make sure you meet the requirements for joining the study.

Screening

- You will be asked about your health and any medications you are taking or have taken in the past. You will be asked about **the history of** your HBV **and** treatment **for HBV**.
- You will have a complete physical examination.
- You will have an eye examination.
- You will have an ECG to check the electrical activity of your heart.
- You will have blood collected for tests on HBV.
- **You will have blood collected for metabolic tests (to test how your body uses the food that you eat).**
- If you are able to become pregnant, you will have a pregnancy test. If you are pregnant, you cannot enter the study.
- You will have blood collected for routine blood tests and for coagulation (how quickly your blood clots), liver damage, immunologic studies (to see how your body fights infections), and virologic studies (to compare to blood collected later in the study to see how the study product affects HBV).
- You will have imaging (such as ultrasound) of your abdomen performed if you have not had an ultrasound within 24 weeks before entering the study. You will also have an ultrasound performed near the **W**eek 24 visit.
- You may have blood collected to determine if you have tuberculosis, a disease that affects the lungs, or a purified protein derivative (PPD) test. In order to get a PPD test, you will receive a tiny shot where the tuberculosis germ is placed under your skin on your arm. A small, pale bump will form, which normally goes away in a few hours. You will return to the clinic in 48-72 hours to see if you have had a reaction by measuring any swelling that has occurred.

Optional intensive pharmacokinetic testing for 12 participants

The study includes optional intensive pharmacokinetic (PK) testing for 12 participants. Whether you choose to participate or not in this part of the study will not affect your participation in the rest of the study. Pharmacokinetics is the testing of the way the body absorbs, distributes, and gets rid of drugs. If participants are still needed for the PK testing, you will be asked if you would like to participate in the part of the study that includes intensive PK testing. If you agree, you will come to the clinic and stay for up to 12 hours after taking the first dose of study product and have blood collected at the following timepoints: pre-dose, 15 minutes, 30 minutes, 1 hour, 1 hour and 30 minutes, 2 hours, 3 hours, 4 hours, 5 hours, 8 hours, 12 hours, and 24 hours post-dose. You will come back to the clinic in 12 hours for the second time (24 hours after the first dose of study product), and you will have blood collected one additional time. A catheter may be used to perform the blood draws. A catheter is a plastic tube to make multiple blood draws easier because it remains inserted in the vein.

If you are one of the 12 participants who agrees to participate in the intensive PK testing, you may be able to stay overnight to complete the required collections. The study nurse or study doctor will also describe what will happen if you stay overnight.

Entry

If you have met all of the screening requirements and decide to join the study, you will be randomized to receive either SLGN or placebo. This will be determined by chance, as if by rolling dice. You will have a 75% chance of receiving SLGN, and a 25% chance of receiving placebo for SLGN.

You will take two pills once a week. Neither you nor the study staff will be able to choose whether you are receiving SLGN or placebo, and neither you nor your doctor will be told which you are receiving.

The study product should be taken on the same day at the same time each week. You will take the study product at the entry visit. You will fast (not eat or drink anything) for at least 8 hours before you take the study product. You will also fast for 4 hours after you take the study product. However, you will be allowed to have water **up to** 1 hour before and 2 hours after you take the study product.

You should not eat or drink grapefruit juice, grapefruits, Seville oranges, or Seville orange juice 72 hours before the first time you take the study product and until 7 days after you take the last dose of study product.

- You will be asked about your health and any medications you are taking or have taken in the past. You will be asked about your HBV treatment history.
- You will be asked about your tobacco use.
- You will have blood collected for tests on HBV.
- **If you are able to become pregnant, you will have a pregnancy test. If you are pregnant, you cannot continue to receive the study treatment.**
- You will have blood collected. Some of your blood will be stored for future studies. One of these blood samples will be used for genetic testing (testing of your genes) to help explain how the study product works. Genes are present in each cell of your body and carry the information that determines your traits, such as eye color or the likelihood of having certain health problems. The research will not include whole genome sequencing (WGS).
- **You will have urine collected for routine tests.**
- You will take the study product once a week.
- You will be asked questions to see how you take your HIV medications.
- You will have a drop of blood collected on a paper card and stored for pharmacokinetic testing (see explanation below).
- If you are not **participating in the intensive PK testing**, you will have blood collected at 30 minutes, 4 hours, and 24 hours after you take the first dose of study product.

After the entry visit, you will be seen in the clinic about 10 times. At some of the visits in the first 6 months, you will take the study product in the clinic and will have blood collected over the few hours after you take it. You will be allowed to do some of the evaluations remotely using technology. For example, some of the evaluations may be performed by telephone, or via telehealth.

You will take the study product once a week for the first 6 months of the study. After 6 months, you will not take the study product any longer, but you will remain on study for another 6 months and will continue the other study evaluations.

During Study
The study staff can answer any questions you have about each study visit, the evaluations that will occur, and how long each visit will be. Some of the evaluations that were done at the screening and entry visits will be done again. These are shown in the Table below.

After the entry visit, you will take the study product at the clinic for the **W**eek 4 **and W**eek 12 visits. For all other visits, you will take the study product 6-24 hours before the clinic visit.

The site staff can tell you how much blood will be collected at any particular visit. Depending on the visit, about 45-75 mL (3-5 tablespoons) of blood will be collected. At some visits, about 15-**2**50 mL (1-1**7** tablespoons) will be collected.

Remote Data Collection
You will be asked to come to the clinic at study entry, and at **W**eeks 4 **and** 12, if possible, for in person DOT. For the other study visits, a remote visit can be conducted using technology-assisted DOT.

Sometimes, you may prefer to, or the study staff may need to, conduct a scheduled visit with you remotely (for example, by telephone, or via telehealth). The site staff will attempt to contact you and obtain as much of the required information from you as possible. During this remote visit, you will be asked to schedule an in-person visit as soon as possible to complete the rest of the evaluations that cannot be done remotely.

If you are participating in a remote visit, your study nurse or doctor can help you choose an app for your remote visit.

If your final visit is scheduled to take place at a time when it is not possible to conduct an in-person visit, the site will re-schedule that visit. The staff will try to conduct your final visit in person.

If the results of your liver function tests are higher than normal during the study, you will have some blood tests repeated to see if it is safe for you to continue in the study.

Early Discontinuation
You may have to stop participating in the study if you are not able to take your HIV or CHB medications or study product, or if you or your sexual partner become pregnant. Other reasons you might have to stop participating in the study are noted later in this informed consent.

- You will have an eye exam.
- You will have blood collected for HBV tests.
- If you are able to get pregnant, you will have blood or urine collected to see if you are pregnant.
- You will have blood collected for routine blood tests and for coagulation, liver function tests, immunologic studies, and virologic studies.
- Some of your blood will be stored for future studies.

- You will have urine collected for routine tests.
- You will be asked questions about how you are taking your other CHB and HIV medications.

The following table can be used as a reference for you.

Table 1: Study Evaluation Schedule

Evaluation or Test	Screening	Entry	Post-Entry Visits		Early Discontinuation
			While you are taking study product	After you finish study product	
Consent	✓				
Review of HIV and HBV Status	✓				
Medical and Medication History	✓	✓			
Ultrasound (if you have not had imaging within 24 weeks before entering the study)	✓			Near **W**eek 24	
Clinical Assessments (physical exam, vital signs, use of tobacco, medication and study product changes)	✓	✓	All visits	All visits	✓
Eye Examination	✓		Any time on study if you have any vision or eye problems	Between **W**eeks 24 and 48	✓
ECG	✓		✓		
Blood Collection	✓	✓	All visits	All visits	✓
Urine Sample		✓	All visits	All visits	✓
Pregnancy Test (if you are able to become pregnant)	✓	✓	**At most** visits		✓
Observation of Taking Study Product		✓	At all visits in clinic and remote		
HIV and CHB Adherence Assessments		✓	All visits	All visits	✓
Tuberculosis test	✓				
Blood Collection for Genetic Testing		✓	✓	At **W**eek 48	✓

Unplanned Visits

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

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your blood will be stored and used for study-required pharmacokinetic, immunologic, virologic, and genetic testing. You will not be told any of the test results from your blood that is collected and stored for later testing. You will be given any clinically relevant results from standard testing that is done shortly after your samples are collected.

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

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study. Please refer to Attachment I to consent for use of your samples in other studies.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 48 people will take part in this study**.**

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 12 months.

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 stopped or cancelled**. Continuing in the study may be harmful to you.**

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

- Continuing the study product 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 product as required by the study
- You stop taking your study-required treatment for HIV or CHB
- You or your partner becomes pregnant

If you must stop taking the study product, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures. As shown in the Table 1: Study Evaluation Schedule above, you will have clinical assessments done, blood and urine samples taken, and a pregnancy test performed. You will also have adherence assessments performed.

If I have to permanently stop taking the study product during the study or once I leave the study, would the study product continue to be provided?

During the study:

If you must permanently stop taking study-provided product before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:

After you have completed your study participation, the study will not continue to provide you with the study product you received on the study.

WHAT ARE THE RISKS OF THE STUDY?

The study product 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 SLGN. These lists include the more serious or common side effects with a known or possible relationship to the study product. If you have questions concerning the additional 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 product. 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.

Risks of Selgantolimod (SLGN; also known as GS-9688)

Very Common:
- Nausea
- Vomiting
- Headache
- Fatigue (Tiredness)
- Dizziness
- Upper respiratory tract infection (infection of the nose, sinus, or throat)
- Chills

Common:
- Iridocyclitis (uveitis or inflammation around the iris of the eye). This condition can cause symptoms such as painful, red, watery eyes and blurry vision.

Some of the blood that is collected from you will be used to look at the level of alanine aminotransferase (ALT), which is made by your liver. If the level of ALT is high, it may indicate damage to your liver and so you may be asked to stop taking the study product. You will be asked to come to the clinic for extra visits to have additional blood draws to make sure that the

ALT level goes back to **a safe range**. Once the ALT level returns to **a safe range**, you may be allowed to take the study product again.

Risks of Collecting Blood
Having blood collected may cause some discomfort, lightheadedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases, fainting, or infection. This is no riskier than a normal visit to the clinic.

Risks of ECG
Side effects associated with an ECG are minimal and rare. You should not feel anything during the ECG, but it may be uncomfor**table**, or cause skin irritation, when the sticky electrodes placed on your skin are removed.

Risks of Eye Examination
You will be given drops in your eyes to numb and dilate them. The doctor will use several lights to look at the front of the eye and the inside of each eye. The risks are minimal and include temporary blurred vision. It takes about 4 hours for the drops to wear off and your vision to return to normal.

Risks of Remote Data Collection
The study staff will do everything they can to keep your information private. However, the use of technology, such as videos or text messages, sent to study staff could be seen by someone who should not see them. Telephone numbers used for these communications could also be seen. In order to reduce the risk, videos are deleted after the necessary information is documented.

If you are participating in a remote visit, the study nurse or doctor can help you choose an app for your remote visit.

Risks to Unborn Babies
The effects of SLGN in individuals trying to get pregnant or who are pregnant have not been studied. However, in animal studies, SLGN did not show any effect on fertility (ability to get pregnant) but did show a possible effect on teratogenicity (birth defects). As the results indicate a possible link to fetal harm, participants of childbearing potential and participants with sexual partners of childbearing potential must agree to the contraception requirements for the study. Please refer to the Pregnancy section of the informed consent form.

Risks of Genetic Testing
The results of the genetic testing will not be shared with you and will remain confidential. However, there is a small risk of worry and anxiety related to unintentionally sharing of your information. The study has multiple processes in place to reduce such risks to the lowest possible.

Unknown Risks
Other side effects that are unknown at this time could happen during the study. All drugs have a possible risk of an allergic reaction, which if not treated right away, could become life-threatening. During the study, you will be told about any new information that may affect your decision to stay in the study. If any changes are made to this informed consent form, you will be asked to sign and date an updated consent form if you choose to stay in the study. If you decide to leave the study early, the study staff will talk with you about your treatment options.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if the drug in this study harms unborn babies. Tests in pregnant animals do show some risk. The risks to unborn babies are listed in the section called "What are the Risks of the Study?" If you are having sex that could lead to pregnancy, you must agree to take precautions to avoid pregnancy in yourself or your partner.

Because of the risk involved, you must use birth control that you discuss with the study staff. You must have started using birth control at least 45 days before entering the study. You must continue to use the methods below until 7 days after stopping study product.

You may choose one of the birth control methods listed below:

- Complete abstinence
- Intrauterine device (IUD)
- Male bilateral tubal occlusion or vasectomy (minor surgery to cut or block the tubes in your scrotum, which prevents sperm from leaving your body)
- Subdermal contraceptive implant (a small capsule or rod placed under your skin in your upper arm that releases a hormone, or chemical in your body, which prevents pregnancy)

You may choose two of the birth control methods listed below (one hormonal and one barrier method):

- Birth control drugs that prevent pregnancy given by pills, shots, or placed under the skin
- Male or female condoms with or without a cream or gel that kills sperm
- Vaginal ring
- Cervical cap, diaphragm, or sponge with spermicide
- Transdermal contraceptive patch

You must agree to refrain from egg and sperm donation, as well as in vitro fertilization during study **product use** and until 7 days after stopping study product.

It may be possible that study product in sperm can be a risk to an embryo/fetus.

If you can become pregnant, you must have a pregnancy test before you can enter this study and at each study visit while you are taking study product and through 7 days after you take the last dose. The test must show that you are not pregnant. If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices.

If your sexual partner can become pregnant, you must agree to use at least one, and preferably two, methods of birth control during study product and until 7 days after stopping study product. If you become pregnant while on study, **you will stay on study but off study drug and** the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If your sexual partner becomes pregnant while you are on study, you should let the doctor know. If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects

information about pregnancies in people taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, no direct health benefit is expected. Information learned from this study may help others who have hepatitis B and HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

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

- **C**ontinuing your prescription drugs for HBV
- **T**reatment with other experimental drugs, if you qualify
- **N**o additional treatment

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

WHAT ABOUT CONFIDENTIALITY?

For participants at a site in the US

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

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

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

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

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

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

All information collected about you as part of the study will be sent securely to the ACTG statistical and data management center in the United States for combining with information from other study participants and statistical analysis of study results. Your name and other personal identifiers will not be sent. Your research site is responsible for sending your information in accordance with the laws, regulations, and policies of your country and research site.

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

WHAT ARE THE COSTS TO ME?

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?

«Compensation»

You will be paid up to a total of $xx.xx if you complete this study. You will be paid for the visits you complete according to the following schedule:

- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.

If you do not complete the study, for any reason, you will be paid for each study visit you do complete.

You will be paid _____ ***["after each visit," "annually," "bi-weekly," etc.]***
If you have any questions regarding your compensation for participation, please contact the study staff.

[OR]

You will not receive any monetary compensation for your participation in this study.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries.

- *This site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.*

  OR

- *The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health.*

The US National Institutes of Health (NIH) does not have a mechanism to provide direct compensation for research related injury, whether or not CTI is available.

You will not be giving up any of your legal rights by signing and dating 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. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

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

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact *[for sites outside the US, add contact information for national regulatory body]*:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00059658.

SIGNATURE PAGE

<u>Intensive Pharmacokinetic (PK) testing</u>:

Please choose the response that matches whether you are willing to participate in the intensive PK portion of the study by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selection.

____ (initials) I agree to participate.

OR

____ (initials) No, I do not agree to participate.

If you have read this consent form, all your questions have been answered and you agree to take part in this study, please sign your name below and date.

Participant's Name (print)	Participant's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date

ATTACHMENT I: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES

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

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

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

There is no limit on how long your extra samples will be stored.

When a researcher wants to use your samples and information, their research plan must be approved by the ACTG. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review their plan. IRBs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher’s location. This means that researchers who are not part of the protocol team may use your samples without asking you for your consent.

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

You may withdraw your consent for research on your extra samples at any time, and the specimens will be discarded. However, any information from samples that have already been analyzed may still be used.

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

If you agree, your extra samples may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research.

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

OR

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

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

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

A5128, Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.

A5243, Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.

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

ATTACHMENT II: AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

If you decide to be in this study, the study doctor and study staff will use and share health data about you to conduct the study. Health data may include:

- Your name.
- Address.
- Phone number.
- Date of birth.
- Medical history.
- Information from your study visits, including all test results.

Health data may come from your study records or from existing records kept by your regular doctor or other health care workers.

For this study, the study staff may share health data about you with authorized users. Authorized users may include:

- Representatives of The National Institute of Allergy and Infectious Diseases (NIAID) or the industry sponsor Gilead Sciences, Inc.
- Representatives of Advarra IRB (an Institutional Review Board that reviews this study).
- The Food and Drug Administration (FDA) and other US federal and state agencies.
- Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported.
- Governmental agencies of other countries.
- Outside individuals and companies, such as laboratories and data storage companies, that work with the researchers and sponsor and need to access your information to conduct this study.
- Other research doctors and medical centers participating in this study, if applicable.
- A data safety monitoring board which oversees this study, if applicable.

Your health data will be used to conduct and oversee the research, including for instance:

- To see if the study drugs work and are safe.

- To compare the study drugs to other drugs.
- For other research activities related to the study drugs.

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

Your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about you at any time by writing to the study doctor at the address listed on the first page of this form. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign and date this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing and dating this form.

_____

Printed Name of Participant

_____ _____

Signature of Participant Date

INFORMED CONSENT FOR PREGNANCY

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
PREGNANCY INFORMED CONSENT

Sponsor / Study Title:	**National Institute of Allergy and Infectious Diseases/ "Safety, Tolerability, and Impact of Oral TLR8 Agonist Selgantolimod on HBsAg in Participants with Both Chronic Hepatitis B and HIV"**
Protocol Number:	**A5394**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

INTRODUCTION

Because you or your sexual partner are now pregnant, you are being asked if you want to continue taking part in this research study. This study was designed so that women who were pregnant could not join the study. However, because you were already in the study when you became pregnant or your partner became pregnant, you will be allowed to stay in the study. However, you will no longer receive the study product (Selgantolimod [SLGN] or placebo for SLGN).

The effects of SLGN in individuals trying to get pregnant or who are pregnant have not been studied. However, in animal studies, SLGN did not show any effect on fertility (ability to get pregnant) but did show a possible effect on teratogenicity (birth defects). It is not known if the drug in this study harms unborn babies. Tests in pregnant animals do show some risk. It may be possible that study product in sperm can be a risk to an embryo/fetus.

This is a consent form. It gives you more information about this study and how it may affect your pregnancy and your baby. The study staff will talk with you about this information. You may also talk with your own doctor about what is best for you and your baby. If you agree to stay in this study, you will be asked to sign this consent form. You will get a copy to keep. You are free to ask questions of the study staff at any time.

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

If you choose to stay in this study, you will not be provided study product. You will continue to attend study visits and have evaluations performed as stated in the main study A5394 Selgantolimod in CHB and HIV consent form. You will continue to have clinical assessments

done and blood and urine samples taken, as stated in the main study A5394 consent form. If you are continuing to participate in this study, additional pregnancy tests will not be required. Clinical assessments include a physical exam, vital signs, use of tobacco, and any medications you are taking. You will also have adherence assessments performed where you will also be asked questions about how you are taking your chronic hepatitis B (CHB) and HIV medications.

This study will not provide care related to your pregnancy or your sexual partner's pregnancy, the delivery of your baby, or the care of your baby. You must arrange for your care or your sexual partner's care, and your baby's care outside of this study.

Additionally, if you agree to continue to participate in this study, the study staff will ask for information about your pregnancy or your sexual partner's pregnancy and about the infant after birth.

Long-term follow-up is recommended for a baby whose mother takes anti-HIV drugs during pregnancy. The study staff will talk with you about long-term follow-up and the possibility of enrolling your baby in a long-term follow-up study.

WHAT ARE THE RISKS RELATED TO STAYING IN THE STUDY?

There are no additional risks to staying in the study than were stated in the main study A5394 Selgantolimod in CHB and HIV consent form that you already signed.

Risks of Collecting Blood

Having blood collected may cause some discomfort, lightheadedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases, fainting, or infection. This is no riskier than a normal visit to the clinic.

Risks of Remote Data Collection

You will be allowed to do some of the evaluations remotely using technology. For example, some of the evaluations may be performed by telephone, or via telehealth.

The study staff will do everything they can to keep your information private. However, the use of technology, such as videos or text messages, sent to study staff could be seen by someone who should not see them. Telephone numbers used for these communications could also be seen. In order to reduce the risk, videos are deleted after the necessary information is documented.

If you are participating in a remote visit, the study nurse or doctor can help you choose an app for your remote visit.

Unknown Risks

Other side effects that are unknown at this time could happen during the study. During the study, you will be told about any new information that may affect your decision to stay in the study. If any changes are made to this informed consent form, you will be asked to sign and date an updated consent form if you choose to stay in the study. If you decide to leave the study early, the study staff will talk with you about your treatment options.

ARE THERE BENEFITS TO STAYING IN THIS STUDY?

You, your sexual partner, or your baby will receive no benefit from continuing in this study. Information learned from this study may help others who have hepatitis B and HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

You have the choice of not continuing to participate in this study.

Please talk to your doctor about this and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

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

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

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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

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

National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

All information collected about you as part of the study will be sent securely to the ACTG statistical and data management center in the United States for combining with information from other study participants and statistical analysis of study results. Your name and other personal identifiers will not be sent. Your research site is responsible for sending your information in accordance with the laws, regulations, and policies of your country and research site.

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

WHAT ARE THE COSTS TO ME?

In addition to any costs that are described in the study consent you already signed, this study will not cover any cost related to your pregnancy, delivery of your baby, or care of your baby.

WILL I RECEIVE ANY PAYMENT?

«Compensation»

You will be paid up to a total of $xx.xx if you complete this study. You will be paid for the visits you complete according to the following schedule:

- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.

If you do not complete the study, for any reason, you will be paid for each study visit you do complete.

You will be paid _____ ["after each visit," "annually," "bi-weekly," etc.]

If you have any questions regarding your compensation for participation, please contact the study staff.
[OR]

You will not receive any monetary compensation for your participation in this study.

WHAT HAPPENS IF MY BABY OR I AM INJURED?

If you or your baby are injured as a result of being in this study, you will both be given immediate treatment for your injuries.

- *This site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.*

  OR

- *The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health.*

The US National Institutes of Health (NIH) does not have a mechanism to provide direct compensation for research related injury, whether or not clinical trials insurance (CTI) is available.

You will not be giving up any of your legal rights by signing and dating this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Continuing to take part in this study is completely voluntary. You may choose not to continue in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

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

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact *[for sites outside the US, add contact information for national regulatory body]*:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00059658.

SIGNATURE PAGE

If you have read this consent form, all your questions have been answered and you agree to take part in this study, please sign your name below and date.

Participant's Name (print)	Participant's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date