# IGHID 11627 - Combination Therapy with the Novel Clearance Modality (VRC07-523LS) and the Latency Reversal Agent (Vorinostat) to Reduce the Frequency of Latent, Resting CD4+ T Cell Infection (The VOR-07 Study)

**NCT number** NCT03803605
**Document Date** 03/18/2020
as per Clarification Memo #2

**Clarification Memo # 2**

**IGHID 11802 - Combination Therapy with the Novel Clearance Modality (VRC07-523LS) and the Latency Reversal Agent (Vorinostat) to Reduce the Frequency of Latent, Resting CD4+ T Cell Infection (The VOR-07 Study)**

**Protocol Version 4.0, May 9, 2019**
**IND Number: 138852**
**DAIDS-ES ID 38536**

**Date of Clarification Memo: March 18, 2020**

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**Summary of Revisions and Rationale**

1. Clarification added to section 8.1 to permit study team to conduct some site visits remotely under certain conditions.
2. COVID-19-related modification

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**Implementation**

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This Clarification Memo does not change the informed consent form.

The plan is to incorporate the modifications included in this Clarification Memo into the next full protocol amendment. Text noted below with a strikethrough will represent deletion; text appearing below in **bold** will represent an addition.

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1. In Section 8.1, Efficacy Assessments (on page 57 before the Research Laboratory Assays sub-section), the paragraph below is being added.

   **Remote Data Collection**
   **Study visits may be conducted remotely (e.g., telephone, facetime) in the following situations:**
   - **a participant is unable to attend a visit because of a debilitating illness; the site must inform the protocol team in advance**
   - **the site is temporarily unable to conduct non-essential visits in the clinic per University policies at the time of the visit; the site must inform the protocol team in advance**
   - **at the discretion of the protocol team if the risk of an on-site visit is felt to pose more risk than potential benefit to the participant; a message from the team will be sent to the study team**

   **Regardless of the situation, the study team should designate which visits were conducted remotely and attempt to obtain as much of the visit-specific required information, based on the Schedule of Events, and record it on the relevant study specific checklist. The reason for conducting the visit remotely must also be recorded and documented in the participant's study file.**

2. In section 7.2, PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY, in the Early Study Discontinuation sub-section (page 51), 1st bullet is being revised as shown

below:

- Failure by the participant to attend multiple clinic visits.
  **NOTE: This criterion is not applicable when study visits are being conducted remotely, as described in section 8.1.**

**Letter of Amendment #2**

**IGHID 11802 - Combination Therapy with the Novel Clearance Modality (VRC07-523LS) and the Latency Reversal Agent (Vorinostat) to Reduce the Frequency of Latent, Resting CD4+ T Cell Infection (The VOR-07 Study), A Phase 1 Study**

**Protocol Version 4.0, dated 09 May 2019**

**Letter of Amendment (LoA) #1 Date: August 12, 2019**

**Clarification Memo #1 Date: September 17, 2019**

**DAIDS-ES Document Number: DAIDS-ES ID 38536**

**IND Number: IND 138852**

**Letter of Amendment (LoA) #2 Date: January 30, 2020**

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This Letter of Amendment affects the IGHID 11802 study, including the study main informed consent form. Submission to the UNC Institutional Review Board (IRB) overseeing this research will occur as soon as possible after DAIDS review and approval. The UNC IRB must approve this Letter of Amendment before implementation.

Upon receiving final IRB and any other applicable Regulatory Entity (RE) approval(s) for this LoA, UNC will implement per unit SOP. UNC's Regulatory Department retains a copy of this LoA and any associated DAIDS and IRB correspondence in the study's regulatory file. Any future full amendment of the IGHID 11802 protocol will incorporate this Letter of Amendment.

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**Summary of the Revisions and Rationale**

The protocol team is implementing this amendment for the following reasons:

1. To clarify that the acetylation assay and VOR PK samples at the Day 29 and Day 89 visits are collected after taking the 10$^{th}$ Vorinostat dose.

2. To clarify that a POCT urine test is done on Day 0 and Day 60. Serum pregnancy test will only be done at screening.

3. To clarify that the Product Lot # will not be on the IP label due to limited space. The lot number is written on the VRC07 523-LS chain of custody form and in the IDS pharmacy logs.

4. To clarify the dispensing of Vorinostat to participants, providing increased reinforcement of dosing regimen of every 3$^{rd}$ day.

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**Implementation**

In changes listed below, additions to current protocol will appear as **bolded text** while deletions to current protocols will appear as ~~crossed-out text.~~

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**Protocol Changes**

1. Clarification to the collection of research labs after 10th dose of Vorinostat in each series.
   a) Section 1.3, Schedule of Events, page 12

   *Please note that the grey cells in the isolated segment of the Schedule of Events table below indicate no change. Deleted text appears as ~~crossed-out text~~ and any added text appears as **bolded text** within the table.*

| | Step 1 | Step 2 | | Step 3 | | Step 4 |
|---|---|---|---|---|---|---|
| | All Visit | All Visits | Day 29 | All visits | Day 89 | All visits |
| Research Lab Procedures | | | | | | |
| All other samples | | | | | | |
| Single PK sample (VOR)[4] | | | X | | X | |
| Acetylation, Virology and Viral Sequence Analysis | | | X[4] | | X[4] | |

**[4] Draw samples approximately 4 hours post dose (+/- 1 hour)**

   b) Research Laboratory Assays, page 58
   This modification is added to correct a typographical error. There are only 2 VOR PK samples collected on the study, but erroneously listed as 3 in this text.

   Vorinostat PK samples
   Pharmacokinetic samples will be collected at **2** ~~3~~ time points in the study **per SOE**. These will be processed and stored for testing as required.

   c) Research Laboratory Assays, page 58
   **Acetylation,** Virology and Viral Sequence Analysis
   Samples will be collected per the SOE. Samples will be processed, stored, and analyzed as required.

2. Clarification of Pregnancy Testing
   a) Section 1.3, Schedule of Events, page 11.

   *Please note that the grey cells in the isolated segment of the Schedule of Events table below indicate no change. Deleted text appears as ~~crossed-out text~~ and any added text appears as **bolded text** within the table.*

| | Step 1 | Step 2 | | Step 3 | | Step 4 |
|---|---|---|---|---|---|---|
| | Screen | Day 0 | All other visits | Day 60 | All other visits | All visits |
| Clinical Lab Procedures | | | | | | |
| All other samples | | | | | | |
| Serum Pregnancy Test | X | ~~X~~ | X[3] | ~~X~~ | X[3] | X[3] |
| **Urine Pregnancy Test (POCT)** | | **X** | | **X** | | |

[3] Serum pregnancy test will be performed at any time **during the study**, if pregnancy suspected. ~~serum pregnancy test must be completed on day of intervention to confirm pregnancy status~~

b) Section 8.2 Safety and other Assessments

Clinical Laboratory Testing for Safety, page 61

Serum **and Urine** Pregnancy Test, 2nd paragraph
A negative ~~serum~~ **urine** pregnancy test **(POCT)** is required ~~at each visit~~ prior to **each** VRC07-523LS infusion, and within 72 hours of the first VOR dose in Step 2 and Step 3 regardless of documented procedures that prohibit pregnancy.

3. Clarification of Investigational Product Lot # on IV bag
   a) Section 6.2.4 Preparation, page 48

VRC07-523LS, Section 3, Intravenous Infusion Preparation Instructions
g) Label the IV bag with:
(last bullet)
- ~~lot number~~

4. Clarification of Vorinostat Dispensing
   a) Section 6.1.2 Dosing and Administration

Vorinostat, page 43

The study provides the Vorinostat 400 mg to the participants. In Step 2 and Step 3, participants will take their first dose of VOR 400 mg PO at home two (2) days after the VRC07-523LS infusion. ~~All participants will be dispensed 5 doses of VOR 400 mg at the infusion visits on Day 0 and Day 60.~~ All participants will be provided with instructions for the safe administration of VOR at home. **VOR will be dispensed at the following study visits:**

**Day 0 – 2 doses**
**Day 7 – 3 doses**

**Day 14 – 5 doses**
**Day 60 – 5 doses**
**Day 74 – 5 doses**

Participants will return to the CTRC on ~~the day of their 5th dose (~~Day 14 and Day 74~~)~~ for safety labs and evaluations. ~~and to receive their last 5 doses of VOR 400 mg.~~

**Informed Consent Changes**

1. Page 6 - Day 0, Visit 3
   2nd bullet point - If female, we will do a pregnancy **urine** ~~blood~~ test.
   8th bullet point - Give you ~~5~~ **2** doses of VOR 400 mg to take home with you.

2. Page 6 – Day 7, Visit 4
   1st bullet point – Come to clinic. **Bring your empty medication bottle, Post-infusion and VOR Dosing Logs.**
   6th bullet - Review and discuss your VOR dosing **log.**
   **Add 7th bullet – Give you the next 3 doses of VOR and a new VOR dosing log.**
   **Add 8th bullet – Review the VOR dosing schedule with you and provide you with a dosing log that will list the days you need to take your doses.**

3. Page 7, Day 29, Visit 6
   1st bullet – Come to clinic **approximately 4 hours after taking you 10th (last) dose of VOR. Discuss with your study coordinator, the time you will take your last dose of VOR and the time you should be at your clinic visit.**

4. Page 7, Day 60, Visit 8
   2nd bullet point - If female, we will do a pregnancy **urine** ~~blood~~ test.

5. Page 8, Day 89, Visit 11
   1st bullet – Come to clinic **approximately 4 hours after taking you 10th (last) dose of VOR. Discuss with your study coordinator, the time you will take your last dose of VOR and the time you should be at your clinic visit.**

**Letter of Amendment #2**

**IGHID 11802 - Combination Therapy with the Novel Clearance Modality (VRC07-523LS) and the Latency Reversal Agent (Vorinostat) to Reduce the Frequency of Latent, Resting CD4+ T Cell Infection (The VOR-07 Study), A Phase 1 Study**

**Protocol Version 4.0, dated 09 May 2019**

**Letter of Amendment (LoA) #1 Date: August 12, 2019**

**Clarification Memo #1 Date: September 17, 2019**

**DAIDS-ES Document Number: DAIDS-ES ID 38536**

**IND Number: IND 138852**

**Letter of Amendment (LoA) #2 Date: January 30, 2020**

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## SIGNATURE PAGE

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

Protocol Principal Investigator: _____
Print/Type

Signed: _____ Date: _____

Title: _____

**Clarification Memo # 1**

**IGHID 11802 - Combination Therapy with the Novel Clearance Modality (VRC07- 523LS) and the Latency Reversal Agent (Vorinostat) to Reduce the Frequency of Latent, Resting CD4+ T Cell Infection (The VOR-07 Study)**

**Protocol Version 4.0, May 9, 2019**

**IND Number: 138852**

**DAIDS- ES ID 38536**

**Date of Clarification Memo: September 17, 2019**

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**Summary of Revisions and Rationale**

The protocol team would like to clarify the Prohibited Medications found in section 6.4 of the protocol, removing a few medications no longer regarded as prohibited.

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**Implementation**

This Clarification Memo does not change the informed consent form.

The plan is to incorporate the modifications included in this Clarification Memo into the next full protocol amendment. Text noted below with a strikethrough will represent deletion; text appearing below in **bold** will represent an addition.

Prohibited Medications (section 6.4 Concomitant Medications, page 49)

1. Prohibited HIV ART: Ongoing use of investigational ART. Prior use of investigational ART is permitted, provided it has been replaced with another class of ART and last dose was taken >90 days prior to study screening visit;
2. Concomitant use with oral or parenteral corticosteroids, immunosuppressive agents (including but not limited to azathioprine, and cyclosporine) or any immunotherapy or immunomodulatory agents;
   **Note: On-study use of short course steroids for treatment of acute conditions may be approved on a case-by-case basis by the PI. The PI may adjust additional doses of study product and its timing based on their determination of safety and end-points.**
3. ~~Use of any agent that suppresses lymphocytes or monocyte function;~~
4. Use of chemotherapeutic agents, growth factors, cytokines, or chemokines, white lineage colony stimulating factors (e.g., granulocyte-colony stimulating factor [G-CSF] and GM-CSF);
5. Chronic use of topical corticosteroids that are applied to large areas of the skin (exceeding the cumulative area of the palm of the participant's hand) ~~or any corticosteroids or antihistamines used on or near the infusion site~~.
6. Standard and live vaccinations (e.g., varicella, measles, mumps, rubella, MMR; yellow fever, oral polio) are permitted but timing of vaccine must be discussed and approved by the study PI or designee.
7. ~~Antihistamine can be administered only if needed to treat an anaphylactic reaction.~~

**Letter of Amendment #1**

**IGHID 11802 - Combination Therapy with the Novel Clearance Modality (VRC07-523LS) and the Latency Reversal Agent (Vorinostat) to Reduce the Frequency of Latent, Resting CD4+ T Cell Infection (The VOR-07 Study), A Phase 1 Study**

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This Letter of Amendment affects the IGHID 11802 study, including the study main informed consent form. Submission to the UNC Institutional Review Board (IRB) overseeing this research will occur as soon as possible after DAIDS review and approval. The UNC IRB must approve this Letter of Amendment before implementation.

Upon receiving final IRB and any other applicable Regulatory Entity (RE) approval(s) for this LoA, UNC will implement per unit SOP. UNC's Regulatory Department retains a copy of this LoA and any associated DAIDS and IRB correspondence in the study's regulatory file. Any future full amendment of the IGHID 11802 protocol will incorporate this Letter of Amendment.

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**Summary of the Revisions and Rationale**

The protocol team is implementing this amendment for the following reasons:

- To relax some of the inclusion and exclusion criteria currently limiting enrollment.
- Suggested changes do not increase the risk to participants.
- To correct the blood volume for Visit 3 (Day 0) in the estimated blood volume table.

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**Implementation**

In changes listed below, additions to current protocol will appear as **bolded text** while deletions to current protocols will appear as ~~crossed-out text.~~

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**Protocol Changes**

1. Section 5.1 Inclusion Criteria (pages 35 - 38)
   Note changes to selected criteria below:

#4 - On continuous antiretroviral therapy (ART defined in 5.1.5) for at least 24 months prior to screening.

*Note: Continuous ART prior to screening is defined as not missing more than ~~4(four)~~ **9** total days ~~and never more than 2 consecutive days~~ in the 3 months prior to screening.*

2. Section 5.2 Exclusion Criteria (pages 38 – 41)
   Note changes to selected criteria below:

   #12 - Prior **receipt of** ~~use of any~~ HIV immunotherapy within **6**~~12~~ months prior to screening.

   ~~#13 – Prior use of an HIV vaccine prior to screening.~~

   #15 - Prior receipt of humanized or human mAbs **within 2 months prior to screening,** whether licensed or investigational, will have eligibility determined by the study PI on a case-by-case basis.

   #27 - Diabetes Mellitus type 1 ~~or type 2~~

   ~~*Not exclusionary: type 2 cases controlled with diet alone or a history of isolated gestational diabetes*~~
   ***NOTE: Individuals with type 2 diabetes who meet inclusion criteria for glucose (Section 5.1.23) are not excluded.***

   #29 - **Hypertension - Exclude for blood pressure consistently >150 mm Hg systolic and >100 mm Hg diastolic.**

   - ~~If a person has been found to have elevated blood pressure or hypertension during screening or previously, exclude for blood pressure that is not well controlled. Well-controlled blood pressure is defined as consistently ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic, with or without medication, with only isolated, brief instances of higher readings, which must be ≤ 150 mm Hg systolic and ≤ 100 mm Hg diastolic. For these volunteers, blood pressure must be ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic at enrollment.~~
   - ~~If a person has NOT been found to have elevated blood pressure or hypertension during screening or previously, exclude for systolic blood pressure ≥ 150 mm Hg at enrollment or diastolic blood pressure ≥ 100 mm Hg at enrollment.~~

   *Note: Elevated BP occurring during research leukapheresis procedures completed within the past 12 months are excluded from this requirement. ~~Other isolated incidences of~~*

~~*elevated BP should be reviewed by study PI (or designee) to determine whether they are exclusionary.*~~ *Acceptable isolated elevations must be noted as acceptable and signed by study PI or designee.*

3. Estimated Blood Volumes Associated with the Study Visits (page 64)

| Visit or Week # | Blood Volume (mL) | Visit or Week # | Blood Volume (mL) |
|---|---|---|---|
| Visit 1 | 50 | Visit 8 Day 60 | 116 |
| Visit 2 | 153 | Visit 9 Day 67 | 18 |
| Visit 3 Day 0 | ~~61~~ **163** | Visit 10 Day 74 | 18 |
| Visit 4 Day 7 | 15 | Visit 11 Day 89 | 173 |
| Visit 5 Day 14 | 16 | Visit 12 | 50 |
| Visit 6 Day 29 | 158 | Visit 13 | 135 |
| Visit 7 | 70 | | |

**Informed Consent Changes**

1. The Informed Consent Version and Date have been updated from Version 4.~~0, May 9,~~ 2019 to Version 4**.1, August 12,** 2019.

2. **Are there any reasons that you should not be in this study?** (Page 3)
   a) Deleted the 9th bullet
      - ~~Have previously received an HIV vaccine~~
   b) Amended text in the 13th bullet
      - Have **Type 1** diabetes

3. **Study Visits Table** (Page 6)
   a) Adjusted volume of blood drawn at Day 0 (Visit 3)
      - ~~61~~**163** mL or **411** Tbsp.

**Letter of Amendment #1**

**IGHID 11802 - Combination Therapy with the Novel Clearance Modality (VRC07-523LS) and the Latency Reversal Agent (Vorinostat) to Reduce the Frequency of Latent, Resting CD4+ T Cell Infection (The VOR-07 Study), A Phase 1 Study**

**Protocol Version 4.0, dated 09 May 2019**

**DAIDS-ES Document Number: DAIDS-ES ID 38536**

**IND Number: IND 138852**

**Letter of Amendment (LoA) #1 Date: August 12, 2019**

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## SIGNATURE PAGE

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

Protocol Principal Investigator: _____
Print/Type

Signed: _____ Date: _____

Title: _____

# Combination Therapy with the Novel Clearance Modality (VRC07-523LS) and the Latency Reversal Agent (Vorinostat) to Reduce the Frequency of Latent, Resting CD4+ T Cell Infection (The VOR-07 Study)

## Phase 1 Study

**Protocol Number: IGHID 11802**

**National Clinical Trial (NCT) Identified Number: NCT 03803605**

**Grant Principal Investigator: David Margolis, MD**

**Protocol Principal Investigator: Cynthia Gay, MD, MPH**

**University of North Carolina at Chapel Hill**

**DAIDS-ES Document Number: DAIDS-ES ID 38536**

**IND Number: IND 138852**

**Funded by: National Institutes of Health**

**Version Number: v.4.0**

**09 May 2019**

# IGHID 11802 – Combination Therapy with the Novel Clearance Modality (VRC07-523LS) and the Latency Reversal Agent (Vorinostat) to Reduce the Frequency of Latent, Resting CD4+ T Cell Infection (The VOR-07 Study)

## DAIDS-ES ID 38536

## SIGNATURE PAGE

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Investigator of Record: _____
Print/Type

Signed: _____ Date: _____

Title: _____

## KEY ROLES AND CONTACT INFORMATION

**Grant Principal Investigator**
**David M. Margolis, MD**
Professor of Medicine, Microbiology & Immunology
University of North Carolina at Chapel Hill
Division of Infectious Diseases
120 Mason Farm Road, 2016 Genetic Medicine Building, CB 7042
Chapel Hill, NC 27599-7042
Phone: (919) 966-6388
Email: *dmargo@med.unc.edu*

**Protocol Chair/Principal Investigator**
**Cynthia Gay, MD, MPH**
Associate Professor
University of North Carolina at Chapel Hill
Division of Infectious Diseases
130 Mason Farm Road, 2nd Floor Bioinformatics Building, CB 7030
Chapel Hill, North Carolina 27599-7030
Phone: (919) 843-2726
Fax: (919) 966-8928
Email: *cynthia_gay@med.unc.edu*

**Co- Investigators**
**Joseph Eron, MD**
Professor of Medicine, School of Medicine,
Chair Division of Infectious Disease Division,
Clinical Core, UNC Center for AIDS Research
University of North Carolina at Chapel Hill
130 Mason Farm Road, 2nd Floor Bioinformatics, CB 7030
Chapel Hill, North Carolina 27599-7030
Phone: (919) 843-2722
Fax: (919) 966-8928
Email: *joseph_eron@med.unc.edu*

**Michelle Floris-Moore MD, MS**
Associate Professor of Medicine
Division of Infectious Diseases
Department of Medicine
University of North Carolina at Chapel Hill
130 Mason Farm Road, CB 7030
Bioinformatics Building, Room 2103
Chapel Hill, North Carolina 27599-7030
Phone: (919) 966-4733
Fax: (919) 966-6714
Email: *michelle_floris-moore@med.unc.edu*

**Nancie M. Archin, PhD**
Research Assistant Professor
University of North Carolina at Chapel Hill
Division of Infectious Diseases
120 Mason Farm Rd, CB 7042
Genetic Medicine Building, RM 2049H
Chapel Hill, NC, 27599-7042
Phone: (919) 966-6389
Email: *nancie_archin@med.unc.edu*

**Nilu Goonetilleke, PhD**
Assistant Professor
Depts. Microbiology & Immunology/Medicine
University of North Carolina at Chapel Hill
120 Mason Farm Road, CB 7042
2023 (Office 2017), Genetic Medicine Building
Chapel Hill, NC 27599-7264
Phone: (919) 962-3129
Email: nilu_goonetilleke@med.unc.edu

**Ron Swanstrom, PhD**
Charles P. Postelle, Jr. Distinguished Professorship in Biochemistry
Director, UNC Center for AIDS Research and
Department of
Microbiology and Immunology
University of North Carolina at Chapel Hill
22-006 Lineberger Cancer Center, CB 7295
Chapel Hill, NC 27599-7260
Phone: (919) 966-5710
Email: *risunc@med.unc.edu*

**Statistician**
**Michael Hudgens, PhD**
Professor
Department of Biostatistics
Director, Center for AIDS Research (CFAR)
Biostatistics Core
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599
Phone: (919) 966-7253
Email: *mhudgens@bios.unc.edu*

**Statistician**
**Katie Mollan, MS**
Senior Biostatistician
Center for AIDS Research (CFAR) Biostatistics Core
3126 McGavran-Greenberg Hall
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599
Phone: (919) 966-8421
Email: *kmollan@unc.edu*

**Clinical Program Manager**
**JoAnn Kuruc, MSN, RN**
Clinical Program Director, The UNC Cure Center
University of North Carolina at Chapel Hill
Division of Infectious Diseases
130 Mason Farm Road, 2nd Floor Bioinformatics Building, CB 7030
Chapel Hill, North Carolina 27599-7030
Phone: (919) 966-8533
Fax: (919) 843-7625
E-Mail: *joann_kuruc@med.unc.edu*

**DAIDS Medical Officer**
**Lawrence Fox, MD, PhD**
Captain, US Public Health Service
Senior Medical Officer, HIV Research Branch
Division of AIDS, NIAID, NIH, DHHS
Phone: 240-627-3069
Fax: 240-627-3106
Email: *LFOX@niaid.nih.gov*

**DAIDS Program Officer**
**Tia Morton, RN, MS**
Nurse Consultant/Program Officer
DAIDS/TRP
5601 Fishers Lane, Rm 9E48
Bethesda, MD 20852
Phone: 240-627-3073
Email: *fraziert@niaid.nih.gov*

## TABLE OF CONTENTS

## STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the NIH Institute Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug sponsor, funding agency, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

**Title:**

Phase I Study to Assess the Safety and Activity of Combination Therapy using a Novel Monoclonal Antibody, VRC07-523LS, and the Latency Reversal Agent, Vorinostat, to Reduce the Frequency of Latent, Resting CD4+ T Cell Infection in participants with HIV-1 infection suppressed on ART (The VOR-07 Study)

**Study Description:**

Participants with HIV-1 Infection on ART with a CD4 T cell count ≥ 350 cells/$mm^3$ and viral suppression for ≥ 24 months. Participants will receive two series of combination therapy consisting of one (1) intravenous (IV) dose of VRC-HIVMAB075-00-AB (VRC07-523LS) followed by 10 oral (PO) doses of Vorinostat (VOR) taken every 72 hours. Each series will last approximately 1 month and the two series will be separated by at least one month. Combination ART is (ART) maintained throughout the study.

**Objectives:**

Primary Objective:

1. To evaluate the safety and tolerability of combination therapy with VRC07-523LS and VOR in HIV-infected participants on ART.

Other Objectives:

1. Explore the effect of two cycles of VRC07-523LS and VOR on the frequency of latent, resting CD4+ T cell infection.
2. Explore the influence of VOR given with VRC07-523LS on low-level plasma viremia as measured by low level viremia assay in participants who maintain suppression on ART.
3. Compare HIV RNA expression within resting $CD4^+$ T cells in HIV-infected participants on stable ART before and after combination therapy with VRC07-523LS and VOR measured at baseline (Step 1) and after the second series (Step 4).
4. Explore the impact of combined therapy with VRC07-523LS and VOR on the quantity of integrated proviral DNA quantification in T cell populations.
5. Characterize viral envelope sequences detected in plasma or cells that are not neutralized by VRC07-523LS from baseline to post-treatment with VRC07-523LS and VOR.
6. Evaluate the pharmacokinetics of VRC07-523LS combined with VOR and determine whether anti-drug antibody (ADA) to VRC07-523LS can be detected in recipients administered VRC07-523LS in combination with VOR.

**Endpoints:**

Primary Endpoint:

1. Safety: Occurrence of at least one ≥ Grade 3 adverse event (AE) including signs/symptoms, lab toxicities, and/or clinical events that is possibly, probably, or definitely related to VOR or VRC07-523LS

from the first day of study treatment through the end of study. Safety data will include local and systemic signs and symptoms, laboratory measures of safety/toxicity, and all adverse and serious adverse events.

Other Endpoints:

1. Change in the frequency of HIV infection per million resting $CD4^+$ T cells (RCI) from baseline to post-treatment with VRC07-523LS combined with VOR.
2. Change in HIV RNA expression within resting $CD4^+$ T cells in HIV-infected participants on stable ART from baseline to after the receipt of two series of VRC07-523LS given with VOR.
3. Change in HIV-1 RNA by low level viremia assay from baseline to post-treatment with VRC07-523LS and VOR.
4. Change in the chromosomally integrated viral reservoir as measured by quantitative-polymerase chain reaction (Q-PCR) from baseline to post-treatment with VRC07-523LS and VOR.
5. Change in frequency of viral envelope sequences detected in plasma or cells that are not recognized by VRC07-523LS from baseline to post-treatment with VRC07-523LS and VOR.
6. Pharmacokinetics of VRC07-523LS in combination with VOR.

**Population:** Healthy men and women of any race with HIV-1 infection, ages 18 through 64, suppressed on ART therapy for $\geq$ 24 months.

**Phase:** Phase I

**Description of Sites/Facilities Enrolling Participants:** This study will be conducted at a single site, The University of North Carolina (UNC) at Chapel Hill (USA). The study will enroll up to12 participants.

**Description of Study Intervention:** Participants will receive two treatment interventions (series):

1. *VRC07-523LS* –
   a. *40 mg/kg via IV infusion per series (total of 2 infusions)*
2. *VOR* –
   a. *400 mg PO every 72 hours for 10 doses per series (total of 20 doses of VOR 400 mg in the study)*

In Step 1, all participants will undergo study screening and enrollment. Participants will complete a baseline Leukapheresis (#1). In order to advance to Step 2, participants must be found to have a baseline measurement of the frequency of resting CD4 T cell infection ≥ 0.3 infectious units per million (IUPM) determined by Quantitative Viral Outgrowth Assay (QVOA) (lower limit of detection is 0.3 IUPM), as a further decrease from this low frequency of infection cannot be definitively measured given the QVOA assay threshold.

These criteria assure that eligible enrolled participants will have a measurable endpoint, thus decreasing risk of study participation for participants who would not have a measurable outcome.

Participants progressing to Steps 2 and 3 will receive two series of a single VRC07-523LS infusion followed by multiple doses of VOR.

In the first series (Step 2), participants will receive one VRC07-523LS 40 mg/kg infusion (infusion #1) on Day 0 followed by the 1st dose of VOR 400 mg PO taken at home on Day 2. Participants will take VOR 400 mg PO every 72 hours for a total of 10 doses.

In the second series (Step 3), participants will receive one VRC07-523LS 40 mg/kg infusion (infusion #2) on Day 60 followed by the 1st (of the 2nd series of VOR) dose of VOR 400 mg PO on Day 62. As in the previous Step, participants will take VOR 400 mg PO every 72 hours for a total of 10 doses.

Step 4 consists of 2 visits. The post-study treatment leukapheresis (#2) will be completed 5 – 8 weeks after the 2nd VRC07-523LS infusion. The End of Study Visit (EOS) will be scheduled to 2 – 4 weeks following the final leukapheresis (#2) visit.

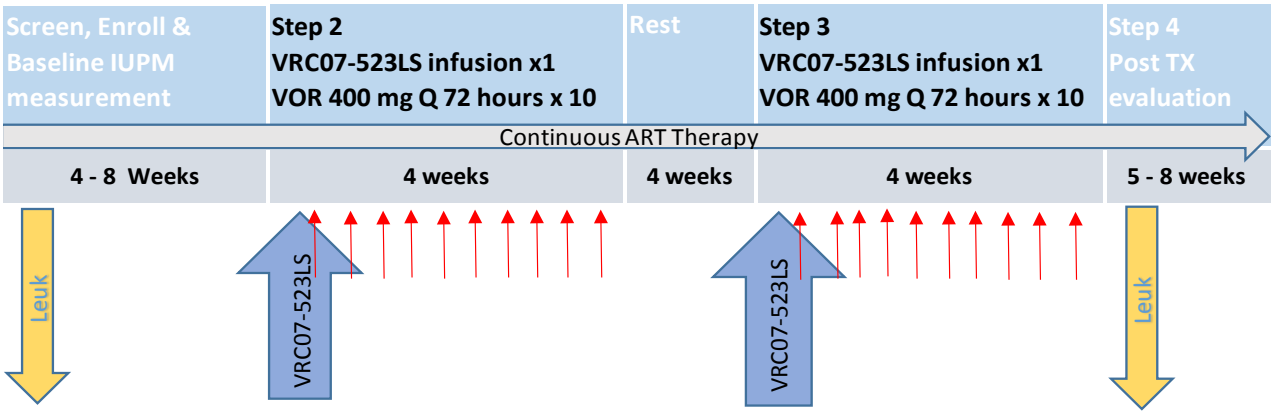
**Study Duration:** The study will take approximately 8 months to enroll up to 12 participants and will be completed, inclusive of data analysis within 18 months of the enrollment of the last participant.

**Participant Duration:** Each participant will be enrolled on the study for approximately 28 weeks.

## 1.2 SCHEMA

This is an open-label study to examine the safety of two series of combination therapy each consisting of a single VRC07-523LS 40mg/kg infusion followed by 10 oral doses of VOR taken every 72 hours in healthy HIV-infected adults suppressed on ART.

Safety laboratory samples will be collected throughout the study per the Schedule of Evaluations (Section 1.3). Participants will keep a daily diary of solicited symptoms for 3 days after each administration of VRC07-523LS.




**Step 1**

- Consent
- Eligibility confirmed and Enrollment
- Baseline leukapheresis (#1) and research evaluations
- Advancement Criteria Met
  IUPM determined

**Step 2**

- Day 0 - VRC07-523LS infusion (#1)
- Day 2 - VOR 400 mg PO – 1st dose taken at home
- 10 doses of VOR 400 mg PO taken every 72 hours
- Immunology and virology research sample collection
- Safety evaluations

**Step 3**

- Day 60 - VRC07-523LS infusion (#2)
- Day 62 - VOR 400 mg PO – 1st dose in second series taken at home
- 10 doses of VOR 400 mg PO taken every 72 hours
- Immunology and virology research sample collection
- Safety evaluations

**Step 4**

- Post treatment leukapheresis (#2)
- Safety evaluations
- Immunology and virology research sample collection

## 1.3 SCHEDULE OF EVENTS

| Code: d = day h = hour | Step 1 | | Step 2 – Series 1 | | | | | | Step 3– Series 2 | | | | | Step 4 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screen | Enroll | Day 0 | Day 4 - 6 | Day 7 | Day 14 | Day 29 | Pre-Visit | Day 60 | Day 64- 66 | Day 67 | Day 74 | Day 89 | Evaluation † | End of Study ‡ |
| **Study Visit** | **1** | **2** | **3** | | **4** | **5** | **6** | **7** | **8** | | **9** | **10** | **11** | **12** | **13** |
| **Study Visit Window** | | ≤ 30d of Visit 1 | ≤ 6 wks of leuk | | +/- 1 day | +/- 2 days | | ≤ 7d of Day 60 | -3d/+ 14d | | +/- 1 day | +/- 2 days | | | |
| **Clinical Procedures** | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | |
| Assign PID | X | | | | | | | | | | | | | | |
| Assign SID | | X | | | | | | | | | | | | | |
| Medical History and Updates | X | X | X | | X | X | X | X | X | | X | X | X | X[1] | X |
| Physical Exam (weight) | X | | | | | | | X | | | | | | | X |
| Targeted Physical Exam (weight) | | | X | | X | X | X | | X | | X | X | X | X[1] | |
| Height | X | | | | | | | | | | | | | | |
| Concomitant Medication review | X | X | X | | X | X | X | X | X | | X | X | X | X[1] | X |
| ART Medication and Adherence Review | X | X | X | | X | X | X | X | X | | X | X | X | X[1] | X |
| Vital Signs | X | X | X | | X | X | X | X | X | | X | X | X | X[1] | X |
| Adverse Event Assessment | X | X | X | X | X | X | X | X | X | | X | X | X | X[1] | X |
| Assess Venous Access | X | | | | | | | | | | | | | | |
| Electrocardiogram (ECG) | X | | | | | | | | | | | | | | |
| Solicited AE Assessment | | | X | | | | | | X | | | | | | |
| Telephone Assessment of Solicited AEs | | | | X | | | | | | X | | | | | |
| Advancement Criteria | | X | | | | | | | | | | | | | |
| Pre-Study treatment Safety Assessment | | | X | | | | | X | | | | | | | |
| VOR 400 mg PO doses | | | | X | X | X | X | | | X | X | X | X | | |
| VRC07-523LS Infusion | | | X | | | | | | X | | | | | | |
| Leukapheresis Procedure | | X | | | | | | | | | | | | X | |
| **Clinical Laboratory Procedures** | | | | | | | | | | | | | | | |
| CBC with differential | X | | X[2] | | X | X | X | X | | | X | X | X | | X |
| CBC for leukapheresis | | X | | | | | | | | | | | | X | |
| Serum Chemistry (screening) | X | | | | | | | | | | | | | | X |

| Code: d = day h = hour | Step 1 | | Step 2 – Series 1 | | | | | | Step 3– Series 2 | | | | | Step 4 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screen | Enroll | Day 0 | Day 4 - 6 | Day 7 | Day 14 | Day 29 | Pre-Visit | Day 60 | Day 64- 66 | Day 67 | Day 74 | Day 89 | Evaluation † | End of Study ‡ |
| Serum Chemistry (safety) | | | X[2] | | X | X | X | X | | | X | X | X | X[1] | |
| Liver Function Tests | X | | X[2] | | X | X | X | X | | | X | X | X | X[1] | X |
| Fasting Lipid Panel | X | | | | | | | | | | | | | | |
| PT/PTT/INR | X | | | | | | | | | | | | | | |
| FSH test | X | | | | | | | | | | | | | | |
| Serum Pregnancy Test | X | | X | X[3] | X[3] | X[3] | X[3] | X[3] | X | X[3] | X[3] | X[3] | X[3] | X[3] | X[3] |
| CD4 T Cell Differential Panel | X | | X | | | | | X | | | | | X | | X |
| HIV-1 RNA PCR | X | | X | | | | | X | | | | | X | | X |
| HBsAg & HCV Ab | X | | | | | | | X | | | | | | | |
| RPR | X | | X | | | | | X | | | | | | | |
| Interferon-gamma release assay (IGRA) | X | | | | | | | | | | | | | | |
| Urinalysis | X | | | | | | | X | | | | | | | X |
| **Research Laboratory Procedures** | | | | | | | | | | | | | | | |
| Low level Viremia Assay | | X | X | | | | X | X | | | | | X | X[1] | |
| ADA Analysis | | | X | | | | X | X | X | | X | X | X | | X |
| Single PK sample (VOR) | | | | | | | X | | | | | | X | | |
| PK sample (VRC07-532LS) | | | X | | | | X | | | | | | X | | |
| HLA Typing | | X | | | | | | | | | | | | | |
| CMV IgG Test | | X | | | | | X | | | | | | X | | |
| EBV VCA IgG Test | | X | | | | | X | | | | | | X | | |
| caRNA Assay | | X | | | | | | | | | | | | | |
| Acetylation, Virology and Viral Sequence Analysis | | X | X | | | | X | | X | | | | X | | X |
| Resting Cell Assay | | X | | | | | | | | | | | | X | |

† Visit to occur 5 – 8 weeks after Day 60.
‡ Visit to occur 2-4 weeks after Visit 12.

[1] Labs can be collected within 72 hours prior to the leukapheresis procedure
[2] Clinical and research sample drawn pre-dose. Safety Labs at Day 0 must be reviewed by PI prior to VRC07-523LS infusion. Pre-dose Safety labs (CBC, chemistries and LFTS) can be obtained within 7 days prior to Day 0.
[3] Serum pregnancy test will be performed at any time, if pregnancy suspected, a serum pregnancy test must be completed on day of intervention to confirm pregnancy status.

# 2 INTRODUCTION

The Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), and Division of AIDS (DAIDS) have collaborated to develop and evaluate VRC07-523LS, a highly potent and broadly neutralizing HIV-1 human monoclonal antibody (mAb) targeted against the HIV-1 CD4 binding site. A similar antibody, VRC01 mAb, is currently in clinical trials under IND 113,611 (prevention indication) and IND 126,001 and IND 126,664 (therapeutic indication). The VRC01mAb was originally discovered in an HIV-1-infected participant whose immune system controlled the virus without anti-retroviral therapy (ART) for over 15 years (1, 2). Through advances in B-cell immunology, cloning and structure-guided optimization techniques, numerous HIV-1 neutralizing mAbs, including VRC07 ("07" denotes sequential numbering when discovered), VRC07-523 ("523" denotes sequential numbering when engineered variant generated), and later VRC07-523LS ("LS" denotes 2 amino acid mutations), were isolated with potency and breadth greater than those of early antibodies (3).

The VRC07 (wild-type) heavy chain was identified by 454 deep sequencing based on its similarity to the VRC01 mAb and paired with the VRC01 (wild-type) light chain. The mutations that together define the 523 designation are a glycine to histidine mutation at residue 54 of the heavy chain, a deletion of the first two amino acids, glutamate and isoleucine, from the light chain, and a valine to serine mutation at the third amino acid residue of the light chain. The LS designation specifies methionine to leucine (L) and asparagine to serine (S) (M428L/N434S, referred to as LS) changes within the C-terminus of the heavy chain constant region. The LS mutation was introduced by site-directed mutagenesis to increase the binding affinity for the neonatal Fc-receptor (FcRn), resulting in increased recirculation of functional IgG (4, 5), thus increasing plasma half-life.

The resultant molecule, VRC-HIVMAB075-00-AB (VRC07-523LS), is an investigational drug currently being evaluated for the prevention of HIV-1 infection in healthy adults. We propose its study herein towards future uses to clear established HIV infection.

## 2.1 STUDY RATIONALE

The inability to eliminate HIV-1 from quiescent, latently infected reservoirs (6-8) remains the critical limitation to HIV eradication. Although combination antiretroviral therapy (cART) effectively suppresses viremia, cART drugs do not eliminate the latent viral reservoir. With a half-life of 3.6 years of the latent reservoir, over 70 years of suppressive ART would be required to achieve HIV eradication through ART alone (9, 10). Given the expanding numbers of HIV-infected individuals on ART, there is a need for innovative therapies to eradicate HIV-1 infection (11). One approach to eradicate HIV infection, a 'kick and kill' strategy, is to 1) expose latent, persistent HIV by interfering with mechanisms that maintain latency, and 2) eliminate exposed latently infected cells by an enhanced immune response *without interrupting* ART. Antibodies could be used to enhance HIV-specific immune responses as they can mediate effector functions such as antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular viral inhibition, and phagocytosis through binding of the Fc portion to receptors on the surface of cells such as macrophages and natural killer cells. Further, novel and engineered anti-HIV antibodies are under study to prevent, treat, and clear infection via these functions (12).

Over the past several years, there has been a successful effort to isolate broadly neutralizing antibodies (bNAbs) to HIV-1 from chronically infected individuals (2, 12-26). Studies have provided considerable insight into the sites these antibodies target on HIV-1 and the mechanisms by which

they neutralize HIV-1 (14, 15, 24, 27). This proposal builds upon the data generated by U01 AI095052, which investigated the anti-latency activity of Vorinostat (VOR), defining optimal dosing strategies (28-30), resulting in our current optimized strategy of interval dosing with VOR every 3 days. These studies found VOR to be well-tolerated, and optimized dosing intervals result in repeated induction of cell-associated HIV RNA expression, potentially allowing clearance of latent infection. Preclinical studies with VRC07-523LS to date support the proposed human dose and interval between doses to achieve passive immunity. The use of VRC07-523LS, which will provide antibody exposure over the period of latency reversal by VOR based on pharmacokinetic data in humans, allows the provision of a validated immunotherapy that may direct ADCC to clear reactivated HIV-1. We will assess the safety and tolerability, as well as the ability of VRC07-523LS to reduce the frequency of latent, resting CD4+ T cell infection in stably treated HIV-infected participants, when combined with pulsatile VOR administration. This study will evaluate the safety of the combined treatment and examine the effect of VOR and VRC07-523LS on persistent replication-competent HIV within resting CD4+ T cells.

## 2.2 BACKGROUND

One approach to eradicate HIV infection, a 'kick and kill' strategy, is to 1) expose latent, persistent HIV by interfering with mechanisms that maintain latency, and 2) eliminate exposed latently infected cells by an enhanced T-cell immune response without interrupting ART. Studies have demonstrated that Histone Deacetylase (HDAC) is a critical regulator of HIV latency (28-30). Our own work has shown that the HDAC inhibitor, Vorinostat, can induce the expression of latent HIV-1 in vivo (28). As effective dosing strategies for latency reversal agents (LRAs) *in vivo* are advancing, parallel testing of approaches to harness the immune response to clear residual HIV following the disruption of latency are critical. Recent work suggests that the antiviral $CD8^+$ T cell response extant in the majority of HIV-1 infected individuals is insufficient to clear the latent reservoir. Attempts to strengthen HIV-specific immune responses using a therapeutic vaccine have been disappointing (34-36), likely in part due to the inability of the vaccines to produce sustained expansion of HIV specific $CD8^+$ T cells. Further, archived immune escape viral variants within the latent reservoir may present a challenge (37).

Antibodies can mediate effector functions such as ADCC, antibody-dependent cellular viral inhibition, and phagocytosis through binding of the Fc portion to receptors on the surface of cells such as macrophages and natural killer cells. Novel and engineered anti-HIV antibodies are under study to prevent, treat, and clear infection via these functions (38).

**VRC01**
VRC01 was a first-in-class broadly neutralizing antibody (bnAb) that targets the same $CD4^+$ binding site of the HIV-1 envelope as VRC07-523LS. VRC01 was engineered for increased efficacy using next-generation sequencing, computational bioinformatics, and structure-guided design. VRC01 has been assessed as safe and well tolerated at the 5-40 mg/kg doses administered intravenously (IV) and at 5 mg/kg subcutaneously (SC) in both HIV-infected and HIV-uninfected adult populations. The pharmacokinetic (PK) parameters of passively administered VRC01 were also evaluated. For healthy adults who received VRC01 at the 5-40 mg/kg doses administered IV (n=18), the clearance was 0.016±0.003 L/h and an overall mean value for the elimination half-life was 15.4±3.9 days. At 5 mg/kg SC (n=5), the clearance was 0.029±0.007 L/h, and the mean elimination half-life was 16.6 ± 2.9 days. Studies are ongoing to further describe the PK and biological activity of VRC01 after repeat dosing in HIV-infected and -uninfected adults. **VRC01LS** is a VRC01 variant with 2 amino acid mutations (M428L/N434S, referred to as LS) conferring an increased plasma half-life.

**VRC07-523**
Numerous HIV-1 neutralizing mAbs from the VRC01 family, including VRC07 ("07" denotes sequential numbering when discovered) have been isolated from the same individual (donor 45). The VRC07 (wild-type) heavy chain was identified by 454 deep sequencing based on its similarity to the VRC01 mAb and paired with the VRC01 (wild-type) light chain. The mutations that together define the 523 designation are a glycine to histidine mutation at residue 54 of the heavy chain, a deletion of the first two amino acids, glutamate and isoleucine, from the light chain, and a valine to serine mutation at the third amino acid residue of the light chain. A resulting variant, VRC07-523, was 5- to 8-fold more potent than VRC01, neutralized 96% of viruses tested, and displayed minimal autoreactivity.

**VRC07-523LS**
VRC07-523LS is an engineered variant of VRC07 that was discovered in the same HIV-1 infected participant as VRC01. The LS designation specifies methionine to leucine (L) and asparagine to serine (S) (M428L/N434S, referred to as LS) changes within the C-terminus of the heavy chain constant region. The LS mutation was introduced by site-directed mutagenesis to increase the binding affinity for the neonatal Fc-receptor (FcRn), resulting in increased recirculation of functional IgG (4, 5), thus increasing plasma half-life. VRC07-523LS neutralizes more HIV envelope strains than VRC01 at lower concentrations. VRC07-523LS was found to be 5-to 8-fold more potent than VRC01, with an inhibitory concentration IC50 <50 mcg/mL against 96% of HIV-1 pseudoviruses representing the major circulating HIV-1 clades and IC50 <1 mcg/mL against 92% of HIV-1 viruses tested and displayed minimal levels of autoreactivity (3). VRC07-523LS was also shown to have a prolonged half-life over VRC07 by about 2-fold. *In vivo* proof-of-concept studies showed that VRC07-523LS is about 5-fold more potent than VRC01LS in Rhesus macaques and displays a longer half-life (9.8 days) than VRC07 (4.9 days) after a single dose at 10 mg/kg administered IV (3).

**Preclinical studies of VRC07-523LS**
The proposed VRC07-523LS dose for this study is based on human studies of VRC01, and preclinical and clinical studies of VRC07-523LS.

In nonhuman primate studies, a single dose of VRC07-523LS 10 mg/kg administered IV in cynomolgus macaques had a half-life of about 12 days, and persisted at least 28 days (last collection point) in rectal and vaginal secretions and tissues. Complete protection from SHIV-SF162P3 challenge was demonstrated with a single IV dose of VRC07-523LS at 20 mg/kg.

A repeat dose IV and SC toxicity study with VRC07-523LS was performed in male and female Sprague-Dawley rats in accordance with "Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies." Treatment with VRC07-523LS at doses up to 400 mg/kg/dose IV or 40 mg/kg/dose SC with three doses at 10 day intervals was generally well tolerated as most findings were reversible and no longer seen at the end of the recovery period.

Increased neutralization potency *in vitro* and prolonged half-life of VRC07-523LS correlate with improved protection against SHIV infection *in vivo* in animal studies, suggesting a potential clinical application against HIV-1 infection in humans in therapeutic settings.

Several *in vitro* preclinical safety studies were performed with VRC07-523LS to assess potential off-target binding. To measure potential anti-phospholipid cross-reactivity, binding of VRC07-523LS to cardiolipin was assessed using an enzyme-linked immunosorbent assay (ELISA) and demonstrated

minimal binding compared with 4E10, an earlier-generation HIV-1 specific mAb which binds strongly to cardiolipin. VRC07-523LS was also tested for cross-reactivity against a panel of various nuclear antigens using a licensed systemic lupus erythematosus diagnostic test kit (Luminex AtheNA Multi-Lyte® ANA-II test) and did cross-react with a small subset of nuclear antigens consistent with some reactivity with nuclear antigens. In addition, VRC07-523LS was assessed for anti-phospholipid properties in a clinical activated partial thromboplastin time (aPTT) assay and compared to the anti-HIV mAbs 4E10 and VRC01 as well as palivizumab; only 4E10 showed evidence of antiphospholipid activity. By immunohistochemistry, VRC07-523LS displayed minimal binding to HEp-2 cells at 50 mcg/mL and no binding at 25 mcg/mL (3).

A tissue cross-reactivity (TCR) study was performed in accordance with "Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies" to determine the potential cross-reactivity of VRC07-523LS with cryosections of human and Sprague-Dawley rat tissues. VRC07-523LS staining was similar between the human and rat tissues examined, although staining tended to be somewhat more intense and frequent in the human tissue compared to the Sprague-Dawley rat tissues. According to ICH S6 (R1), monoclonal antibody binding to cytoplasmic sites generally is considered of little to no toxicologic significance. See the Investigator's Brochure (IB) for further details.

**Clinical Studies of VRC01**

VRC-07-523LS is a similar product to VRC01 and its variant VRC01LS, and there is substantial clinical experience with both VRC01 and VRC01LS mAbs as described below.

**VRC 601**

VRC 601 (NCT01950325) was the first study of the VRC01 mAb in HIV-infected participants (31). It was a dose-escalation study to examine safety, tolerability, dose, PK, and anti- antibody immune responses. VRC 601 opened in September 2013 as a single site study at the NIH Clinical Center, Bethesda, Maryland and in total, 23 HIV-infected participants, including 15 aviremic ARV-treated participants and 8 viremic non-ARV treated participants, were infused with one or two doses of VRC01 at doses up to 40 mg/kg IV.

All IV infusions and SC injections were well tolerated with no serious adverse events (SAEs) or dose limiting toxicity (DLT). VRC 601 demonstrated evidence of VRC01-mediated antiviral effect. Analysis of the VRC 601 viral load data obtained from 8 viremic adults shows that VRC01 has a statistically significant *in vivo* virological effect on HIV viral load when administered as a single 40 mg/kg IV dose (**Figure 1**; (31)). None of these adults were taking ART when enrolled into the study and had not started ART during the time period when the viral load data were collected. Six of the eight adult participants had ≥1 $\log_{10}$ copies/mL decrease in viral load and two participants had a viral load drop of 0.26 and 0.18 $\log_{10}$ copies/mL respectively.

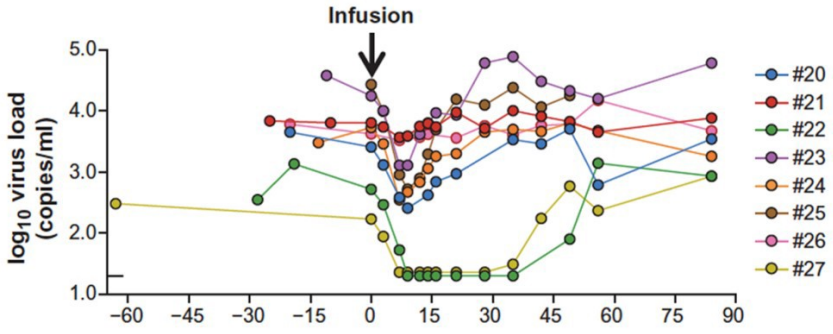



**Figure 1. The effect of VRC01 on plasma viral load after infusion.** Plasma virus load over time for eight viremic participants before and after infusion with VRC01 (day 0, indicated by arrow). Limit of detection of the assay is indicated with a tick at 20 copies/mL.

These interim data indicate the following for a single dose of VRC01 at 40 mg/kg IV: a statistically significant decline in viral load after infusion at days 5 to 16; a median time of 5 days to reach ≥ 0.5 $log_{10}$ decrease in viral load; and a median time of 7 days to greatest decrease in viral load post infusion.

In VRC 601, participants were administered a single dose of VRC01 at 40 mg/kg and, therefore, a sustained effect on viral load was not expected. However, data demonstrated an anti-viral effect and led to the hypothesis that repetitive VRCO1 dosing could have a beneficial clinical effect. This hypothesis was tested in two clinical trials, AIDS Clinical Trials Group (ACTG) A5340 and NIH 15-I-0140, in which ART suppressed participants underwent an analytical treatment interruption (ATI) after receiving VRC01 40 mg/kg (32). No product-related safety concerns were identified in the 24 participants enrolled. Viral rebound occurred despite VRC01 serum concentrations well above 50 mcg/mL with a mean time to rebound of 4 to 6 weeks (32). While the mean time to rebound was statistically significantly different from historical controls in previous ACTG ATI studies at 4 weeks, there was no difference at 8 weeks. VRC01 was also found to exert selection pressure on emergent viruses (**Figure 2,** (32)).

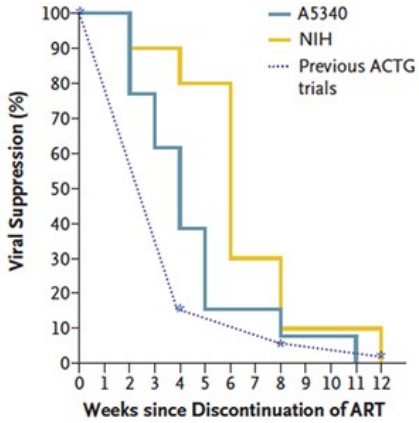



**Figure 2. Viral suppression mediated by VRC01.** Kaplan-Meier curve of plasma viremia suppression (< 200 copies/mL) after VRC01 administration in A5340 and NIH trial participants as compared with historical ACTG trials who underwent interruption of therapy without other immunotherapeutic interventions (40).

**VRC 602**

VRC 602 was a dose-escalation study of the VRC01 mAb in HIV-uninfected adults to examine safety, tolerability, dose, and PK of VRC01 (1). There were 3 open-label, dose escalation groups for IV administration and 1 double-blinded, placebo-controlled group for SC administration. All IV infusions and SC injections were well tolerated with no SAEs or DLTs. PK analysis from VRC 602 revealed a VRC01 terminal half-life of 15 days across all IV infused dose groups. After the first infusion, 28-day trough levels were 35 mcg/mL and 57 mcg/mL for the 20 mg/kg and 40 mg/kg dose groups, respectively. Following the second infusion, the 28-day trough values rose to 57 mcg/mL and 89 mcg/mL for the 20 mg/kg and 40 mg/kg dose groups, respectively. In addition, post infusion VRC01 retained the expected neutralizing activity in serum and no anti-VRC01 antibodies were detected (1).

**HVTN 104**

HVTN 104 was a phase 1 clinical trial designed to evaluate the safety and drug levels of VRC01 administered in multiple IV or SC doses and different dosing schedules to 88 healthy, HIV-uninfected adults at six HIV Vaccine Trials Network (HVTN) CRSs in four US cities: Boston, New York, Philadelphia, and Cleveland. The first participant enrolled in HVTN 104 on September 9, 2014 and study product administration for all participants was complete as of November 30, 2015. The study had 5 arms: Group 1 evaluated the IV administration of a 40 mg/kg loading dose, with 2 subsequent 20 mg/kg doses given at 8 week intervals. Groups 2, 4, and 5 evaluated 3 infusions of 40 mg/kg, 10 mg/kg, or 30 mg/kg, respectively, given 8 weeks apart. Group 3 evaluated 5 mg/kg given every 2 weeks subcutaneously for 24 weeks after an initial IV administration at 40 mg/kg in order to inform the design of perinatal prophylaxis studies.

A total of 249 IV infusions and 208 SC injections of VRC01 were administered in HVTN 104. The infusions and injections were well tolerated, with 28% of infusions and 14% of injections associated with mild pain and/or tenderness. 55% of VRC01 and 50% of placebo recipients experienced mild pain and/or tenderness at the infusion or injection site sometime during the trial. One participant experienced moderate pain and/or tenderness following an SC injection of VRC01. Mild infusion site erythema/induration reactions were reported for 2 VRC01 participants and 1 placebo recipient. Two moderate erythema/induration reactions were reported, 1 following IV VRC01 and 1 following VRC01 SC injection. For 76% of the infusions and injections administered in the trial, no systemic reactogenicity symptoms were reported. 56% of VRC01 and 75% of placebo recipients experienced systemic reactogenicity symptoms following at least one study product administration. These were all graded as mild in the placebo recipients. Among VRC01 recipients with any systemic symptom, the maximum severity was mild in 70%, moderate in 23%, and severe in 6% (3 participants). The most commonly reported symptoms were malaise/fatigue (30%), headaches (32%), and myalgias (26%).

The severe systemic reactogenicity symptoms reported in 3 VRC01 recipients in HVTN 104 are detailed as follows:

- One participant developed severe malaise, myalgia, headache and chills, mild nausea, and moderate arthralgia symptoms within 3 days after the first infusion of study product. The participant had a concomitant AE of laboratory confirmed influenza A infection diagnosed on Day 2 treated with ibuprofen. Symptoms resolved by Day 7.
- One participant reported a viral illness adverse event (AE) of moderate intensity beginning 3 days prior to the 9$^{th}$ SC injection (10$^{th}$ study product administration), characterized by nausea and vomiting, sore throat, runny nose but no fevers; a household contact was also ill. At baseline on Day 0 of the 9$^{th}$ SC injection, mild malaise/fatigue was still present. At the early assessment time point on Day 0, mild malaise/fatigue was still present and was accompanied by grade 1 nausea. Within 3 days of the injection, the participant developed severe malaise, myalgia, headache, chills, and arthralgia; these all resolved on Day 6, which was the date the AE for viral illness resolved. There was no reported use of concomitant medications for these symptoms.
- One participant reported severe malaise/fatigue on the day of the first infusion, resolving spontaneously the next day. During this reactogenicity period, this participant also reported a grade 1 headache on Day 1, resolving the next day.

There were no study product discontinuations due to reactogenicity symptoms. There were 235 AEs occurring in 70 participants (79.5%), with similar rates of occurrence across all treatment groups (81% among VRC01 recipients; 75% in placebo recipients). 74% of AEs were graded as mild, 22.5% as moderate, and 3.4% as severe. Only 9 AEs (3.8% of all AEs) occurring in 8 participants were deemed product-related by the investigators; all were mild and transient. Those occurring following VRC01 administration included elevations of hepatic transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] in 1 individual), elevated creatinine, neutropenia, localized injection site pruritus, diarrhea, generalized rash, and Varicella zoster infection. No VRC01- related hypersensitivity reactions or Cytokine Release Syndrome symptoms were observed during the study. Study product administration was discontinued in 8 participants. Reasons for discontinuing study product included: AEs (3 participants), relocation from study site (2), unable to adhere to visit schedule (1), unable to contact (1), and pregnancy (1).

**Safety summary of VRC01**

In summary, VRC01 has been well-tolerated when administered IV or SC. As of February 22, 2018, more than 2600 HIV-uninfected adult participants, approximately 88 HIV-infected adult participants and 40 HIV-exposed infants, have received one or more VRC01 administrations in unblinded VRC01 studies. There have been no SAEs assessed as related to VRC01 and no study safety pauses for AEs (Investigator's Brochure (IB), version 4.0, February 26, 2018).

VRC01 SC or IV administrations are generally associated with mild or moderate local reactions of pruritus, redness, and pain/tenderness, which resolve within a few minutes to a few hours after the administration is completed. When present, most systemic reactions after administration of VRC01 SC or IV are mild and include: malaise, myalgia, headache, chills, nausea, and joint pain. Unsolicited AEs of grade 3 or higher severity and deemed related to study product were not reported in these trials.

Other AEs attributed to study product administration have included mild or moderate AST elevation, ALT elevation, creatinine elevation, and decreased neutrophil count. Mild or moderate elevated transaminases were reported in 4 of 21 (19%) HIV-infected participants in VRC 601 (all of whom were taking ARVs). These laboratory changes resolved spontaneously and did not require discontinuation of study product administration. Among HIV-uninfected participants in VRC 602 or HVTN 104, 1 participant had grade 1 (mild) transiently elevated ALT assessed as possibly attributed to VRC01 in the VRC 602 study and 2 participants had grade 1 (mild) transiently elevated ALT/AST values assessed as related to VRC01 in HVTN 104. These 3 participants all received VRC01.

In HVTN 104, there were 3 product discontinuations for AEs, 2 of which were deemed related to study product infusion or injection. One discontinuation was for a 20-minute episode of chest tightness occurring approximately 25 minutes after SC injection of placebo in a participant who is a chronic smoker on nicotine replacement while continuing to smoke. One discontinuation was in a participant who reported a generalized rash that began three days after SC injection of VRC01, and resolved within 4 hours with ibuprofen and the application of an inert cream. The third discontinuation was in a young, otherwise healthy participant who experienced a brief episode of syncope, deemed not related to study product, approximately 4 hours after IV infusion of VRC01. In addition, one person in HVTN 104 had study product discontinued due to pregnancy occurring during the trial. Of note, the safety experience with VRC01 has remained consistent whether 1 or 2 doses were administered, as in VRC 601 and 602, or multiple doses were administered, as in HVTN 104. There were no observed trends toward recurrence of lab abnormalities or AEs deemed related to study product, nor observed increases in frequency or severity of local or systemic reactogenicity symptoms with multiple administrations of VRC01 in these trials.

The ongoing efficacy trials (HVTN 704/HPTN 085 and HVTN 703/HPTN 081) have accumulated significant additional VRC01 clinical experience; but these trials remain blinded and, thus, do not yet contribute to the unblinded VRC01 safety profile. However, in the ongoing blinded phase of these trials, urticaria or similar reactions have been reported at an overall frequency of about 1%. These reactions have been treated by stopping the infusion and providing supportive care, including anti-histamine and steroid therapy, as indicated, and no serious health consequences have been reported. No participants who experienced urticaria have been re-challenged with VRC01. Overall, VRC01 administration in the dose range from 10 to 40 mg/kg IV and at 5 mg/kg SC has been assessed as well-tolerated and safe for further evaluation.

**Clinical Studies of VRC01LS**

**VRC 606**
VRC01LS began evaluation in the VRC 606 study in November 2015. VRC 606 is a dose-escalation study to examine safety, tolerability, dose, and pharmacokinetics of VRC01LS. There were 4 open-label, dose escalation groups (Groups 1-4) to assess VRC01LS administered IV and SC once per participant and 2 open-label groups (Groups 5 and 6) to assess VRC01LS at 5 mg/kg SC or at 20 mg/kg IV administered every 12 weeks for a total of 3 administrations per participant. At 4 weeks post administration, serum concentrations of VRC01LS were approximately 5-fold higher than corresponding levels of VRC01. The half-life of VRC01LS in healthy HIV-uninfected adults was also approximately 4-fold longer than VRC01 with the maximal concentration observed 1-5 hours following IV administration (33).

The safety and PK data for the first 37 subjects who received administrations of VRC01LS have been published in 2018 (33). In summary, VRC01LS has been generally well tolerated when delivered IV or SC and there were no SAEs or dose-limiting toxicity (Investigator's Brochure, version 4.0, February 26, 2018).

The solicited local and systemic signs and symptoms following administration of VRC01LS were mild or moderate for local and systemic reactogenicity. Mild malaise and myalgia were the most common solicited AEs reported by 10 and 6 participants, respectively. The most frequent local reaction was pain/tenderness at injection site reported by 14 participants, but which occurred in only 2 participants by the IV route and which were mild in both cases; the remainder occurred with SC administration). No systemic symptoms were reported during product administration.

Six AEs were assessed as possibly related to VRC01LS administration and all were mild in severity. Only one of the treatment-related AEs occurred in one participant receiving VRC01LS via the IV route and included diarrhea (in the 5 mg/kg, IV group) and which resolved the same day. The remainder of the AEs possibly related to VRC01LS SC administration included diarrhea on the day of administration and which resolved the same day, lightheadedness on the day following administration and symptoms resolved within 24 hours, an injection site reaction which resolved 14 days post administration and elevated aminotransferase levels (56 and 69 IU/L) on Day 14 post injection and which both resolved within 15 days of onset. No volunteer had a positive HIV enzyme immunoassay (EIA) response during the study.

**VRC 607**
Evaluation of VRC01LS in HIV-infected adults in the VRC 607 study was initiated in April 2017. As of 01/17/2018, 7 participants have been enrolled and received VRC01LS at 40 mg/kg IV. No local or systemic reactogenicity were reported during VRC01LS administrations in VRC 607. None of the 7 participants reported any local reactogenicity on a 3-day diary card. As to systemic solicited reactogenicity, one participant reported mild symptoms of headache, chills, and nausea that resolved within 7-11 days after product administration. One SAE of gout was assessed as not related to study product administration. All other unsolicited AEs were Grade 1 (mild) or Grade 2 (moderate) and assessed as unrelated to study product.

**HVTN 116**
An additional study of VRC01LS, HVTN 116 [NCT02797171], is currently recruiting with 19 of 101 participants enrolled as of July 31, 2017. Serum VRC01LS concentrations as high as 20 mcg/mL were observed in VRC 606 at 165 days (approximately 24 weeks) after a 5 mg/kg IV infusion and were, on average, over 65 mcg/mL at 165 days after a 20 mg/kg IV infusion (**Figure 3**).

VRC01LS concentration on Day 84 after a single 5mg/kg SC administration was, on average, over 10 times greater than VRC01 concentration on Day 84 after a single 5mg/kg SC VRC01 administration. VRC01LS concentrations were over 40 times higher than those of VRC01 when comparing VRC01 concentrations on Day 84 after a single 20 mg/kg IV infusion to VRC01LS concentrations on Day 84 after a single 20 mg/kg IV infusion.

Overall, VRC01LS administration in the dose range from 1 to 40 mg/kg IV and at 5 mg/kg SC have been assessed as well-tolerated and safe for further evaluation.

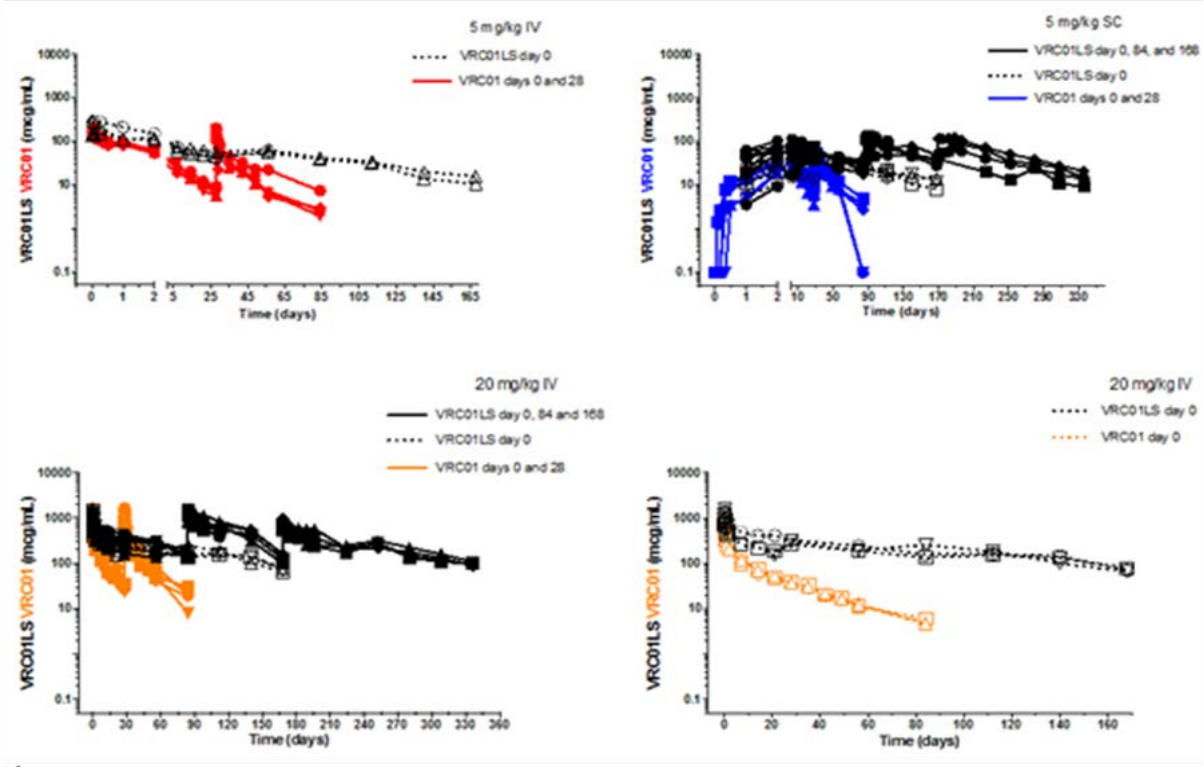



**Figure 3.** VRC01LS serum concentrations in VRC 606 compared to VRC01 serum concentrations with IV and SC administration.

**Clinical Studies of VRC07-523LS**

**VRC 605**

A phase 1, open-label, dose-escalation study of VRC07-523LS, VRC 605 (NCT03015181), is underway in healthy, HIV-uninfected adults to evaluate the safety and pharmacokinetics of 1 to 3 administrations of the antibody. The doses being evaluated are a single administration of 1 mg/kg and 5 mg/kg IV and SC, and 20 mg/kg and 40 mg/kg IV, and three administrations (q 12 weeks) of 5 mg/kg SC and 20 mg/kg IV VRC07-523LS. Study objectives include evaluating the safety and tolerability of the study regimen and the pharmacokinetics of each dose level; determining the presence or absence of detectable ADA to VRC07-523LS; and evaluating for evidence of functional activity of VRC07-523LS.

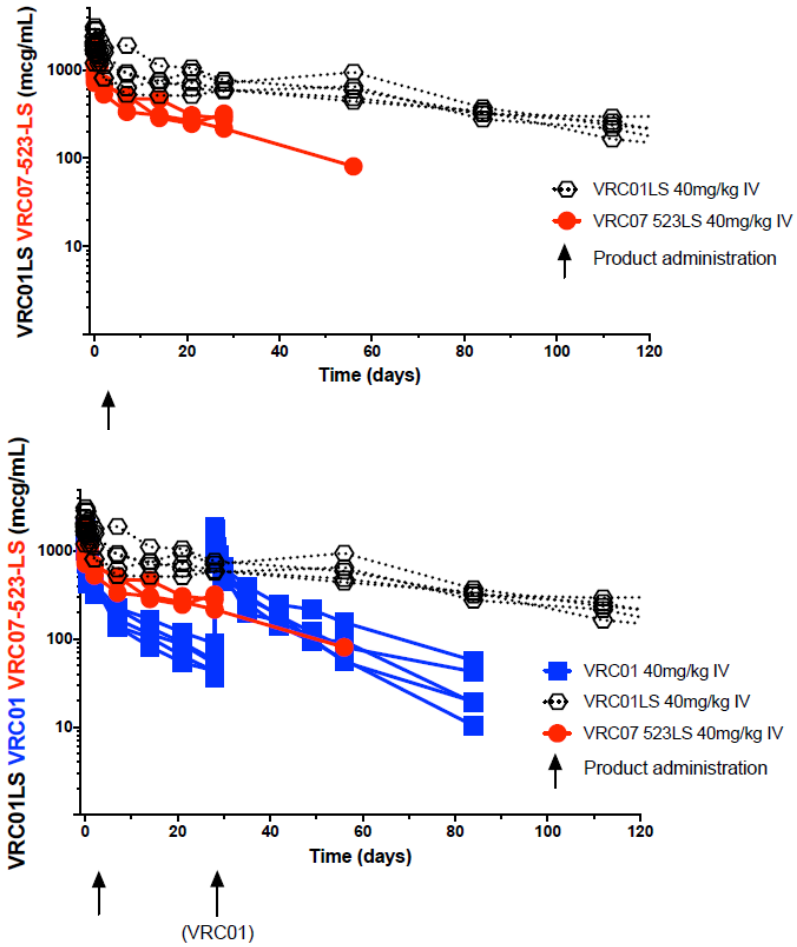



**Figure 4:** Group 5 received a 40mg/kg IV dose of VRC07-523LS and demonstrated serum concentrations >10 mcg/mL beyond 30 days and serum concentrations comparable to VRC01 40mg/kg IV and VRC01LS 40mg/kg IV.

PK results following VRC07-523LS infusion of 40mg/kg (the dose proposed in this protocol) are shown in **Figure 4**, showing serum concentrations >10 mcg/mL beyond 30 days. In addition, serum concentrations of VRC07-523LS have been found to be comparable to VRC01 40mg/kg IV and VRC01LS 40mg/kg IV.

Additional interim PK results for VRC07-523LS 5 mg/kg dose by IV and SC routes as compared with VRC01LS are shown in **Figure 5**.

As of January 15, 2018, the VRC 605 study is fully enrolled. Twenty-five (25) of 26 participants have received at least 1 dose of VRC07-523LS (25 IV and 12 SC). One participant withdrew prior to receiving study product. There have been no SAEs and no safety pauses for AEs. Overall, 15 and 25 participants (60%) have had at least one AE, with the maximum severity being Grade 1 for 7 participants, Grade 2 for 6 participants, Grade 3 for 1 participant, and Grade 4 for 1 participant. The grade 3 AE was for an elevated creatinine 56 days after last product administration based on an increase of 1.5 to 2 times the baseline value but still within the normal range, felt most likely related to dehydration following exercise. The Grade 4 AE was for elevated liver enzymes likely caused by concomitant initiation of fluoxetine, known to cause hepatoxicity and not related to VRC07-523LS. This event was independently evaluated by the NIH hepatology consult service. The product

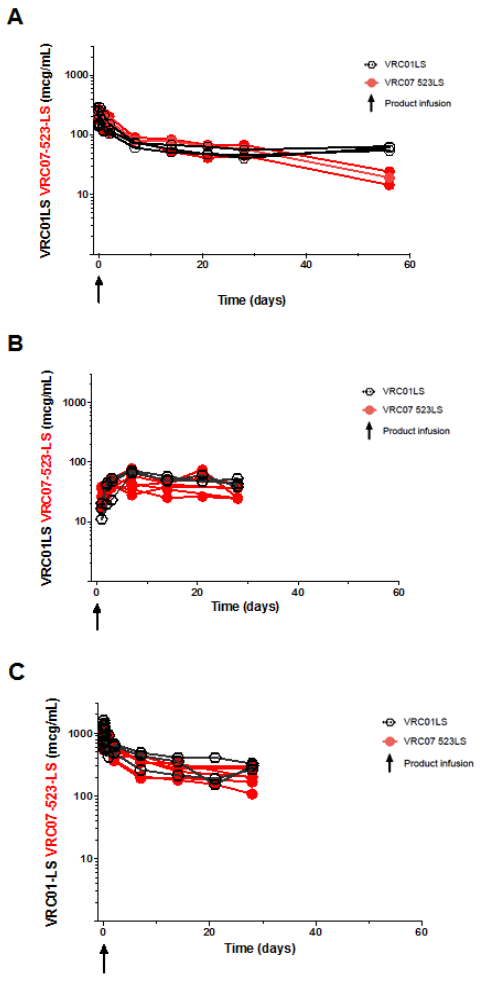



**Figure 5.** Interim VRC 605 PK results for VRC07-523LS. (A) 5 mg/kg IV (Group 2) shown with VRC01LS comparator (administrations completed). (B) 5 mg/kg SC (Group 5, no VRC01LS comparator (administrations ongoing).

administrations were discontinued for this participant due to the concomitant illness. While the participant was followed for safety, her liver enzymes decreased, but then increased again after starting on citalopram, which reinforced that the original event was likely incited by an underlying sensitivity to selective serotonin reuptake inhibitor (SSRI) medications.

Six mild of moderate AEs were assessed as related to study product, including mild dizziness, 4 occasions of infusion reactions (1 mild and 3 moderate, reported for 2 participants), and mild abdominal pain. All AEs assessed as related to the study product have resolved without residual effects.

Two participants developed infusion reactions shortly after IV product administration. Symptoms were typical of infusion reactions observed with other monoclonal antibodies. No atypical symptoms or delayed symptoms were seen. One participant enrolled in the 40 mg/kg IV group experienced a moderate infusion reaction with chills, rigors, fever, myalgia, and headache beginning 15 minutes after completion of the infusion. The participant was treated with acetaminophen and ibuprofen. All symptoms resolved within 12 hours. A separate participant in the 20 mg/kg IV group experienced 3 separate infusion reactions (n = 2 moderate, n = 1 mild) after each product infusion. The participant experienced nausea, chills, rigors, malaise, tachycardia, headache, myalgia (mostly back), and arthralgia (mostly hips and knees). Symptoms began 15 minutes to 1 hour after completion of each product administration and completely resolved within 12 hours. The participant was treated with acetaminophen and ibuprofen.

Overall, product administrations have been generally well tolerated with no unexpected reactions. For solicited local reactions in the week after VRC07-523LS administrations, one of 17 participants (5.9%) who received the product by IV administration reported mild bruising at administration site. For solicited systemic adverse events reported 3 days after product administration, 4 of 17 participants (25%) receiving VRC07-523LS IV reported mild or moderate systemic reactogenicity symptoms. The reported symptoms were malaise (n = 2 mild, n=1 moderate), myalgia (n = 2 mild, n = 1 moderate), mild headache (n = 2), and moderate chills (n = 2). Five of 8 participants (62.5%) receiving VRC07-523LS SC reported mild systemic reactogenicity symptoms: malaise (n = 3), myalgia (n = 2), headache (n = 3), chills (n = 1), nausea (n = 1), and joint pain (n = 2).

As of February 15, 2018, preliminary interim PK results are insufficient to determine the clearance rate or half-life for each dose. Based on interim data, the overall average compartmental half-life is currently

estimated to be 33 ± 10 days. The 28 day trough following one dose of VRC07-523LS 40 mg/kg IV was 272 (53 mcg/mL) (n=3) (IB, version 4.0, February 26, 2018).

**Vorinostat (VOR)**

VOR is a potent inhibitor of HDAC activity and binds directly to the catalytic pocket of HDAC enzymes. VOR, at low nanomolar concentrations, inhibits the enzymatic activity of HDAC1, HDAC2, and HDAC3 (Class I) and HDAC6 (Class II) (34-36). Concentrations of VOR that cause the accumulation of acetylated histones also induce cell cycle arrest, differentiation, or apoptosis of transformed cells (35). VOR induces apoptosis in a wide variety of transformed cells in culture, including cutaneous T-cell lymphoma (CTCL) cell lines, circulating atypical T-cells derived from patients with CTCL, human lymphoma cell lines and murine erythroleukemia (MEL) cells. VOR also inhibits proliferation of cultured transformed human cells derived from leukemias, non-small cell lung carcinomas, colon carcinomas, central nervous system tumors, melanomas, ovarian carcinomas, renal cell carcinomas, prostate and breast cancers. In cultured human transformed cell lines, VOR has synergistic or additive activity in combination with other cancer therapies, including radiation, kinase inhibitors, cytotoxic agents, and differentiating agents (34, 35, 37-44). In vivo, VOR demonstrates anti-neoplastic activity in a variety of rodent tumor models including xenograft models of human prostate, breast, and colon carcinoma. While it has been assumed that the effects of VOR on histone acetylation underpin its biological activities, a number of other proteins are regulated by histone acetyltransferases (HATs) and HDACs and may be targeted by VOR (45). Several non-histone proteins, (e.g., tubulin, Hsp90, and p53) are known to be reversibly acetylated on lysine residues and undergo hyperacetylation following exposure to VOR (46-48). Acetylation of these proteins may also contribute to the antitumor activity of VOR. Please refer to the VOR Clinical Investigator's Brochure (CIB), edition 8, 8/1/2013, for detailed information.

**VOR and HIV**

The U.S. Food and Drug Administration has approved Vorinostat (VOR) for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent, or recurrent disease on or following two systemic therapies. Due to its potency as an HDAC inhibitor, its effect on HIV infection within resting CD4+ T cells might be more profound than VPA. The effect of VOR was compared to VPA in J89, a Jurkat T cell line infected with a single HIV genome encoding the enhanced green fluorescence protein (EGFP) within the HIV genome. Histone acetylation at nucleosome 1 of the HIV promoter was assayed by chromatin immunoprecipitation. EGFP mRNA expression was monitored by flow cytometry and RTPCR, and p24 antigen production by ELISA. Both VPA and VOR induced chromatin remodeling at nucleosome 1, HIV transcription, and virus production in the J89 cell line (49). Limiting-dilution outgrowth assays compared the ability of VOR, VPA, and maximal mitogen stimulation to induce virus expression from the resting CD4+ T cells obtained at four occasions from three aviremic, cART-treated HIV-infected participants. HIV p24 capsid antigen was measured by ELISA, and infectious units per billion (IUPB) calculated by a maximum likelihood method. Comparable and clinically relevant concentrations of both compounds also induced virus outgrowth ex vivo from participants' cells at similar frequencies.

**Nonclinical Pharmacology of VOR**

VOR is approximately 71% bound to human plasma proteins over the range of concentrations 0.5 to 50 µg/mL. VOR has a low propensity to cause or be affected by drug-drug interactions. In animal models and in vitro human systems, the major pathways of metabolism of VOR involve glucuronidation and hydrolysis followed by β-oxidation. Additionally, the glucuronidation of VOR is mediated by multiple uridine diphosphate glucuronosyltransferase isozymes (UGTs), making it less susceptible to drug interactions through modulation of UGTs. VOR is not recovered intact in urine to any appreciable extent.

Therefore, compounds known to affect renal elimination are not expected to affect the pharmacokinetics of VOR. VOR is not an inhibitor of CYP drug metabolizing enzymes in human liver microsomes at steady state Cmax of the 400 mg dose (Cmax of 1.2 μM vs. IC50 of >75 μM). Gene expression studies in human hepatocytes detected some potential for suppression of CYP2C9 and CYP3A4 activities by VOR at concentrations higher (≥ 10 μM) than pharmacologically relevant. Thus, VOR is not expected to affect the pharmacokinetics of other agents metabolized by CYP enzymes. As VOR is not eliminated via the CYP pathways, it is anticipated that VOR will not be subject to drug-drug interactions when co-administered with drugs that are known CYP inhibitors or inducers. However, no formal clinical studies have been conducted to evaluate drug interactions with VOR.

**Nonclinical Toxicology of VOR**

VOR has been investigated in nonclinical acute and oral repeated-dose toxicity studies, reproductive, developmental toxicity studies, and genetic toxicity studies to support oral administration of this compound to humans. The main toxicities observed in animal models were weight loss and loss of appetite, apparent hemolytic anemia (rats only at 3.8 times the equivalent 400 mg human leukopenia (rats only at 1.3 times the equivalent 400 mg human dose), thrombocytopenia (male rats only, statistically significant change at 0.5 times the equivalent 400 mg clinically effective human dose, but within normal range at all doses), and gastrointestinal tract irritation (dogs only, at 8.5 times the equivalent 400 mg human dose). Although statistically significant and dose-dependent, many of the clinical pathology findings were within normal historical ranges indicating that they should not have major toxicological consequences. The toxicities appeared to be rapidly reversible within 12 to 14 days. There has been no evidence of cardiac toxicity based on electrocardiogram (ECG, dogs only), blood pressure (dogs only), heart rate (dogs only), creatinine kinase, organ weight, gross pathology, or histopathology assessments in studies up to one month duration. No serious, irreversible damage to any vital organ has been observed. Importantly, toxicities in rats and dogs were predictive of adverse effects in humans (anorexia, weight loss, fatigue). Toxicities present in animals would be manageable in the clinic, and the onset of serious toxicity is readily forecasted by prodromal symptoms. The nonclinical toxicity profile of VOR is acceptable for an oncology drug.

**Clinical Pharmacokinetics of VOR**

The pharmacokinetics of VOR following 400 mg single-dose in a fasted state; and 400 mg single- and multiple-doses in a fed (high-fat meal) state were evaluated in 23 participants in a Phase I study with relapsed or refractory advanced cancer using a validated assay. VOR is eliminated predominantly 1% of the dose recovered as unchanged drug in urine, indicating that renal excretion does not play a role in the elimination of VOR. Recovery of two pharmacologically inactive metabolites, O glucuronide of VOR (OG-V) and 4 anilino-4 oxobutanoic acid (4A4OA), in urine was more substantial. A population pharmacokinetic model using nonlinear mixed effects (NONMEM, ICON plc) demonstrated that a first order, transit-compartment absorption and linear elimination best described VOR concentration data. The structural model was: (1) $dXa/dt = -Ka \times Xa$, (2) $dXb/dt = Ka \times Xa - Kt \times Xb$, (3) $dXc = Kt \times Xb - (CLt/Vc \times Xc)$. Fixed effects: CLt (731 L/h), Vc (5.21 L), Ka (1.35 1/h), Kt (0.7 1/h). Random effects: CLt (26% CV), Vc (76.8%), Ka (73%). Residual error was: 0.0001 ng/mL (additive), 73.6% (proportional). An exponential model was used for inter-individual variability; and a heteroscedastic model was used for residual variability. Weight (power model, $Vctyp=Vcwt \times Weight\ (kg)^{\theta}$, $\theta=1.17$) was found to be a significant covariate on Vc.

In pre-clinical studies, we and others found that VOR, already licensed for use in patients with cancer, induces HIV chromatin acetylation and promoter expression in cell lines, and virus production *ex vivo* from the resting CD4+ T cells of HIV-infected participants on suppressive ART (49, 50). This effect was

achieved without upregulation of cell surface markers of activation, HIV co-receptors, or de novo HIV infection. We then demonstrated a significant increase in cell-associated RNA production following *in vivo* administration of VOR to ART suppressed individuals, the first direct proof-of-concept of latency reversal (29). In subsequent work, our group demonstrated that serial VOR doses for up to 4 weeks were well-tolerated and that a dosing interval of 72 hours resulted in a significant increase in in rca-HIV RNA levels within circulating resting $CD4^+$ T cells (51).

**Summary of Clinical Experience with VOR**
VOR has been studied in Merck Research Labs (MRL) sponsored studies, Investigator Initiated Study Protocols (IISP) and National Cancer Institute (NCI) sponsored studies. VOR has been orally administered in Phase I, Phase II, and Phase III clinical studies in participants with advanced solid tumors and hematologic malignancies. VOR has been studied both alone and in combination with other chemotherapy agents. As of 02-Jul-2012, over 5,000 participants have received at least one dose of VOR in studies sponsored by Merck and Co., Inc., the NCI, or independent Investigators.

The above studies have found VRC-523LS and similar mAbs as well as VOR to be safe and well-tolerated. Based on our prior work to define optimized VOR dosing intervals and pharmacokinetic data for VRC01LS in humans, the proposed study design will provide antibody exposure over the approximate four week period of latency reversal by VOR. We propose to evaluate the safety of combining VRC523-LS 40 mg/kg infusion followed by oral VOR and to explore the impact of this combined immunotherapy to direct ADCC to clear reactivated HIV-1.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

**Risk of VRC07-523LS**
There is limited human experience with administration of VRC07-523LS in HIV infected and uninfected persons. VRC 605 is evaluating VRC07-523LS prior to the start of this study, and thus far, there have been no SAEs or Grade 3 or higher AEs. Two participants developed infusion reactions shortly after VRC01-523LS administration by IV, with symptoms typical for infusion reactions observed with other monoclonal antibodies.

In addition, the similar CD4-binding site mAb VRC01 has been given to over 2600 participants in several phase 1 and phase 2 clinical trials. More than 8,000 infusions of 10 mg/kg and 30 mg/kg VRC01 have been given to HIV-uninfected adults in HVTN 704/HPTN 085 and HVTN 703/HPTN 081. Both VRC01 and VRC01LS are being tested in an ongoing phase 1 study (HVTN 116).

Standard infusion reactions to mAb administration are typically mild but may include fever, flushing, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, hypertension, pruritus, rash, urticaria, diarrhea, tachycardia, or chest pain (52). Most infusion reactions appear to result from antibody-antigen interactions resulting in cytokine release (52). Administration of mAbs may have a risk of severe reactions, such as acute anaphylaxis, serum sickness, angioedema, bronchospasm, hypotension, and hypoxia, the generation of anti-drug antibodies; they may also be associated with an increased risk of infections. However, these reactions are rare and more often associated with mAbs targeted to human proteins (52) or with the use of murine mAbs, which have a risk of eliciting human anti-mouse antibodies (53). Infusion of mAbs directed against cell surface targets on lymphocytes may

cause a reaction known as “cytokine release syndrome,” with clinical manifestations including fatigue, headache, urticaria, pruritus, bronchospasm, dyspnea, sensation of tongue or throat swelling, rhinitis, nausea, vomiting, flushing, fever, chills, hypotension, tachycardia, and asthenia (54). Cases of cytokine release syndrome occur most often in the first few hours after the first mAb dose, because the cytokine release is associated with lysis of the cells targeted by the mAb and the burden of target cells is greatest at the time of the first mAb treatment (54).

Since VRC07-523LS targets a viral antigen rather than human cell surface antigens and is a human mAb, severe infusion reactions are expected to be rare. Most infusion-related events occur within the first 24 hours after beginning administration.

1. Mild Reaction to mAb Administration:

   Standard infusion reactions can occur and most appear to result from antibody-antigen interactions resulting in cytokine release (53, 54). These reactions include:

   - fever
   - flushing
   - chills
   - rigors
   - nausea
   - vomiting
   - pain
   - headaches
   - dizziness
   - tachycardia
   - chest pain

2. Severe Reaction mAb Administration:

   These reactions are rare and more often associated with mAbs targeted to human proteins or with the use of murine mAbs, which have a risk of eliciting human anti-mouse antibodies (42) and include:

   a) acute anaphylaxis
   b) serum sickness –this type of reaction is usually delayed and these symptoms are may not appear until several days after the exposure to the mAb. This type of reaction is more common with chimeric types of mAb (43).
      a. Symptoms include urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after the exposure to the mAb and are noted to be more common with chimeric types of mAb (43).
   c) angioedema
   d) bronchospasm
   e) hypotension
   f) hypoxia
   g) the generation of anti-drug antibodies (ADA)
   h) increased risk of infections

3. Cytokine Release Syndrome

   These symptoms occur most often in the first few hours after the first mAb dose, because the cytokine release is associated with lysis of the cells targeted by the mAb and the burden of target cells is greatest at the time of the first mAb treatment (54).

- fever
- urticaria
- pruritus
- bronchospasm
- dyspnea
- fatigue
- chills
- tachycardia
- rhinitis
- headaches
- nausea
- vomiting
- flushing
- sensation of the tongue or throat swelling
- hypotension
- asthenia

4. Reactions related to the rate of infusion:

   These reactions have been described for several FDA- licensed mAbs. With licensed therapeutic mAbs, cytokine-mediated infusion reactions, including cytokine release syndrome, are typically managed by temporarily stopping the infusion, administering histamine blockers, and restarting the infusion at a slower rate (55). Supportive treatment may also be indicated for some signs and symptoms.

   To date, the clinical trial safety experience with VRC01-class mAbs has been reassuring.

   a) In HVTN 104, IV administration of VRC01 was generally well-tolerated with mild pain and/or tenderness commonly reported at the site of the IV infusion. Mild to moderate systemic reactogenicity symptoms were reported by VRC01 recipients following at least one of the infusions, but there was no clear relationship with frequency or severity to the dose of VRC01 (56).
   b) No hypersensitivity reactions or cytokine release syndrome symptoms were reported in HVTN 104 (56).
   c) The ongoing blinded HVTN 704/HPTN 085 and HVTN 703/HPTN 081 trials have reported an approximately 1% rate of urticaria or similar reactions.
   d) In the ongoing VRC 605 trial of VRC07-523LS, there have been no SAEs and no safety pauses.
   e) Severe reactions associated with mAb administration, such as acute anaphylaxis, serum sickness, anti-drug antibodies, and increased risk of infections have not been observed to date in trials of VRC01-class mAbs.

***Risks Associated with Vorinostat***

1. Reaction to VOR administration:
   The three major clinical categories of adverse experiences attributable to VOR include a constellation of gastrointestinal symptoms, constitutional complaints, and cytopenias. Most of the adverse experiences were manageable. In fact, most of the very common adverse experiences were reversible and could be managed using conventional supportive care for chemotherapy. On the whole, treatment with oral VOR was well tolerated for use in the outpatient oncology setting.

   Adverse experiences considered by the Investigators to be at least possibly related to VOR in ≥10 % of participants across all Merck & Co., Inc. sponsored VOR clinical studies include (in descending frequency): nausea, fatigue, diarrhea, anorexia, vomiting, thrombocytopenia,

anemia, weight decreased, blood creatinine increased, dysgeusia, hyperglycemia, neutropenia, and constipation.

UNC has studied the effect of VOR on latent HIV virus. Other research institutions (both in the U.S. and internationally) also used the drug for this purpose. In UNC studies, approximately 23 different participants, have received up to 47 doses of 400 mg VOR, with most people taking an average of 14 doses. Several of these participants took VOR in different studies. We have observed only mild toxicities that we felt were related to VOR. In all, we have seen very few side effects, and none of the side effects or abnormal labs observed were significant or required medical attention.

Participants are permitted to receive appropriate supportive care measures as considered appropriate by the Study PI (or designee) including:

a) *Diarrhea:* Diarrhea should be treated promptly with appropriate supportive care per guidelines. Supportive care should begin at the first sign of poorly formed or loose stool, occurrence of more bowel movements than usual in one day or unusually high volume of stool. Supportive care should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever.
b) *Dehydration*: Altered taste and decreased food and liquid intake are associated with VOR administration. Participants should also be advised to drink a lot of clear fluids (at least 2 liters/day) to help prevent dehydration.
c) *Nausea and Vomiting*: Nausea and vomiting should be managed according to standard practice.
d) *Anemia*: Treatment with VOR can cause dose-related anemia that may result in fatigue, lethargy, or shortness of breath. If hemoglobin is reduced during treatment with VOR, the incident will be evaluated and the dose will either be maintained or terminated in the case of toxicity.
e) *Thrombocytopenia*: Treatment with VOR can cause dose-related thrombocytopenia. If platelet counts are reduced during treatment with VOR, this incident will be evaluated and dosing will either be maintained or terminated in the case of toxicity.
f) *Hyperglycemia* has been observed. Serum glucose should be monitored. Adjustment of diet and/or therapy for increased glucose may be necessary.
g) *Hypokalemia or hypomagnesemia* should be corrected prior to administration of VOR, and monitoring potassium and magnesium in symptomatic participants (e.g., participants with nausea, vomiting, diarrhea, fluid imbalance, or cardiac symptoms.)
h) *Unknown effects, such as detectable HIV RNA* (viral load) and other factors related to HIV infection, with this participant population, since there is limited data on the use of VOR in this particular population.

2. Overdose

We include this section for completeness. A person who takes any dose of VOR more than prescribed will be considered to have taken an overdose. Specific information is not available on the treatment of an overdose. There are no noted adverse experiences reported when a person took an overdose of VOR. No specific antidote has been identified for an overdose of VOR.

Participants should be advised not to make up missed doses. If a participant has an episode of emesis after taking VOR, the participant should be instructed not to take an additional dose. If a

participant on this study takes more than the prescribed dose of VOR, he/she will be observed closely for signs of toxicity. Supportive treatment will be provided, as clinically indicated.

3. Pregnancy
   No human safety data for the use of Vorinostat during pregnancy are available. Vorinostat has been assigned to pregnancy category D by the FDA based on a study in animals which found that Vorinostat crosses the placenta and may harm the developing fetus.

***Risks Associated with Leukapheresis***

These include common side effects due to blood drawing. However, more serious side effects could occur such as flushing, infection due to contaminated equipment, and damage to red blood cells. These serious side effects occur in less than 1 in 10,000 procedures. No such adverse events have occurred in our prior studies.

The following are the most common:

a) Pain or bruising at the site of needle sticks
b) Phlebitis - Formation of a blood clot at the blood draw site
c) Citrate toxicity (10%)
    a. Oral paresthesia (tingling around the mouth)
    b. Paresthesia (tingling/cramping in hands, fingertips, and feet)
d) Stiffness in the arms due to the immobilization during donation
e) Fatigue or tiredness
f) Fluctuations in blood pressure or heart rate

Less common:

a) Infiltration – the needle dislodges and comes out of the vein causing the fluid to go into the tissue,
b) Muscle aches or cramps
c) Chills
d) Fever
e) Nausea or vomiting
f) Lightheadedness or headache
g) Vasovagal reaction resulting in decrease in BP and heart rate

Rare:

a) Seizures or fainting
b) Transient weight gain, ankle swelling, or increased urination for 24 hours due to fluid retention
c) Infection due to contamination of equipment
d) Skin rashes, flushing, or other allergic responses
e) Damage to or loss of red blood cells due to machine malfunction
f) Possibility of air entering the vein and causing chest pains, shortness of breath, or shock or death

***Risks of Blood Drawing***

Blood drawing may cause pain, and bruising and may infrequently cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. Problems from use of an IV for blood drawing are generally mild and may include pain, bruising, minor swelling or bleeding at the IV

site, and rarely, infection, vein irritation (called phlebitis), or blood clot. Risk will be minimized by using sterile technique and universal precautions.

***Risks of Intravenous Infusion***
Problems from use of an IV are generally mild and may include pain, bruising, minor swelling or bleeding at the IV site, and rarely, infection, vein irritation (called phlebitis), or blood clot. Risk will be minimized by using sterile technique and universal precautions.

The placement of an intravenous catheter can allow for the development of bacteremia because of the contact between the catheter and unsterile skin when it is inserted. This will be prevented through careful decontamination of local skin prior to catheter placement and through the use of infection control practices during infusion. Product contamination will be prevented by the use of aseptic technique in the pharmacy and universal precautions during product administration.

***Unknown Risks***

New therapies can lead to unexpected, incidental findings that could have a potential effect on the participant's health. Upon confirmation of a potential health or reproductive effect, the study team will notify participants impacted by the new information and will advise proper medical follow-up when indicated. If findings require more immediate medical attention, the study PI in conjunction with the study coordinators will assist participants in getting an appropriate care appointment.

***Study participation***
Participation in this study may make participants ineligible for other clinical trials for a period of time or indefinitely after completing this protocol. Participation in this study may make participants ineligible for future clinical trials with vorinostat.

### 2.3.2 KNOWN POTENTIAL BENEFITS

The addition of VOR and VRC07-523LS to a person's ART regimen or the donation of one's blood cells to this research study provides no direct medical benefits to participants. However, participation contributes to ongoing HIV research, potentially resulting in new treatments for HIV infection.

### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Given that most HIV-1-infected patients on effective ART have persistent low-level viremia and despite this viremia have blunted HIV-1 specific immune responses, interventions with the potential to improve HIV-specific immune clearance and limit viremia should be tested. Therapies that improve clearance of persistently HIV-1-infected cells will likely be a necessary component of any HIV remission or eradication strategy. Based on the data outlined above, there is sufficient expectation that the proposed treatment interventions will be safe and well-tolerated. This study seeks to evaluate whether a combination treatment will result in a reduction in the frequency of resting cell infection such that this result would advance the field. Although participants in this early phase study will most likely receive no direct benefit for their participation in this study, there remains a strong desire among HIV-infected individuals, and the HIV community at-large, to pursue HIV cure and remission strategies. The potential adverse effects, stigmatization, and financial costs encountered by HIV-infected persons receiving life-long antiretroviral therapy along with the potential harm of persistent immune activation/inflammation are strong reasons to pursue HIV cure and remission research. In short, an HIV cure or sustained

remission in the absence of ART remain desirable goals that would have substantial benefits for many individuals if achieved.

## 3 OBJECTIVES AND ENDPOINTS

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|---|---|---|
| Primary | | |
| To evaluate the safety and tolerability of combination therapy with VRC07-523LS and VOR in HIV-infected participants on ART. | <u>Safety</u><br>Occurrence of at least one ≥ Grade 3 adverse event including signs/symptoms, lab toxicities, and/or clinical events that is possibly, probably, or definitely related to VOR or VRC07-523LS any time from the first day of study treatment through Step 4.<br><br>Safety data will include local and systemic signs and symptoms, laboratory measures of safety/toxicity, and all AEs and SAEs. Safety data will be routinely collected throughout the duration of the study. | The study will use standard safety grades used in HIV clinical trials. Should these grades be exceeded, it is currently felt that such risks would be unacceptable in a research study of this nature. |
| Tertiary/Exploratory | | |
| 1. Explore the effect of two cycles of VRC07-523LS and VOR on the frequency of latent, resting CD4+ T cell infection.<br><br>2. Compare HIV RNA expression within resting $CD4^+$ cells in HIV-infected participants on stable ART before and after VRC07-523LS given with VOR at leukapheresis #1 (Step 1) and leukapheresis #2 (Step 4).<br><br>3. Explore the influence of VOR given with VRC07-523LS on low-level plasma | 1. Change in QVOA from resting CD4+ cells in HIV-infected participants on stable ART before and after VRC07-523LS given with VOR from baseline to post-VRC07-523LS/VOR.<br><br>2. Change in HIV RNA expression within resting CD4+ cells in HIV-infected participants on stable ART before and after VRC07-523LS given with VOR from baseline to post-VRC07-523LS/VOR.<br><br>3. Change in HIV-1 RNA by SCA from baseline to post-VRC07-523LS/VOR. | These various measures of persistent HIV infection will allow us to detect an effect of VOR and VRC07-523LS (if any), validate expected exposures to these agents, and seek evidence of selective pressure exerted by VRC07-523LS on persistent HIV. |

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|---|---|---|
| viremia as measured by single copy assay (SCA) in participants who maintain suppression on ART. | | |
| 4. Explore the impact of VOR and VRC07-523LS therapy on the quantity of integrated proviral DNA in T cell populations. | 4. Change in the chromosomally integrated viral reservoir as measured by quantitative-polymerase chain reaction (Q-PCR) from baseline to post-VRC07-523LS/VOR. | |
| 5. Characterize viral envelope sequences detected in plasma or cells that are not recognized by VRC07-523LS from baseline to post-VRC07-523LS/VOR. | 5. Change in diversity of viral envelope sequences detected in plasma or cells that are not recognized by VRC07-523LS from baseline to post-VRC07-523LS/VOR. | |
| 6. Evaluate the pharmacokinetics of VRC07-523LS and VOR and determine whether anti-drug antibody (ADA) to VRC07-523LS can be detected in recipients administered VRC07-523LS in combination with VOR. | 6. Serum concentrations of VRC07-523LS in combination with VOR. | |

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

This is a phase I, single-site study to evaluate the effects of VOR given in combination with VRC07-523LS on persistent HIV-1 Infection in HIV-infected individuals suppressed on ART.

We hypothesize that combination therapy with VRC07-523LS and VOR will be safe and well-tolerated by HIV-1-infected participants suppressed on ART.

This study will also explore the ability of a novel clearance modality (VRC07-523LS) to reduce the frequency of latent, resting CD4+ T cell infection when combined with a latency reversal agent (VOR).

This study will enroll up to twelve evaluable participants with durable viral suppression to complete all 4 Steps. We estimate that it will take approximately 8 months to complete enrollment.

All eligible participants will receive the same treatment. Each participant will receive a total of two (2) infusions of VRC07-523LS at 40mg/kg/dose and twenty (20) PO doses of VOR 400 mg. Participants will continue their baseline ART regimen throughout the study.

### 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is an open label, non-randomized study to validate the safety of VRC07-523LS when given with Vorinostat. For scientific aims, assays are performed before and after intervention.

### 4.3 JUSTIFICATION FOR DOSE

The dose of VOR (400 mg every (q) 72 hours) has been validated (51). The dose of VRC07-523LS has been validated at 40 mg/kg in study VRC 605 (see above).

The VRC07-523LS dose and timing of administration with combination with VOR is based on human studies of VRC01, preclinical and clinical studies of VRC01LS, preclinical and clinical studies of VRC07-523LS, and PK data for VOR in humans. PK results following VRC07-523LS infusion of 40mg/kg (the dose proposed in this protocol) are shown in **Figure 4 (above)**, showing serum concentrations >10 mcg/mL beyond 30 days which encompasses the duration of VOR dosing on the study.

In addition, serum concentrations of VRC07-523LS are comparable to VRC01 40mg/kg IV and VRC01LS 40mg/kg IV. Additional interim PK results for VRC07-523LS 5 mg/kg dose by IV route as compared with VRC01LS are shown in **Figure 5 (above)**. Panel A of **Figure 5** shows serum concentrations >10 mcg/mL through day 40 following infusion.

### 4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all Steps of the study including the last visit shown in the Schedule of Events in Section 1.3.

## 5 STUDY POPULATION

The study will enroll healthy, HIV-infected adults on ART and durably suppressed (HIV-1 RNA PCR <50 copies/mL for ≥ 24 months) who verbalize comprehension of the purpose of the study and provide written informed consent. Potential participants will be recruited and screened; those determined eligible, based on the inclusion and exclusion criteria, will be enrolled in the study. Final eligibility determination will depend on information available at the time of enrollment, including results of screening laboratory tests, medical history, and physical examinations.

Determination of eligibility, taking into account all inclusion and exclusion criteria, must be made within 30 days prior to enrollment unless otherwise noted in Sections 5.1 and 5.2.

## 5.1 INCLUSION CRITERIA

1. ≥ 18 years and < 65 years of age

2. Ability and willingness of participant to give written informed consent.
   *Note: Due to the lack of foreseeable benefit to study participants, mentally incompetent participants will not be enrolled.*

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

   A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

4. On continuous antiretroviral therapy (ART defined in 5.1.5) for at least 24 months prior to screening.

   *Note: Continuous ART prior to screening is defined as not missing more than 4 total days and never more than 2 consecutive days in the 3 months prior to screening.*

5. Permitted ART regimens include:

   *a)* At least 3 ART agents (not counting ritonavir if less than a 200mg total daily dose or cobicistat as one of the agents).

   *NOTE: One of the agents must include an integrase inhibitor, NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitors), or a boosted-PI (protease inhibitor).*

   OR

   Two (2) ART agents in which one of the agents is either a boosted PI or an integrase inhibitor.

   *NOTE: Other fully suppressive antiretroviral combinations will be considered on a case-by-case basis.*

   *NOTE: Prior changes in, or elimination of, medications for easier dosing schedule, intolerance, toxicity, improved side effect profile or within a drug class are permitted if an alternative suppressive regimen was maintained but not within 30 days prior to screening.*

   *<u>NOTE</u>: Changes in drug formulation or dose are allowed (e.g., TDF to TAF, ritonavir to cobicistat, or separate ART agent dosing to fixed-dose combination), but none within 30 days prior to screening.*

6. Ability and willingness of participant to continue ART throughout the study.

7. Able and willing to adhere to protocol therapy, schedule, and is judged adherent to antiretroviral therapy.

8. Plasma HIV-1 RNA <50 copies/mL at 3 time points in the previous 24 months prior to screening and never ≥50 copies/mL on 2 consecutive time points in the last 24 months.

   *NOTE: The documented plasma HIV-1 RNA must be performed by any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent.*

9. At least 1 documented plasma HIV-1 RNA result <50 copies/mL ≥24 months but ≤ 36 months prior to screening.

10. Plasma HIV-1 RNA level <50 copies/mL on an FDA-approved HIV RNA assay at screening, performed at US CLIA Certified Laboratory (or its equivalent).

11. CD4 cell count ≥ 350 cells/$mm^3$ obtained within 90 days prior to study entry, performed at any US CLIA Certified Laboratory (or its equivalent).

12. Hepatitis C (HCV) antibody negative result within 60 days prior to study entry or, if the participant is HCV antibody positive, a negative HCV RNA within 60 days prior to study entry.

13. Hepatitis B surface antigen (HBsAg) negative within 60 days prior to study entry.

14. Interferon-gamma release assay (IGRA) for tuberculosis (TB) with negative results within 60 days prior to study entry.

    *NOTE: Participants with a prior positive TB IGRA and documented evidence of completed prophylaxis treatment may enroll in the study and do not need to undergo IGRA at screening. Participants with a prior positive IGRA who have not completed prophylaxis treatment will be excluded.*

15. Men and women who are not of reproductive potential (see below) are eligible without requiring the use of contraceptives. Acceptable documentation of sterilization and menopause is specified below.
    a) Written or oral documentation communicated by clinician or clinician's staff of one of the following:
       a. Physician report/letter
       b. Operative report or other source documentation in the patient record (a laboratory report of azoospermia is required to document successful vasectomy in any partner assigned male sex at birth, hysterectomy, oophorectomy, non-surgical permanent sterilization, or tubal ligation.)
       c. Discharge summary
    b) Documented or participant-reported absence of a period for ≥ one year must be confirmed with Follicle stimulating hormone-release factor (FSH) measurement elevated into the menopausal range as established by the reporting laboratory.

16. All participants must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization, egg donation) while on study and for 4 months after their last infusion.

17. All men participating in sexual activity that could lead to pregnancy must agree to consistently use at least one of the following forms of birth control for at least 21 days prior to Visit 3 and for 4 months after their last infusion:
    a) Condoms (male or female) with or without a spermicidal agent
    b) Diaphragm or cervical cap with spermicide
    c) Intrauterine device (IUD)
    d) Tubal ligation
    e) Hormone-based contraceptive
    f) Successful vasectomy

    *NOTE: For female partners who are receiving ritonavir or cobicistat, estrogen-based contraceptives are not reliable and an alternative method should be suggested.*

18. Ability and willingness to provide adequate locator information.

19. Ability and willingness to communicate effectively with study personnel; considered reliable, willing, and cooperative in terms of compliance with the protocol requirements.

20. Adequate vascular access for infusion and leukapheresis.

21. Able to swallow pills without difficulty.

22. Agrees not to enroll on another study of an investigational research agent during the study period.

    *NOTE: Investigational research agent is defined as any unlicensed investigational drug not yet approved by the FDA for intended use in humans.*

23. Adequate organ function as indicated by the following laboratory values:

| System | Laboratory Value |
|---|---|
| **Hematological** | |
| Absolute neutrophil count (ANC) | ≥1,500 /mcL |
| Platelets | ≥125,000 / mcL |
| Hemoglobin | ≥ 13 g/dL (male) and ≥ 11 g/dL (females) |
| **Coagulation** | |
| Prothrombin Time or INR | ≤1.5x upper limit of normal (ULN) |
| **Chemistries** | |
| $K^+$ levels | Within normal limits |
| $Mg^{++}$ levels | ≥ 1.2 mEq/L but <1.5 x ULN |
| Glucose | Screening serum glucose ≤ Grade 1 (fasting or non-fasting) |

| | |
|---|---|
| Albumin | ≥ 3.3 g/dL |
| **Renal** | |
| Creatinine clearance determined by the CKD-Epi equation found at: *https://www.qxmd.com/calculate/calculator_251/egfr-using-ckd-epi* | eGFR > 60mL/min |
| **Hepatic** | |
| Serum total bilirubin | Total bilirubin < 1.5 X ULN. If total bilirubin is elevated, direct bilirubin must be < 2 times the ULN range.<br>***NOTE**: If participant is on an atazanavir-containing therapy, then a direct bilirubin should be measured instead of the total bilirubin and must be ≤ 1.0 mg/dL.* |
| AST (SGOT) and ALT (SGPT) | ≤ 1.25 X ULN |
| Alkaline Phosphatase | ≤ 2.0 X ULN |
| Lipase | < 1.6 X ULN |
| **Urinalysis** | |
| Urine Protein | Negative or trace allowed |

ULN = upper limit of normal

## 5.2 EXCLUSION CRITERIA

1. Known allergy or sensitivity to components of VOR

2. Serious adverse reactions to VRC07-523LS formulation components, VRC01 or VRC01LS, including history of anaphylaxis and related symptoms such as hives, respiratory difficulties, angioedema, and/or abdominal pain.

3. Women without documentation of an FSH level indicating menopause, hysterectomy or bilateral oophorectomy, bilateral tubal ligation, or non-surgical sterilization.

4. Receipt of compounds with HDAC inhibitor-like activity, such as valproic acid within 30 days prior to screening. Potential participants may screen after a 30-day washout period.

5. Any investigational research agent within 30 days before study entry.

   *NOTE: Co-enrollment in observational only studies is permitted.*

   *NOTE: Co-enrollment in other studies using FDA approved medication that are not otherwise listed as prohibited will be evaluated by the study PI and permitted on a case-by-case basis.*

6. Plasma HIV RNA ≥150 copies/mL in the 6 months prior to screening.

7. Weight > 115 kg

8. Untreated syphilis infection (defined as a positive rapid plasma reagin (RPR) without clear documentation of treatment).

   *NOTE: In cases of untreated syphilis, participant may rescreen following documentation of adequate treatment of syphilis*

9. Current treatment for HCV with antiviral therapy or participants who have received HCV treatment within 6 months prior to screening.

10. Use of any of the following within 90 days prior to entry: immunosuppressive, immunomodulatory, cytokine, or growth stimulating factors such as systemic corticosteroids, cyclosporine, methotrexate, azathioprine, anti-CD25 antibody, IFN, interleukin-2 (IL-2).

    *Not Exclusionary: [1] corticosteroid nasal spray; [2] inhaled corticosteroids; [3] topical steroids for mild, uncomplicated dermatitis (see 5.2.20 below); or [4] a single course of oral /parental prednisone or equivalent at doses <2mg/kg/day and length of therapy <11 days with completion at least 30 days prior to enrollment.*

11. Current use of Coumadin, warfarin, or other Coumadin derivative anticoagulants.

12. Prior use of any HIV immunotherapy within 12 months prior to screening.

13. Prior use of an HIV vaccine prior to screening.

14. Prior receipt of more than three doses of Vorinostat.

15. Prior receipt of humanized or human mAbs, whether licensed or investigational, will have eligibility determined by the study PI on a case-by-case basis.

16. Received any infusion blood product, immune globulin, or hematopoietic growth factors within 90 days prior to study entry.

17. Pregnancy or breast-feeding.

18. History or other evidence of severe illness, malignancy, immunodeficiency other than HIV, or any other condition that would make the participant unsuitable for the study in the opinion of the investigator, for at least 90 days prior to screening.

19. History of autoimmune disease

    *Not exclusionary: Persons with mild, stable, and uncomplicated autoimmune disease that do not require immunosuppressive medication and that, in the judgement of the site investigator (or designee), is likely not subject to exacerbation and likely not to complicate AE assessments.*

20. Use of topical steroids over a total area exceeding 15 $cm^2$ within 30 days prior to Screening.

21. Treatment for an active AIDS-defining opportunistic infection within 90 days prior to Screening.

22. History of malignancy within the last 5 years.

    *NOTE: A history of non-melanoma skin cancer (e.g., basal cell carcinoma or squamous cell skin cancer) is not exclusionary with documentation of complete resection at least 3 months prior to enrollment).*

23. Compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric illness or a physical illness, e.g., infectious disease.

24. Known psychiatric, medical, occupational, or substance abuse disorders that would interfere with participant's ability to fully cooperate with the requirements of the trial as assessed by the study investigator (or designee).

    *Specifically exclusionary: [1] recent psychosis; [2] ongoing risk for suicide; or [3] recent history of suicide attempt or gesture.*

25. History or other clinical evidence of a significant medical condition that includes but is not limited to:
    a) A process that would affect the immune response
    b) A process that would require medication that affects the immune response
    c) Any contraindication to repeated injections, infusions, or blood draws
    d) A condition or process (e.g., chronic urticarial or recent injection or infusion with evidence of residual inflammation) for which signs and symptoms could be confused with reactions to the study product

26. Current anti-tuberculosis therapy

27. Diabetes Mellitus type 1 or type 2

    *Not exclusionary: type 2 cases controlled with diet alone or a history of isolated gestational diabetes*

28. History of coronary artery disease, congestive heart failure, or cardiac arrhythmia requiring current treatment prior to study screening.

29. Hypertension
    - If a person has been found to have elevated blood pressure or hypertension during screening or previously, exclude for blood pressure that is not well controlled. Well-controlled blood pressure is defined as consistently ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic, with or without medication, with only isolated, brief instances of higher readings, which must be ≤ 150 mm Hg systolic and ≤ 100 mm Hg diastolic. For these volunteers, blood pressure must be ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic at enrollment.
    - If a person has NOT been found to have elevated blood pressure or hypertension during screening or previously, exclude for systolic blood pressure ≥ 150 mm Hg at enrollment or diastolic blood pressure ≥ 100 mm Hg at enrollment.

      *Note: Elevated BP occurring during research leukapheresis procedures completed within the past 12 months are excluded from this requirement. Other isolated incidences of*

*elevated BP should be reviewed by study PI (or designee) to determine whether they are exclusionary. Acceptable isolated elevations must be noted as acceptable and signed by study PI or designee.*

30. Unstable asthma (e.g., sudden acute attacks occurring without an obvious trigger) or either of the following in the past 12 months:
    a) >1 exacerbation of symptoms treated with oral/parenteral corticosteroids;
    b) Emergency care, urgent care, hospitalization, or intubation for asthma.

31. Bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions).

32. Seizure disorder: History of seizure(s) within past three years or use of medications used to prevent or treat seizure(s) at any time within the past 3 years.

33. History of asplenia – absence of normal spleen function as indicated by:
    a) Splenectomy
    b) Sickle cell disease

34. History of hereditary angioedema, acquired angioedema, or idiopathic angioedema.

35. Prisoner recruitment and participation is not permitted.

## 5.3 LIFESTYLE CONSIDERATIONS

Each dose of VOR should be taken with food.

## 5.4 SCREEN FAILURES

Screening takes place in a step-wise manner and includes the completion of the following prior to enrollment:

1. Determination of HIV infection status
2. Documentation of stable continuous ART
3. Documentation of HIV RNA values below limit of quantitation for eligibility
4. Participant locator information
5. Assessment of baseline laboratory testing for continued safety monitoring

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. Minimal information required to be maintained with screen failure includes but is not limited to demography, screen failure details, eligibility criteria, and any SAE as well as clinical and laboratory data collected on persons at screening. The information collected on persons who fail screening and do not enroll will be retained in the screen failure section of the study file.

Potential participants who are unable to meet protocol-defined eligibility criteria at the Screening Visit may be eligible to re-screen again at the investigator's discretion.

If a screen failure or the failure to move to Visit 2 is due to the inability to meet one of the laboratory parameters (hematology, chemistry, HIV RNA level, or CD4+ T cell count), a retest of the failed criteria may be performed one time only.

## 5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment venues - There are several venues for recruitment available to the study team:

1. In the UNC ID Clinic and/or other local HIV clinics, there is a large pool of patients with long-term viral suppression on ART interested in participating in research. Many have previously participated in clinical studies. These individuals will be provided with the opportunity to discuss this study with their provider and the study coordinator.

2. Individuals who signed the UNC CFAR database consent, as well as those who signed the consent for the UNC Cure and PHI studies/database, will be identified and approached about the study. Primary care providers or the study coordinator, after consultation with their primary care provider, will provide information about the study and participation.

3. Individuals interested in participating in the study will be provided with appropriate study information and the opportunity to screen. All potential participants will be informed that:
    b) On rare occasions some of the serious side effects described in this protocol as well as other unpredicted adverse events can occur.
    c) Their participation in this study will allow researchers the opportunity to collect valuable information about the use of VRC07-523LS in individuals with durable viral suppression and its ability to improve immune responses.
    d) There will be no direct and immediate benefits to participants in this study, but information learned from this study may be of value to the participant and other people with HIV disease.

4. Targeted study demographics will be addressed. Recruitment for this study will largely be clinic-based, but participant advocacy groups will assist us, and local media may be used if needed. Our studies routinely enroll a representative sample of under-represented populations and women. We will also use recruitment materials such as flyers, palm cards, and posters and use social media websites and employ a community engagement plan.

# 6 STUDY INTERVENTION

## 6.1 STUDY INTERVENTION(S) ADMINISTRATION

### 6.1.1 STUDY INTERVENTION DESCRIPTION

**Vorinostat**:
The oral formulation of vorinostat is available as a 100 mg capsule. The 100 mg dose of vorinostat is provided in white opaque gelatin capsules (size 3). The capsules are supplied in HDPE (high-density polyethylene) bottles. Each bottle contains the protocol-specified count of vorinostat capsules.

**VRC07-523LS**
VRC07-523LS will be supplied as 10 mL glass vials with a 6.25 ± 0.1 mL fill volume and 3 mL glass vials with a 2.25 mL ± 0.1 mL fill volume, at a concentration of 100 ± 10 mg/mL. Each vial contains a clear, colorless to yellow isotonic, sterile solution essentially free of visible particles; some opaque or translucent particles may be present. The formulation buffer is composed of 50 mM histidine, 50 mM sodium chloride, 5% sucrose, and 2.5% sorbitol at pH 6.8.

### 6.1.2 DOSING AND ADMINISTRATION

**Vorinostat**
The study provides the Vorinostat 400 mg to the participants. In Step2 and Step 3, participants will take their first dose of VOR 400 mg PO at home two (2) days after the VRC07-523LS infusion. All participants will be dispensed 5 doses of VOR 400 mg at the infusion visits on Day 0 and Day 60. All participants will be provided with instructions for the safe administration of VOR at home. Participants will return to the CTRC on the day of their 5$^{th}$ dose (Day 14 and Day 74) for safety labs and evaluations and to receive their last 5 doses of VOR 400 mg.

Participants will return to the CTRC for safety assessments as per the SOE (Section 1.3). Participants will be monitored for the development of toxicities.

**VRC07-523LS**
VRC07-523LS will be administered as an IV infusion at the dose of 40 mg/kg in the CTRC. Participants will be monitored and observed for at least 60 minutes after the first infusion and for at least 30 – 60 minutes after the second infusion.

Reference Study Specific SOP entitled 'Infusion Guidelines and Emergency Management Plan' for details.

The following is performed prior to each administration of VRC07-523LS:
1. Initiate, maintain, and verify IV access.
2. Pre-dose assessments and Blood Sampling completed as listed in the SOE (Section 1.3).
3. The calculated dose will be administered based on the participant's weight obtained at Step 1, Visit 1 (baseline). Significant (≥ 10%) change in body weight from baseline should prompt recalculation of dose.

Administration of VRC07-523LS:
1. VRC07-523LS will be administered as an IV infusion:
    a. Day 0 (1$^{st}$ infusion) VRC07-523LS will be infused over 60 minutes using a volumetric pump
    b. Day 60 (2$^{nd}$ infusion) will be infused over 60 minutes using a volumetric pump
2. Vital Signs: Taken immediately before infusion (up to 3 minutes before the infusion); at 15, 30, 45, and 60 minutes after the start of infusion; and at the end of infusion
3. An in-line filter infusion set must be used for all VRC07-523LS administrations (Reference SOP). The pharmacist will supply the in-line filter and the infusion tubing set for delivery to the clinical setting.
4. The infusion rate may vary based on the total volume needed to administer the full dose. The total time needed to administer the dose may be longer than 60 minutes based on factors such as participant tolerance, but should be completed no more than 4 hours after the product is prepared. Infusion access should be maintained and the participant observed for a minimum of

60 minutes following completion of the first infusion and at least 30 – 60 minutes following the completion of the 2nd infusion.

Post Infusion Monitoring:
Each participant will be monitored for a minimum of 60 minutes on site following receipt of their 1st VRC07-523LS infusion. Post infusion monitoring for the 2nd infusion will be at least 30 – 60 minutes. Monitoring will occur in the CTRC. During the monitoring period, participants are observed for clinical AEs and the following procedures are performed:

1. Vital Signs: Following the infusion: every 15 minutes up to 60 minutes after the completion of 1st infusion and every 15 minutes up to 30 - 60 minutes after completion of the 2nd infusion.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1 ACQUISITION AND ACCOUNTABILITY

Study products will be provided directly to the UNC Investigational Drug Services (IDS) by Merck (VOR) and the VRC (VRC07-523LS). The primary IDS pharmacist will be responsible to the study PI for maintaining study drug accountability, reconciliation, and record maintenance during the study, including documentation of the amount of both study treatments (VRC07-523LS and VOR) received in IDS and the amount administered to each participant.

VRC07-523LS and VOR will be stored and dispensed by the UNC Hospitals IDS Pharmacy by prescription on a participant-specific basis. The IDS clinical supplies storage area will be monitored by the IDS staff for temperature consistency.

Vials containing VRC07-523LS and VOR will be stored in an appropriate, locked room accessible only to IDS pharmacy personnel, the Investigators, or designated study personnel. The IDS staff's responsibilities include maintaining, monitoring, and documenting the temperature in the pharmacy supply storage area per institutional guidelines.

### 6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

**Vorinostat**
VOR (N-hydroxy-N'-phenyl-octane-18-diotic acid diamide, N hydroxy-N'-phenyl (9CI) octanediamide, suberoylanilide hydroxamic acid, also known as SAHA, or MK- 0683) is an orally available HDAC inhibitor. The physical and chemical properties of VOR are listed in the table below.

Properties of VOR

| | |
|---|---|
| Molecular Formula | C14H20N2O3 |
| Molecular Weight | 264.32 |
| Physical Appearance | White to light orange powder |
| Solubility | Water (pH = 11.2) ≤5 mg/mL |
| Moisture (Karl Fischer) | ≤1% |
| Melting Point | 159.5 to 160.5°C |
| pKa | 8.5 and 11.1 |
| Hygroscopicity | None |

| | |
|---|---|
| Hydrates | None |
| Chirality | None |

The oral formulation of VOR is available as a 100-mg capsule. Each 100 mg ZOLINZA capsule for oral administration contains 100 mg Vorinostat and the following inactive ingredients: microcrystalline cellulose, sodium croscarmellose and magnesium stearate. The capsule shell excipients are titanium dioxide, gelatin, and may contain sodium lauryl sulfate.

**VRC07-523LS (Labeled as VRC07-523LS HIV mAb Drug Product VRC- HIVMAB075-00-AB)**
VRC07-523LS will be supplied as 10 mL glass vials with a 6.25 ± 0.1 mL fill volume and 3 mL glass vials with a 2.25 mL ± 0.1 mL fill volume, at a concentration of 100 ± 10 mg/mL. Each vial contains a clear, colorless to yellow isotonic, sterile solution essentially free of visible particles; some opaque or translucent particles may be present. The formulation buffer is composed of 50 mM histidine, 50 mM sodium chloride, 5% sucrose, and 2.5% sorbitol at pH 6.8.

Vials are intended for single use only and thus do not contain a preservative.

### 6.2.3 PRODUCT STORAGE AND STABILITY

**Vorinostat:**
Vorinostat capsules should be stored at room temperature (do not store above 30°C) in a dry, limited-access area. Care should be taken to maintain acceptable storage temperature. Vorinostat capsules should not be opened or crushed and must be administered whole.

**VRC07-523LS:**
VRC07-523LS product label designates the long-term storage as -35°C to -15°C (-31°F to 5°F). Clinical site storage in a qualified, continuously monitored, temperature-controlled freezer with temperatures from -45°C to -10°C (-49°F to 14°F) is acceptable.

After thaw, VRC07-523LS vials may be stored for up to 24 hours at room temperature (maximum 27°C). If vials are not used within that time, they may then be refrigerated for up to 14 days at 2-8°C. If stored at 2-8°C, vials must be equilibrated at controlled room temperature (maximum 27°C) for a minimum of 30 minutes and may be held at room temperature for up to 8 hours prior to product preparation. Product may not be stored in direct sunlight.

### 6.2.4 PREPARATION

Both VRC07-523LS and VOR will be stored and prepared in the UNC IDS Pharmacy.

The clean-up and disposal of spilled, wasted, or unused medication and used syringes must be documented appropriately (i.e., witnessed) in accordance with applicable federal regulations, Good Clinical Practice (GCP) procedures, and the procedures for handling biohazardous substances.

**Vorinostat**
There is no preparation for the administration of VOR.

**VRC07-523LS**

In this trial, the dose is limited or established based on the participant's weight. In calculating the dose to administer and the number of vials to thaw, it should be assumed that the concentration is 100 mg/mL and that a volume of at least 6 mL can be withdrawn from a vial. Preparation of VRC07-523LS for IV administration will require a 100 mL bag of 0.9% sodium chloride, USP (normal saline). Note that the normal saline bags referred to as "100 mL bags" in the IV administration instructions will typically have 103 mL volume before any VRC07-523LS is added and this is acceptable in context of the instructions below.

1. Preparation of study product

   Prior to preparation of the first infusion (Day 0), a new prescription will be sent to the IDS pharmacy. The prescription MUST contain the participant's weight based upon the participant's weight at Step 1 Visit 1.

   Any changes in weight of more than 10% (between the weight obtained at Step 1 Visit 1 and the weight on the day of the first infusion or between the weight used at the 1st infusion visit and the weight on the day of the 2nd infusion visit) will require a new prescription, which includes the new weight, and written so that product can be prepared based on that weight change.

   Pharmacists should keep in mind that the preparation instructions below are considered medium risk per USP 38 General Chapter Physical Tests / <797> Pharmaceutical Compounding - Sterile, and should follow the requirements of their country, their institution, and their pharmacy regulatory authority regarding these procedures.

   VRC07-523LS is a highly concentrated protein solution and may develop white, opaque to translucent particles after thawing. When particles are observed, they may disappear after a few hours at room temperature or storage at 2°C to 8°C.

   Ensure that only the required vials are present in the preparation unit during dilution and that medication labels are strictly segregated to avoid mix-ups.

2. Thawing

   a) Thaw vial(s) for a minimum of 1 hour at controlled room temperature (maximum 27°C) after removing from the freezer.

      Following thaw, unopened vials of VRC07-523LS may be stored for up to 24 hours at controlled room temperature (maximum 27°C) and/or up to 2 weeks (14 days) at 2°C to 8°C.

   b) Keep the material at room temperature during the entire preparation period until use, up to the maximum storage times described in section 6.2.3.

   c) Prior to preparation for administration, vials should be swirled for 30 seconds with sufficient force to re-suspend any visible particles, yet avoiding foaming. DO NOT SHAKE THE VIALS. If particles are observed, return the vials to 2°C to 8°C storage. If the particles re-dissolve within the maximum storage times, described in section 6.2.3 for 2°C to 8°C

storage, the vials may be used for product preparation. If particles continue to be observed, do not use the vialed product for IV administration.

Refrigerated product must be equilibrated at controlled room temperature (maximum 27°C/80.6°F) for a minimum of 30 minutes before preparation and must be used within 4 hours of any subsequent return to room temperature.

d) If the thawed material is not administered within 24 hours of thawing, do not use for another participant.
   - Any empty vials, unused portion of entered vials, or unused IV solution which contains VRC07-523LS should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

e) Preparation is to be done using aseptic technique, in a limited access, laminar flow biosafety cabinet. Ensure that only the required vials are present in the preparation unit during dilution and that medication labels are strictly segregated to avoid mix-ups.

3. Intravenous Infusion Preparation Instructions:

a) After thawing, if product was refrigerated again at 2-8°C, vials of VRC07-523LS should be equilibrated to controlled room temperature (maximum 27°C) for a minimum of 30 minutes and may be held at room temperature for up to 8 hours prior to product preparation.

b) Calculate the total milligrams of VRC07-523LS required based on the participant's weight and 40 mg/kg.
   - Remove the total number of vials required from storage based on a 6 mL or 2 mL withdrawal volume containing 600 mg or 200 mg of VRC07-523LS, respectively.

c) Gently swirl thawed vials for 30 seconds to avoid foaming. DO NOT SHAKE VIALS. Keep the vials upright at all times until ready to withdraw the contents. Do not invert the vial during inspection.

d) Observe vials for particles. If particles are observed, refer to the thawing instructions for further information, section 6.2.4.2.

e) Using aseptic technique, add the calculated volume of VRC07-523LS (total calculated milligrams of VRC07-523LS) to 100 mL IV bag of Sodium Chloride Injection, USP 0.9% that will also permit the addition of the required calculated volume of VRC07-523LS. Alternatively, if the full VRC07-523LS dose volume cannot be accommodated in IV bag containing the 100 mL of Sodium Chloride Injection, USP 0.9%, please refer to the - Pharmacy Manual for further preparation instructions.

The thawed VRC07-523LS product will be added to Sodium Chloride Injection, USP 0.9% 100 mL IV solution bag using aseptic technique. The 100 mL bag of normal saline has the capacity to accept up to 50 mL of added product and this should be sufficient to accommodate all the planned dose levels for the eligible participants in this study.

f) After preparation for administration in IV bags, VRC07-523LS must be completely administered within 4 hours of preparation, including infusion time, when stored at room temperature (maximum 27°C/80.6°F).

Additionally, after product preparation in IV bags, the prepared VRC07-523LS may be stored at 2°C to 8°C up to 48 hours including the infusion time. Product may not be stored in direct sunlight. If stored at 2°C to 8°C, prepared product must be equilibrated at room temperature (maximum 30°C) for a minimum of 30 minutes prior to product administration.

g) Label the IV bag with:
- the participant name,
- DOB,
- participant identifier,
- participant weight,
- the dose of VRC07- 523LS at 40 mg/kg,
- the total amount (mg) of VRC07-523LS added to the 100 mL bag of normal saline,
- the final volume of the bag, and
- lot number

The prepared IV label should also be labeled with DO NOT INFUSE after date and time as follows:
- 48 hours if stored at 2°C to 8°C
- 4 hours, including completion of infusion, if stored at controlled room temperature (not to exceed 27°C/80.6°F)
- Product may not be stored in direct sunlight

h) Any unused portion of a VRC07-523LS vial will not be used for another participant. Any empty vials, unused portion of entered vials, or unused IV solution which contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

4. VRC07-523LS Disposition

a) The empty vials and the unused portion of a vial will be discarded in a biohazard containment bag and incinerated or autoclaved.

b) Any unopened vials that remain at the end of the study will be returned to the production facility or discarded at the discretion of the sponsor in accordance with policies that apply to investigational products.

c) Partially used vials will not be administered to other participants or used for in vitro experimental studies. These vials will be disposed of in accordance with institutional or pharmacy policy.

## 6.3 STUDY INTERVENTION COMPLIANCE

Participants will keep a daily diary of solicited AEs for both local and systemic symptoms for 3 days after each administration of VRC07-523LS.

## 6.4 CONCOMITANT MEDICATIONS

Medications to be reported are prescription medications, over-the-counter medications, and supplements.

All routine prescription medications, over-the-counter medications, supplements, and study provided medications and investigational products will be entered in the study-specific database, starting at the time of enrollment through the EOS.

Whenever a concomitant medication is initiated or a dose changed, investigators must be informed. The study PI as well as all other investigators and clinical personnel on this study are responsible for reviewing the concomitant medications' and study agents' most recent package inserts, investigator's brochures, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

**Prohibited Medications**

1. Prohibited HIV ART: Ongoing use of investigational ART. Prior use of investigational ART is permitted, provided it has been replaced with another class of ART and last dose was taken >90 days prior to study screening visit;
2. Concomitant use with oral or parenteral corticosteroids, immunosuppressive agents (including but not limited to azathioprine, and cyclosporine) or any immunotherapy or immunomodulatory agents;
3. Use of any agent that suppresses lymphocytes or monocyte function;
4. Use of chemotherapeutic agents, growth factors, cytokines, or chemokines, white lineage colony stimulating factors (e.g., granulocyte-colony stimulating factor [G-CSF] and GM-CSF);
5. Chronic use of topical corticosteroids that are applied to large areas of the skin (exceeding the cumulative area of the palm of the participant's hand) or any corticosteroids or antihistamines used on or near the infusion site.
6. Standard and live vaccinations (e.g., varicella, measles, mumps, rubella, MMR; yellow fever, oral polio) are permitted but timing of vaccine must be discussed and approved by the study PI or designee.
7. Antihistamine can be administered only if needed to treat an anaphylactic reaction.

# 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 DISCONTINUATION OF STUDY INTERVENTION

Participants for whom study interventions are discontinued should be counseled on the importance of continuing with the study and strongly encouraged to participate in follow-up visits and protocol-specified procedures.

The study will replace all participants who withdraw for reasons unrelated to drug toxicity. If participant withdrawal occurs prior to the initiation of the VRC07-523LS infusions (Step 2), the participant will have inadequate data, and therefore "new" replacement participants can be enrolled. These participants will not be required to return for additional study visits.

Participants who are withdrawn for safety or drug toxicity reasons will continue on study but off study treatment for safety assessments per the end of treatment study visit (see SOE in Section 1.3). Analyses will be completed on all participant samples, including blood, collected at the end of treatment study visit. The data may or may not be included in the final analyses but all clinical safety data will be included in the final Clinical Study Report (CSR).

Participants who are no longer on treatment but are still followed on the study (with safety evaluations obtained per the SOE in Section 1.3) can be terminated from the study for the following reasons:

- Uncontrolled intercurrent illness that prevents continuing study follow-up or regular study visits.
- Noncompliance with protocol-required evaluations.
- Participant request for discontinuation from the study, i.e., withdrawal of consent.
- The Sponsor, Investigator, or regulatory agency terminates the study.

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

**Study Treatment Discontinuation**

Under certain circumstances, an individual participant's receipt of study product will be prematurely or permanently discontinued. Specific events that will result in stopping a participant's infusions or VOR dosing in this study include:

- Failure to meet requirements established for safety assessment
- Withdrawal from the study
- Pregnancy
- Grade 3 AE assessed as related to the study products (with the exception that self-limited Grade 3 solicited reactogenicity does not require discontinuation from VRC07-523LS administration).
- Grade 4 AE assessed as related to the study products
- Intercurrent illness that is not expected to resolve prior to the next scheduled VRC07-523LS administration which is assessed by the study PI (or designee) to require withdrawal from the administration of VRC07-523LS
- Repeated failure to comply with protocol requirements
- Co-enrollment into a study in which other investigational research agents will be administered before the participants has completed the follow-up visits after receiving the last study product
- Investigator discretion
- Clinically significant hypersensitivity or infusion-related reaction including but not limited to type 1 hypersensitivity reaction, urticaria, or serum sickness associated with study treatment.

If the study Principal Investigator (or designee) decides that a participant should be withdrawn from study treatment, the protocol team must be alerted within 24 hours. All participants who discontinue treatments should comply with protocol-specified visits and follow-up as required by the protocol and evaluation by the study PI (or designee). The only exception to this requirement is when a participant withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a participant is withdrawn before completing the study, the reason for withdrawal must be documented appropriately in the study documents.

**Early Study Discontinuation**
A participant may withdraw or be withdrawn from the study if any of the following occurs:

- Failure by the participant to attend multiple clinic visits.
- Failure to receive the first VRC07-523LS infusion.
- Development of an illness that requires treatment with medications prohibited in this study.
- Poor adherence to ART as judged by the site Principal Investigator or designee.
- Request by the participant to withdraw from the study and study procedures.
- Request of the participant's primary care provider if she/he thinks the study is no longer in the best interest of the participant.
- Participant judged by the study Principal Investigator to be at significant risk of failing to comply with the provisions of the protocol, as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the IRB/Ethics Committee, FDA, NIH, and other government agencies as part of their duties, Principal Investigator, or industry supporter.

**Premature Treatment Discontinuation Evaluations**
Participants who begin but do not complete all doses of VRC07-523LS and VOR will be replaced. The collection of virologic, immunologic, and 2$^{nd}$ leukapheresis samples following premature discontinuation will be determined on a case-by-case basis in discussion with the protocol team.

Participants who complete Steps 2 and 3 but are unable to complete the leukapheresis (#2) in Step 4 will contribute to safety analyses and complete an end of study visit. The ability to complete virologic and immunologic endpoint analysis will be determined on a case-by-case basis in discussion with the protocol team. Replacement will be determined by the protocol team based on the ability to complete endpoint analysis.

**Delaying VRC07-523LS administration**
Under certain circumstances, a participant's scheduled VRC07-523LS infusion may be delayed. The factors to be considered in such a decision include but are not limited to the following:

Within 7 days prior to any study product administration

- Receipt of systemic glucocorticoids (e.g., prednisone or other glucocorticoids) or other immunomodulators (other than nonsteroidal anti- inflammatory drugs [NSAIDs]) – *Please reference paragraph below as these medications are prohibited on study.*
- Pre-infusion abnormal vital signs or clinical symptoms that may mask assessment of study product reaction.
- Inability to dose with VOR due to clinical symptom or laboratory value.
- Intercurrent illness that is not expected to resolve prior to the VRC07-523LS infusion which is assessed by the site principal investigator (or designee) to require delay or withdrawal from the study product administration schedule.

Infusions should not be administered outside the visit window periods.

Participants who take *systemic glucocorticoids or other immunomodulators* will be followed for safety by completing all the study visits and evaluations associated with the Step they are in when the study team learns of the need for a prohibited medication. If this occurs prior to completing all doses of VRC07-523LS and VOR, DO NOT give any more VRC07-523LS infusions or VOR. Collection of research labs for the time points thereafter will be considered on a case-by-case basis. These participants will be replaced.

**Discontinuation of Antiretroviral Therapy**
Participants who discontinue ART for any reason will be followed for safety by completing all the study visits and evaluations associated with the Step they are in when the study team learns of the interruption of ART. If the participant discontinues ART prior to completing all doses of VRC07-523LS and VOR, DO NOT give any more VRC07-523LS infusions or VOR. Collection of research labs for the time points thereafter will be considered on a case-by-case basis in discussion with the protocol team. This participant will be replaced.

If the participant discontinues ART before administration of the first dose of VOR and 1st VRC07-523LS infusion, the first VOR dose should not be given and the participant terminates from the study at this time.

If the participant discontinues ART after the first infusion (Day 0) and multiple doses of VOR but before the 2nd VRC07-523LS infusion (Day 60) or prior to completing the second series of multiple VOR doses, study treatment should be discontinued and the participant should continue on study for safety follow-up as noted in the SOE or per the study PI (or designee). Collection of virologic, immunologic, and the 2nd leukapheresis samples following premature discontinuation will be determined on a case-by-case basis in discussion with the protocol team. This participant will be replaced.

### 7.3 LOST TO FOLLOW-UP

Participants classified as lost to follow-up (LTFU) need to meet both of the following criteria:

- a) Failure to respond or reply to 3 documented phone contact attempts followed by
- b) Failure to respond to a certified letter sent to the address provided by the participant.

Only after documentation of these failed attempts to connect with the participant, will they be determined to be LTFU.

## 8 STUDY ASSESSMENTS AND PROCEDURES

### 8.1 EFFICACY ASSESSMENTS

This section provides a general description of the procedures and assessments associated with this study.

Informed Consent
Prior to performing any study-related procedures or assessments, the study coordinator discusses the study with the potential participant and obtains signed informed consent. This communication will be

documented. Labs/procedures completed during a routine clinical care appointment that are the same as the study screening labs and/or procedures and completed within the 14 days preceding the screening visit can be used to qualify the participant upon approval by the study PI or designee.

Screening

At the screening visit, participants will screen for the study. Only those participants who meet all eligibility criteria specified in Section 5.1 Inclusion Criteria and Section 5.2 Exclusion Criteria will be enrolled. A unique PID will be assigned during the screening visit.

Participants who are unable to meet protocol-defined eligibility criteria at the Screening Visit (Step 1, Visit 1) may be eligible to re-screen again at the study PI (or designee)'s discretion. In such cases, the same PID will be used. If a screen failure or the failure to move to the next Step is due to the inability to meet one of the laboratory parameters (hematology, chemistry, HIV RNA, or CD4 T cell count), a laboratory retest of the failed criteria may be performed one time only. If the repeat value is within eligibility requirements, the participant can enroll on the study.

Enrollment

Step 1 Visit 1 determines eligibility and enrollment occurs at Visit 2.

Advancement to Step 2

**Step 2**

Participants enrolled on the study will advance to Step 2 of the protocol based upon the following criteria:

1. A frequency of resting CD4 T cell infection of ≥ 0.3 IUPM as determined by QVOA in Step 1 Visit 2

   *Note: Participants with prior participation in one of the following UNC protocols in which they had an IUPM measurement ≥0.3, will be able to use this previous measurement for advancement*:

   - *IRB 08-1575 (CID 0819) - Apheresis Procedures to Obtain Leukocytes for Research Studies from HIV Positive Subjects;*
   - *IRB 11-0228 (CID 0807)* - NCT01319383;
   - *IRB 13-3613 (IGHID 1309)* - NCT02042248*;*
   - *IRB 14-0741 (IGHID 1320)* - NCT02208167;
   - *IRB 15-1626 (IGHID 11424)* - NCT02707900*;*
   - *IRB 17-0468 (IGHID 11627)* - NCT03212989
   - *IRB 18-0608 (CP-MGD014-01)* – NCT 03570918
   - *IRB 18-0944 (IGHID 1801) -The HIV Reservoir In Women: Implication For HIV Cure Strategies*

Note: Participants with these results and measurements from one of the above listed studies, would be able to use these results for advancement to Step 2, but would need to repeat the leukapheresis at Visit 2 to be used as a baseline for this study.

Failure to advance to Step 2 will result in discontinuation from study. Further follow-up is not required as no doses of VRC07-523LS will have been administered.

Medical History

Significant medical history should be obtained during the screening visit. All concurrent medical conditions in the last 30 days and any significant medical conditions (e.g., hospitalizations, surgeries, prior medical history) should be collected. Medical history obtained at Screening will include demographic information (e.g., date of birth, gender, race, and ethnicity, etc.), participant's medical history, and HIV medication history.

Prior and Concomitant Medications

All concomitant medications administered from screening until the end-of-study visit must be recorded in the source documents. Prescription and non-prescription medications taken within 4 weeks prior to screening must be recorded on the source document.

All routine prescription medications, over-the-counter medications, supplements, and study provided medications and investigational products will be entered in the study-specific database, starting at the time of enrollment through the EOS.

Antiretroviral (ART) Medication Assessment

During the study, all modifications to the participant's ART regimen, including any ARV interruptions, dose modifications, formulations modifications, starts, and permanent discontinuations since the last study visit or at the study visit must be recorded.

ART Adherence

ART adherence will be reviewed at every visit. Non-adherence will be defined as missing doses for more than 2 consecutive days or more than 4 cumulative days during the study. Assess any missed doses while on study and discuss with Study PI (or designee). Continuance on study will be contingent on adherence.

Physical Examination

Complete physical examination will include examination of skin, head, eyes, ears, nose, throat, lymph nodes, heart, chest, lungs, abdomen, extremities, and neurologic system according to schedule specified in the SOE in section 1.3.

A directed physical exam will be performed at all clinical visits where a complete physical examination is not performed, according to the SOE in section 1.3. A directed physical examination includes vital signs and addresses any previously identified or new event that the participant experiences since the last study visit or any unresolved signs or symptoms previously experienced. This assessment includes updates to signs and symptoms, and clinical assessment of HIV disease.

Signs and Symptoms Assessments

At entry, all signs and symptoms, regardless of grade, that occurred within the 30 days before entry must be recorded.

Active solicitation of AEs will be done at every study visit. Post-entry signs and symptoms, Grade ≥ 2, will be recorded. All signs or symptoms, definitely, possibly, or probably related to study interventions, will be recorded, regardless of grade. Additionally, all signs and symptoms that lead to a change in study treatment or change in ART, regardless of grade, must be recorded.

Treatment Emergent Adverse Events
An event that first appears during treatment, which was absent before or which worsens relative to the pre-treatment state.

Vital Signs
Vital signs (weight, body temperature, pulse or heart rate, respiratory rate, and seated blood pressure) will be recorded according to the SOE in section 1.3. Vital sign measurements will be conducted after resting 5 minutes in the sitting position. Height is only required at Step 1, Visit 1.

Repeat vital signs may also be captured as necessary to elucidate the course of any untoward event or AE.

Electrocardiogram
ECG will be performed at screening and should be read per institutional protocol within 72 hours to establish baseline for further evaluation as clinically indicated.

VRC07-523LS Infusions
All study product administrations will be completed per the SOE, section 1.3. Prior to each infusion, temperature (T), blood pressure (BP), heart rate or pulse (P), respiratory rate (RR), and weight will be collected and a targeted PE (based on signs, reported symptoms, or interim medical history) conducted. The participant will be observed for at least 60 minutes following the 1$^{st}$ infusion of VRC07-523LS and at least 30 – 60 minutes after the 2$^{nd}$ VRC07-523LS infusion.

Solicited AE Assessments
For all participants, baseline assessments will be performed before each infusion and assessments for Solicited AEs will be performed after each infusion. All Solicited AEs are graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 dated July 2017.

The Solicited AE assessment period is 3 full days following each infusion per the SOE in Section 1.3. Participants are instructed to record symptoms using a daily symptom tool. The study coordinator and the participant will be in contact after the 3-day Solicited AE assessment period, or sooner if indicated. In general, a participant who self-reports any reaction following an infusion that is greater than mild is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has completely resolved. Clinic study staff will follow new or unresolved Solicited AEs present at day 3 to resolution.

Solicited AE assessments include assessments of systemic and local symptoms, and study product-related lesions.

Assessment of Systemic and Local Symptoms
Systemic symptoms to be assessed as solicited AEs include increased body temperature, chills, malaise and/or fatigue, headache, myalgia, arthralgia, nausea, urticaria, non-exertional dyspnea, non-exertional tachycardia (assessed by CRS staff, not by the participant), generalized pruritus, facial flushing, and unexplained diaphoresis.

Local symptoms include pain or tenderness at the infusion site. The daily maximum severity reached for each symptom during the assessment period is reported.

Body temperature is measured by oral or infrared thermometry and is reported in degrees Celsius. If temperature is measured in Fahrenheit, the conversion to Celsius should be documented in the participant's chart note. A measurement is taken once daily during the assessment period and should be repeated if participant is feeling feverish.

Assessment of Infusion Site

Typical infusion site reactions are erythema/redness and induration/swelling. The maximum horizontal and maximum vertical measurements for all infusion site reactions are recorded.

All infusion/injection site reactions are monitored until resolution. Areas greater than 25 $cm^2$ are followed daily; otherwise, the frequency of follow-up is based on clinician judgment.

VRC07-523LS Post Infusion Telephone Follow-Up

Participants will have a telephone interview with a study coordinator 4 -6 days following each infusion to review the solicited AE assessment tool. Any incidents or events identified that could be related to the infusion and are still unresolved at Day 3, will require participants to come into clinic for clinical assessment.

Leukapheresis

Participants will undergo 2 leukapheresis procedures. The baseline leukapheresis will be completed at Visit 2. Participants will advance to Step 2 based on the attainment of an IUPM measurement ≥ 0.3. The second leukapheresis will occur 5 – 8 weeks after the 2nd series of a VRC-07 infusion followed by VOR dosing.

All protocol-required leukapheresis product will be transported on the day of collection to the Margolis Laboratory on the UNC campus.

*NOTE: Refer to the UNC Apheresis SOP and Study Specific Lab Manual for procedures specific to this study.*

If participants experience a Grade 3 or higher toxicity before completing the screening leukapheresis, they will be discontinued from study, as completing the leukapheresis procedures is a requirement of the study. Participants who experience a Grade 3 or higher toxicity during the leukapheresis will be evaluated on a case-by-case basis to understand the cause of the Grade 3 event. If the clinical situations (i.e., vasovagal response) that lead to the discontinuation of the leukapheresis procedure is determined by the study PI in collaboration with the Apheresis Medical Director to be situational and poses no apparent harm to the participant, the leukapheresis procedure may be repeated. However, if determined by the study PI, Apheresis Medical Director, and/or the Medical Monitor that repeated leukapheresis would be harmful to the participant, then he/she will be terminated from the study. The only exception to this discontinuation policy will be related to elevations in blood pressure (BP). Transiently elevated BPs to Grades 2 and 3 are frequently observed during this procedure, secondary to the BP cuff placement and nervousness of the participant. Elevated BP observed during the leukapheresis procedure will be monitored via Apheresis Lab policies. These will be noted and documented but will not be used to discontinue study participation.

Clinical Laboratory Tests

Blood and urine specimens will be collected according to the SOE in section 1.3. Safety laboratory tests should be performed and reviewed before study drug administration.

Laboratory Assays
Study specific safety and research assays will be collected at the research visits. Safety and clinically relevant labs will be performed at UNC McLendon Laboratories or LabCorp. Research assays will be processed and stored in associated research laboratories. Additional details on collection, processing, storage, and shipping of laboratory samples will be provided in the Study Specific Laboratory Manual.

End of Treatment/End of Study Visit
An End of Study (EOS) visit should occur approximately 2 - 4 weeks after Visit 12 depending on ability to follow the participant and duration and severity of ongoing AEs. An individual participant will be considered to have completed the study if the participant was followed through their last protocol-specified visit/assessment (EOS). Participants who have treatment discontinued due to a DLT or other clinical event will be followed on study until the clinical event is resolved or deemed stable and irreversible. Participants will complete the EOS visit per the SOE (section 1.3) but will be followed as necessary for acceptable resolution of the clinical event.

Participants will be considered not to have completed the study if consent was withdrawn, the study Principal Investigator discontinues the participant from study for severe lack of compliance, or the participant was lost to follow-up.

A list of evaluations to be performed for the EOS visit is provided in the SOE in section 1.3. The EOS Visit should be performed after the participant has met off-study criteria, or has been followed for at least 7 weeks after the last VRC07-523LS dose. Participants experiencing an unresolved AE will be followed until the AE is either resolved or deemed stable and irreversible.

**Research Laboratory Assays**

The ability of VRC07-523LS infusion in combination with multiple doses of VOR to alter markers of persistent HIV-1 infection in individuals on suppressive ART will be evaluated by measurement of: a) the frequency of resting CD4 T cell infection by QVOA and b) levels of plasma HIV-1 RNA, as measured by low levels of an HIV-1 RNA assay.

Resting CD4 T Cell Infection (RCI)
Lymphocytes are obtained by continuous-flow leukapheresis (samples obtained as per the SOE, section 1.3) and resting CD4 T cells are isolated as previously described (57).

QVOA measurements will be conducted with the leukapheresis samples collected prior to and following combined VOR/VRC07-523LS administration to determine if the frequency of resting CD4 T cell infection, expressed as IUPM, has declined. Since RCI frequency is a definitive measure of the minimum size of the HIV reservoir, a statistically significant decline in response to VRC07-523LS in combination with VOR treatment would be definitive evidence of a reduction in the HIV reservoir.

Plasma for Assays that measure low levels of RNA
Residual low-level viremia will be measured, as evidence suggests that such viremia originates in persistently infected cells, and low-level viremia might be reduced by an augmented antiviral immune response. Plasma for HIV-1 RNA will be obtained as required per the SOE in section 1.3 and stored for batched analyses. Two baseline sample determinations will be obtained during Steps 1 and 2 of the

protocol and 2-4 low level viremia assay measurements after combination therapy with VOR and VRC07-523LS will allow a robust evaluation of changes in plasma levels of cell-free HIV RNA.

Human Leukocyte Antigen (HLA) Typing
HLA testing will be performed at one time point in the study; however, if HLA type is already available in the medical record, it does not need to be repeated. The result will be used for research purposes.

Cytomegalovirus (CMV) IgG Testing
We will perform CMV testing for research purposes only at baseline (Visit 2) and after the 10$^{th}$ dose of VOR in Steps 2 and 3. If positive CMV testing results are available in the medical record, these results will be used for the baseline result. If the previous CMV IgG result in the medical record is negative, the test will be repeated at Visit 2. The 2$^{nd}$ and 3$^{rd}$ tests performed in the research lab will determine whether Vorinostat reactivates CMV enough to detect it in the plasma. The results will not be placed in the participant's medical record.

Epstein-Barr Virus (EBV) Viral Capsid Antigen (VCA) IgG Testing
We will perform EBV testing for research purposes only at baseline (Visit 2) and after the 10$^{th}$ dose of VOR in Step 2 or 3. If positive EBV testing results are available in the medical record, we will use these results for the baseline result. The 2$^{nd}$ and 3$^{rd}$ test performed in the research lab will determine whether Vorinostat reactivates EBV enough to detect it in the plasma. The results will not be placed in the participant's medical record

Vorinostat PK samples
Pharmacokinetic samples will be collected at 3 time points in the study. These will be processed and stored for testing as required.

VRC07-523LS PK samples
Pharmacokinetic samples will be collected at 3 time points: at baseline and after antibody administration at Days 29 (Visit 6) and 89 (Visit 11). These will be processed, stored, and shipped for testing as required.

Anti-Drug Antibody (ADA) Detection Assay
ADA will be measured by using the Meso Scale Discovery (MSD) platform with VRC07-523LS as the target antigen. Anti-VRC07-523LS antibody assays will be performed on serum samples collected at baseline and after antibody administration at Days 29 (Visit 6) and 89 (Visit 11). Serum will be stored at other visits per the SOE. Additional ADA testing may be performed on participants if indicated.

Virology and Viral Sequence Analysis
Samples will be collected per the SOE. Samples will be processed, stored, and analyzed as required.

Cell associated RNA Assay (caRNA)
Samples collected to isolate resting CD4 T cells and run the caRNA assay to have an additional baseline point. It will provide an idea of the baseline variation in caRNA of a given participant. This is important in trying to measure a change in caRNA after the intervention.

## 8.2 SAFETY AND OTHER ASSESSMENTS

All clinical and laboratory information required by this protocol is to be present in the source documents. Reference the Source Document Guidelines on the DAIDS web site for information about what must be included in the source document.
*http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/sourcedocappndx.pdf*

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

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

To grade diagnosis, signs and symptoms, and laboratory results, reference the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, on the DAIDS RSC website at *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*

Medical History and Medical History Updates
The medical history must include all signs and symptoms and all diagnoses regardless of grade within the past 30 days prior to entry.

Document:
- all allergies to any medications and their formulations
- date of birth, gender at birth, race and ethnicity of participant
- nadir CD4 and pre-ART HIV-1 RNA level, if available (if nadir documentation is not available, then collect and record participant recall)

The medical history evaluation will be assessed and recorded at the screening visit. Updates to medical history will occur at all clinical study visits. Any reported sign, symptom, and/or new diagnoses occurring after the participant signs the study consent but prior to the administration of the first dose of study product will be recorded in the medical history (pre-existing condition) unless the reported event is related to a protocol procedure.

**Clinical Laboratory Testing for Safety**

Hematology
Hemoglobin, hematocrit, white blood cell count (WBC), differential WBC, absolute neutrophil count (ANC), and platelet count will be performed in real time at the local laboratory.

STAT CBC with differential is required prior to each leukapheresis procedure done at UNC unless completed within 24 hours of the procedure and the results of that test are available to the Apheresis Lab. Apheresis collections completed at the American Red Cross require a CBC within the 30 days prior to the procedure.

Liver Function Tests
Total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase will be performed in real time at the local laboratory.

*NOTE: For participants on ritonavir boosted atazanavir, total and direct bilirubin should be measured*.

Blood Chemistries
Screening lab evaluation are done fasting and includes electrolytes (sodium, chloride, potassium, CO2/bicarbonate), glucose, blood urea nitrogen (BUN), creatinine, calcium, albumin, magnesium, lipase, and total protein in real time at the local laboratory.

Safety lab evaluations throughout the study include electrolytes (sodium, potassium, chloride, CO2/bicarbonate), BUN, creatinine, calcium, magnesium, and glucose (also reference Pre-Infusion Safety Lab Assessment).

Creatinine and Creatinine Clearance
Creatinine clearance (eGFR) calculations will use the CKD-EPI equation. This calculation can be found at *https://www.qxmd.com/calculate/calculator_251/egfr-using-ckd-epi*

The creatinine clearance (eGFR) will be required for study enrollment eligibility. The study assesses serum creatinine level at all of the safety lab checks and uses the serum creatinine value for toxicity grading.

The creatinine clearance (eGFR) value reported as part of the lab report of serum creatinine level will be re-assessed and re-calculated if incidental finding indicates a value ≥ Grade 3. The re-calculated value using the CKD-EPI equation will be used to determine the severity of the lab abnormality.

Pre-Study Treatment Safety Lab Assessments
Participants will have a Pre-Study Treatment Safety Lab Assessment prior to receipt of VRC07-523LS infusions at Day 0 and Day 60. The safety lab results obtained in this assessment must be within the eligibility criteria parameters established for this study. Labs that fall outside the parameters can be repeated one time only to qualify the participant to proceed on study.

After repeat testing, any lab value that remains outside the guidelines but considered clinically non-significant and documented as such by the study clinical PI (or designee), must be reviewed and approved by the protocol team and/or safety committee prior to the infusion.

Time points for the Pre-Study Treatment Safety Lab Assessment are:

- Step 2, Day 0 – prior to the administration of the first infusion. These labs can be performed up to 7 days prior to the infusion.
- Step 3, Visit 7, Pre-Visit – prior to the administration of the 2nd VRC07-523LS infusion

Follicle Stimulating Hormone (FSH) Test
This test is done at screening to document menopause in women who have been without a period for > 12 months.

Serum Pregnancy Test
A negative serum pregnancy test (to rule out pregnancy) is required on all women at screening.

A negative serum pregnancy test is required at each visit prior to VRC07-523LS infusion, and within 72 hours of the first VOR dose in Step 2 and Step 3 regardless of documented procedures that prohibit pregnancy.

In addition, a serum pregnancy test should be performed at any time if pregnancy is suspected. Because the study has no direct clinical benefit, this added protection is warranted.

Hepatitis Screen
Both hepatitis tests (HCV AB and HBsAg) must be negative or non-detected to be included on the study. A positive HCV AB test reflexed to Hepatitis C RNA revealing a negative result is acceptable.

Eligibility will be determined based on negative testing, per above definition at screening and prior to the Day 60 visit.

RPR
This test is done to rule out clinically active untreated syphilis at screening.

Participant may participate on study following documentation of adequate treatment of syphilis at screening (Visit 1). Participants diagnosed with syphilis while on study, will be referred for and require documentation of treatment prior to the 2$^{nd}$ infusion at Day 60. These infusions can be delayed until a minimum of 14 days post treatment for syphilis per recommendation by the study PI (or designee).

Fasting Lipid Panel
Total cholesterol, HDL, LDL calculation, VLDL calculations and triglycerides are obtained at screening.

Prothrombin Time (PT), INR, and APTT
Evaluated at the Screening Visit.

$CD4^+/CD8^+$
All study required absolute $CD4^+/CD8^+$ count and percentages must be obtained from a laboratory that possesses a CLIA certification or equivalent.

Eligibility will be determined based on a $CD4^+$ cell count ≥ 350 at screening and at Visit 7 (within 7 days prior to Day 60 Visit).

Plasma HIV-1 RNA
All study-required HIV-1 RNA must be performed by a laboratory that possesses a CLIA certification or equivalent.

Eligibility will be determined based on an HIV-1 RNA value <50 copies/mL at screening and at Visit 7 (within 7 days prior to Day 60 Visit).

Urinalysis
A full urinalysis with microscopic evaluation will be performed at screening.

Dipstick testing (including protein, glucose, hemoglobin, pH, and ketone) will be done at select visits. After screening, microscopic analysis will only be done in the event of abnormal results from dipstick testing.

**Clinical Procedures for Safety**

VRC07-523LS Administration
Record the infusion, including dose, and time of the study treatment administration. Record where the IV was inserted (location). If entire dose is not administered for any reason, notify the study PI and document the reason.

The following will be completed at each infusion administration visit:

- Confirm participant name and DOB with study treatment label, research chart, and verbal confirmation of same from participant with a second licensed provider.
- Participant must be seated in a secure chair or lying in a bed for the infusion.
- Document time of administration.
- Have emergency kit at bedside.

Post-Infusion Management
Observe participant and infusion site for a minimum of 60 minutes following the first infusion and a minimum of 30 - 60 minutes following the second infusion.

- Assess for site for a reaction every 15 minutes X 4, document observed reactions for 60 minutes following the first infusion and for every 15 minutes X 2 (at minimum) following the second infusion.
- Assess participant for local and systemic reactions every 15 minutes x 4, document observed reactions for 60 minutes following the first infusion and for every 15 minutes X 2 (at minimum) following the second infusion.
- Observe and assist participant when coming to a standing position for the first time following each infusion
- Obtain vital signs (BP, P, RR, and T) every 15 minutes for 60 minutes following the first infusion and every 15 minute for at least 30 minutes – 60 minutes following the second infusion. Document VS prior to discharge home.

Instruct participant to contact the study coordinator immediately with any concerns after leaving the clinic.

Provide participant post-infusion symptom log and instructions for completion prior to leaving the clinic. Post-infusion assessment includes the following:

- Contact participant between Days 4 and 6 post-infusion in the manner pre-determined by study coordinator and participant
- Review the symptom log at Days 4-6 with participant
- Collect and reconcile the symptom log with the participant at the Day 7 visit following each infusion

Solicited AE Assessments

Participants will be given a "Post-infusion AE Assessment" tool to use as a memory aid for tracking AEs that occur during the 3 days following the infusion. Participants will record daily temperature and symptoms.

For this study, solicited AEs occurring during the 3 days after receipt of study agent will include:

| Localized Symptoms | Systemic Symptoms |
|---|---|
| • Erythema (redness) | • Fatigue |
| • Local pain/tenderness | • Headache |
| • Warmth at infusion site | • Fever >37.7°C or 99.9°F |
| • Induration (hardening or formation of a crust or scab) | • Chills |
| • Itching (generalized and local) | • Rashes |
| • Swelling | • Myalgia |
| • Skin discoloration | • Arthralgia |
| • Skin damage (vesiculation or ulceration) | • Nausea |
| • Vomiting | • Malaise |
| • Urticaria | • Non-exertional dyspnea |
| • Facial flushing | • Non-exertional tachycardia |
| • Unexplained diaphoresis | |

Participants will also record the highest measured temperature daily. Participants should be instructed to take their temperature at least once daily, starting with the day of infusion (day 0), after leaving the clinic and through day 3 post-infusion.

Temperature should be taken orally or via infrared thermometry and in the evening whenever possible. If more than one measurement is made in a day (for example, due to feeling unwell), then the highest temperature taken that day should be recorded.

Participants will have a telephone interview with a study coordinator 4 -6 days following each VRC07-523LS infusion to review the solicited AE assessment tool. Any incidents or events identified that could be related to the infusion and are still unresolved after Day 3, will require participants to come into clinic for clinical assessment. Telephone conversation will be documented and signed off by the study PI.

Events occurring during the Solicited AE Assessment period that may require a clinic visit based on the judgment of a study clinician include:

- Rash,
- Urticaria,
- Fever of 38.6˚C (Grade 2) or higher lasting greater than 24 hours,
- A significant impairment in the activities of daily living (such as those consistent with Grade 2 or higher impairment),
- Arthralgia or other clinical concerns

The study coordinator reviews symptom logs for accuracy and completeness and will collect log at the Day 7 and Day 67 visits. Additionally, participants will undergo clinical laboratory assays and clinical

evaluations to assess safety at every visit. Participants will also be asked to contact the study coordinator, or study PI or designee should they experience any adverse events at any time points during the study.

Reactogenicity Assessment

The participant will assess for reactogenicity (expected) symptoms from days 0 to 3 following each infusion on their post-infusion symptom card.

The daily maximum severity reached for each symptom during the 3-day assessment period will be reported. Study staff will follow new or unresolved reactogenicity symptoms to resolution. In general, participants self-reporting any post-infusion reaction greater than mild are to be evaluated by Study PI (or designee) within 48 hours after onset, unless the reaction is improving and/or has completely resolved. Institute appropriate countermeasures, including medical intervention or procedures, if clinically indicated.

Estimated Blood Volumes Associated with the Study Visits

| Visit or Week # | Blood Volume (mL) | Visit or Week # | Blood Volume (mL) |
|---|---|---|---|
| Visit 1 | 50 | Visit 8 Day 60 | 116 |
| Visit 2 | 153 | Visit 9 Day 67 | 18 |
| Visit 3 Day 0 | 61 | Visit 10 Day 74 | 18 |
| Visit 4 Day 7 | 15 | Visit 11 Day 89 | 173 |
| Visit 5 Day 14 | 16 | Visit 12 | 50 |
| Visit 6 Day 29 | 158 | Visit 13 | 135 |
| Visit 7 | 70 | | |

Cancer Registry

All participants who receive greater than 8 doses of VOR in a study are asked to enter a study cancer registry. The registry is maintained by the clinical program director of the UNC HIV Cure Center. Participants willing to participate in the registry are contacted annually for 5 years following the completion of their VOR dosing regimen. The UNC Cancer Registry is searched annually for new cancer diagnoses registered to any of the VOR recipients. Data on participants included in this registry will be provided in the Annual Reports to the FDA for this study.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

### 8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### 8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

#### 8.3.3.1 SEVERITY OF EVENT

Event severity will be assigned according to the Investigator's assessment.

**Severity Grade for Parameters Not Identified in the Grading Table:**
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as Grade 5.

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| Clinical adverse event NOT identified elsewhere in the grading table | Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated | Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated | Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated | Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death |

#### 8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

Attribution/Assessment of Causality is a determination that describes the relationship or association of the study product with an adverse event.

This assessment of causality or relationship of AEs to the study drug is provided by the Investigator and is determined by 1) temporal relationship of the event to the administration of study drug; 2) whether an alternative etiology has been identified, and 3) biological plausibility. Causality must be assessed separately for each study drug.

The causality assessment categories that will be used for this study are described below.

1. Causality assessments that are considered **not related** to study drug:
    a. *Not related:*
    The event is related to an etiology other than the study drug (the alternative etiology must be documented in the participant's medical record).

    If an SAE is considered "unrelated" to study drug, the Investigator should offer his/her clinical opinion as to what factor(s), agent(s), or process(s) were the likely causative mechanism for the event.

2. Causality assessments that are considered **related** to study drug:
    a. *Possible:*
    There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug; but there may also be alternative etiology, such as characteristics of the participant's clinical status or underlying disease.

    b. *Probable:*
    There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug, and the event could not be reasonably explained by known characteristics of the participant's clinical status or an alternative etiology is not apparent.

    c. *Definite:*
    There is an association between the event and the administration of study drug; a plausible mechanism for the event to be related to the study drug, causes other than the study drug have been ruled out, and/or the event re-appeared on re-exposure to the study drug.

#### 8.3.3.3 EXPECTEDNESS

The study PI (or designee) will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention or is not listed in the most current IBs for the study intervention.

### 8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review of medical record.

The study unsolicited AE reporting period will be from enrollment (Day 0) through the end of study visit. During Step 1 (period between consent and Day 0), any AE that occurs will be collected as concurrent medical history (pre-existing condition) and not as an AE, unless it is due to a protocol–related procedure (leukapheresis).

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured in the research record on the appropriate form. Information collected includes:

- Event description,
- Time of onset,
- Study PI's (or designee's) assessment of severity, relationship to study product and expectedness,
- Time of resolution/stabilization of the event.

All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study research coordinator will record all reportable events with start dates occurring any time on or after the enrollment visit until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the research coordinator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

<u>Clinical Laboratory Changes:</u>

Safety laboratory assessments will be carried out locally at UNC and evaluated by the Investigator (or designee) to ensure participant safety. The Investigator (or designee) is responsible for reviewing the results of all laboratory tests as they become available.

- Laboratory values that fall outside of a clinically accepted reference range or differ significantly from previous values must be evaluated for clinical significance by the Investigator (or designee). The Investigator (or designee) may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests.
- If the Investigator (or designee) determines the laboratory value is an abnormal change from baseline and is of clinical significance for that participant, it is considered an AE.
- Generally, Grade 1 and Grade 2 laboratory findings need not be reported as AEs unless deemed clinically significant by the Investigator (or designee).
- Consistent with the DAIDS designation of Grade 3 events as severe or medically significant and Grade 4 events as life-threatening, Grade 3 and Grade 4 laboratory findings should be reported as AEs or SAEs, as appropriate.

- The test result or finding should be reported as the AE. Such laboratory values should generally be recorded as “increased” or “decreased” (e.g., change from baseline potassium of 5.0 to 3.5 mEq/L = potassium decreased).

The study PI (or designee) is responsible for appropriate reporting of adverse events to the regulatory authorities. The study PI (or designee) will also report all suspected unexpected serious adverse reactions. The study PI (or designee) must report suspected unexpected serious adverse reactions to the UNC IRB, unless otherwise required and documented by the UNC IRB.

### 8.3.5 ADVERSE EVENT REPORTING

Adverse events will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, on the DAIDS RSC website at *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*

Participants will be monitored for adverse events. Toxicities will be characterized in terms including duration, intensity, and time to onset. Safety endpoints will include all adverse experiences, in addition to laboratory safety assessments, and vital signs. All AEs will be recorded on the appropriate study form. All AEs will be recorded in the database if any of the following criteria have been met:

- Study-related grade ≥ 1 AEs
- Grade ≥ 3 AEs
- Autoimmune-related AEs regardless of grade
- HIV viral loads ≥ 50 copies/mL
- Infusion reactions regardless of grade
- AEs that led to a change in study intervention regardless of grade
- AEs meeting SAE definition or EAE (Expedited Adverse Event) reporting requirement

Grade 1 or 2 Toxicity

Participants who develop a Grade 1 or 2 AE or lab toxicity that occurs following a VRC07 infusion or dose of VOR dosing that is thought to be possibly, probably, or definitely related to study treatment should be discussed with the study team. Grade 1 or 2 AEs that may be related to the VRC07-523LS or VOR should be handled according to standard clinical practice and documented. Participants who experience a Grade 1 or 2 AE that is judged related to the study treatments by the study PI (or designee), may continue study treatment at the discretion of the study PI (or designee).

Participants who experience a Grade 1 or 2 AE that is judged not to be related to the study drug/product by the study PI (or designee), may continue study treatment at the discretion of the study PI (or designee).

Grade 3 Toxicity

For participants who develop a Grade 3 AE following administration of VRC07-523LS or VOR that is judged by the study PI (or designee) to be at least possibly study treatment-related, the protocol team, inclusive of the DAIDS Medical Officer, must be notified within 24 hours. Participants experiencing Grade 3 AEs should be followed closely and if the AE does not return to Grade ≤ 2 within 2 weeks, the study team should again be notified within 24 hours and the SMC will be notified. Continued receipt of study

products is at the discretion of the study PI (or designee) in consultation with the protocol team and the SMC.

For participants who experience a Grade 3 AE that is judged not related to the study treatment by the investigator, continued study participation is at the discretion of the study PI (or designee) in consultation with the protocol team and SMC.

Grade 4 Toxicity

For participants who develop a Grade 4 AE following administration of VRC06-523LS or VOR that is judged by the study PI (or designee) to be at least possibly study treatment-related, the protocol team, the DIADS Medical Officer and SMC must be notified within 24 hours. Participants experiencing Grade 4 AEs should be followed closely with additional clinical assessments and laboratory testing as clinically indicated. If the AE does not return to Grade ≤ 2 within 2 weeks, the protocol team and SMC should again be notified within 24 hours.

All study treatments will be discontinued in the event of Grade 4 AEs possibly related to study treatment.

**Local or Systemic Reactions to VRC07-523LS**

Grade 1 or 2
Local reactions of mild (Grade 1) or moderate (Grade 2) severity will usually resolve spontaneously. If needed, they may be managed with local application of cold packs, oral acetaminophen, oral non-steroidal anti-inflammatory agents, or a combination of these measures as appropriate.

NOTE: Topical steroids should not be applied to the infusion site.

Grade 3 or 4
For severe (Grade 3) or potentially life-threatening (Grade 4) local reactions, the protocol team, inclusive of the DAIDS Medical Officer, must be notified within 24 hours. For Grade 4 local reactions, definitive medical and/or surgical intervention should be undertaken as appropriate. Further infusions will not be administered.

Systemic Reactions
The protocol team, inclusive of the DAIDS Medical Officer, must be contacted within 24 hours for any non-local Grade 3 or 4 systemic reactions thought definitely, possibly, or probably related to the VRC07-523LS infusion or the administration of VOR doses. Further infusions and VOR doses will not be administered.

If an adverse event of special interest (AESI) occurs (see section 8.3.8), the study coordinator, in collaboration with the study PI (or designee), will evaluate the severity and seriousness of the AE and the relationship to the study treatment, and will document the findings.

The protocol team, inclusive of the DAIDS Medical Officer, should be contacted within 24 hours of notification of any reactions thought definitely, possibly, or probably related to the VRC07-523LS infusion.

**Infusion Site reaction**
Infusion Site Erythema or Redness and Infusion Site Induration or Swelling will not be considered interference with usual social and functional activities such that:

- Grade 1 is: 2.5 to < 5 cm in diameter OR 6.25 to < 25 $cm^2$ surface area;
- Grade 2 is: ≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 $cm^2$ surface area;
- Grade 3 is: ≥ 10 cm in diameter OR ≥ 100 $cm^2$ surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage;
- Grade 4 is: Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

**Allergic or Hypersensitivity Reactions**
Record all allergic and hypersensitivity reactions with both grade severity and attribution.
Serious allergic or hypersensitivity reactions (≥ Grade 3) that are deemed possibly related to the study treatment by the study PI (or designee) will be reported to the protocol team and SMC within 24 hours of notification and to the NIH, UNC IRB, FDA, and study product sponsors within 48 hours per their reporting requirements.

**Dose Limiting Toxicity (DLT)**

- Hematologic dose-limiting toxicity will be defined as any confirmed toxicity ≥ Grade 2, that cannot clearly be attributed to another reversible cause. These participants will not receive further doses of VOR or VRC07-523LS.

- Follow participants per protocol schedule of events until the lab abnormality or toxicity resolves to ≤ Grade 1 or the participant's baseline.

- Non-hematologic dose-limiting toxicity will be defined as any confirmed symptomatic ≥ Grade 3, if related (definitely, probably, or possibly) to VOR or VRC07-523LS

**Monitoring HIV RNA levels**
In the event of viremia of ≥ 50 copies/mL the following should occur per standard of care:

- Adherence to ART should be carefully assessed and documented.
- A standard HIV RNA assay should be repeated within 1-4 weeks.
- HIV resistance testing will be performed at the time of drawing a confirmatory sample.
- HIV RNA will be repeated every 2 weeks, or sooner as clinically indicated, until <50 copies/mL and the participant can continue on study.
- If persistent viremia is documented, ongoing administration of study treatment will be reviewed on a case-by-case basis with the participant, their HIV provider, and the study team.

In the event of confirmed viremia and documented adherence to ART, ART should be managed by the primary care provider in discussion with the study team. The results of the HIV resistance tests will be shared with the participants and their care providers.

**Immediately Reportable Events**
Immediately Reportable Events (IREs) are events that must be reported immediately to the sponsor within 24 hours of the study site's awareness of the event:

- All SAEs
- Pregnancy in a study participant or partner of a study participant

- All ≥ Grade 2 Cytokine Release Syndrome/Infusion-Related Reactions
- Administration of a dose significantly greater (specifically, + 20 % or higher) than the planned dose, and results in an event of clinical consequence
- AEs leading to permanent discontinuation of study drug in an individual participant
- Withdrawal of the participant from study drug administration during or after receipt of any doses of VRC07-523LS or VRC07-523LS in combination with VOR for any reason
- Product quality issues with an associated clinical consequence.

In those cases, in which the IRE is considered related to study drug, the study drug may be discontinued and the participant will continue participation in the study for observational safety and analysis (except for cases where the participant is withdrawn from the study by the study PI (or designee) or withdrew their consent). At any time after completion of the study, if an Investigator becomes aware of a serious adverse event that s/he suspects is related to study drug, the study PI (or designee) should report the event to NIH, VRC, Merck, FDA, and the UNC IRB, if applicable.

The study PI (or designee) is responsible for appropriate reporting of AEs to the regulatory authorities.

The Protocol Core Team will monitor the conduct and safety of the study via monthly meetings and regular summaries. Accrual, baseline characteristics, conduct of the study (including premature study discontinuations), any interruptions of ART, virologic failures, and all reported toxicities and events will be monitored during the study and discussed with the protocol team on a monthly basis or more frequently, if needed.

The study protocol team will review the individual safety data monthly to assess relation of all reported toxicities and AEs to the study treatment. A study unique independent Safety Monitoring Committee (SMC) will receive monthly study progress and safety monitoring reports. Study feasibility and the achievement of study milestones will be assessed in these reports.

The DAIDS program and medical officers will review and assess the monthly safety reports, as well as EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs, as applicable.

### 8.3.6 SERIOUS ADVERSE EVENT REPORTING

All SAEs occurring during the study must be reported to the UNC IRB per the UNC IRB reporting requirements. A written report (Serious Adverse Event Report Form) will be submitted to DAIDS and DAIDS MO within 24 hours of site becoming aware of the SAE. Additional information will be supplied as requested. All SAEs occurring during the study will be reported to DAIDS following guidelines for expedited AE reporting and to the FDA according to their regulatory guidelines.

After 30 days following the last dose of study drug administration, only SAEs the study PI (or designee) considers related to study drug or a protocol procedure, should be reported. Information regarding SAEs will be submitted to the DAIDS on required SAE reporting forms, which must be completed and signed by the study PI or designee, and sent within 24 hours of the site becoming aware of the SAE.

All Grade 3 or Grade 4 AE/SAEs considered related to study drug must be followed until recovery to baseline or Grade 1 with the date of resolution recorded in the source documents. In addition, the

investigator should report all follow-up for reportable Grade 3 or Grade 4 AE/SAEs to the UNC IRB. Resolution of an event is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to etiology other than the study drug or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (participant's or health care practitioner's refusal to provide additional information, or lost to follow-up after demonstration of due diligence with follow-up efforts).

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term facility).
- Surgery or procedure planned before entry into the study (must be documented in the source document).

The study PI (or designee) will be responsible for notifying the FDA, VRC, and Merck, Inc. of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

### 8.3.7 REPORTING EVENTS TO PARTICIPANTS

We are engaged in a number of similar studies of persistent HIV infection, using VOR and other interventions. We report the scientific findings of our work in the literature, and have regular (annual or more frequent) presentations with the local and national HIV+ and affected community. Due to the lack of evidence thus far that our studies have a clinical impact, we discuss the scientific findings in a general way with each participant after EOS visits. Our studies have extremely stringent stopping criteria, and thus far we have had no relevant or study-related SAEs to report. We would inform all study participants by letter or electronic messaging of any AEs determined by the External Study Safety Monitoring Committee to merit such notice.

### 8.3.8 ADVERSE EVENTS OF SPECIAL INTEREST

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the protocol team, for which ongoing monitoring and rapid communication to the protocol team is required. These events might warrant further investigation in order to characterize and

understand it. Depending on the nature of the event, rapid communication by the protocol team to the UNC IRB, FDA, NIH, and product manufacturers (i.e., regulators) might also be warranted.

AESI for this protocol include those listed below. Updates to AESI will be added as an amendment to this protocol.

- Systemic lupus erythematosus (SLE)
- Systemic scleroderma (SSD) (Systemic sclerosis [SSc]), including diffuse systemic form and CREST syndrome
- Sjogren's syndrome (SS)
- Polymyositis/Dermatomyositis syndrome (PM/DM)
- Raynaud's syndrome
- Antiphospholipid antibody syndrome (APS)
- Idiopathic thrombocytopenic purpura (ITP)
- Crohn's disease
- Ulcerative colitis

### 8.3.9 REPORTING OF PREGNANCY

We do not anticipate women participants becoming pregnant as we exclude women of child bearing potential from study participation. However, we will do the following should a pregnancy occur on study.

If the participant becomes pregnant during the study, all study treatment must be discontinued immediately. Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a participant or participant's partner (spontaneously reported to them) that occurs during the study or within 6 weeks of completing the study. All participants or their partners who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported the UNC IRB, the DAIDS Medical Officer, and the FDA (US Food and Drug Administration).

If a male participant impregnates his partner while he is participating in this study, the pregnancy must be reported and the study PI (or designee) should make a concerted effort to follow the pregnancy and outcome. The study PI (or designee) will make every effort to obtain a medical release and a separate pregnancy outcome consent from the pregnant partner granting permission to follow the health of both the pregnant partner and her unborn child to the UNC IRB, DAIDS, VRC, Merck and FDA without delay and within 24 hours if the outcome is an SAE (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

Pregnancy and pregnancy outcome will be recorded. Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Telephone: 800-258-4263; Fax: 800-800-1052.

<u>Pregnancy Outcomes and Reporting</u>
If a woman has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site study staff should request permission via a separate pregnancy outcome consent to contact her regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted at the end of the pregnancy.

Pregnant women will discontinue study treatment and will be encouraged to continue on study and complete the evaluations included in the post-treatment evaluation section. At the end of the pregnancy, outcome and adverse events for participant and infant will be recorded. If pregnancy is suspected in a woman on study after study treatment, then a pregnancy test should be obtained. If pregnancy is confirmed, then further study treatment will be discontinued and the woman should continue on study (off study medication) safety follow-up visits as noted in the SOE. Stored plasma/PBMC for stored plasma for virologic studies should not be obtained to minimize blood volume. The site study staff should request permission via a separate pregnancy outcome consent to contact her regarding pregnancy outcomes at the end of pregnancy. A visit 6 months following the end of pregnancy will be conducted to assess for evidence of adverse events (AEs) in the participant and infant and documented.

## 8.4 NEW SAFETY INFORMATION

### 8.4.1 DEFINITION OF NEW SAFETY INFORMATION (NSI)

The Office for Human Research Protections (OHRP) considers new safety information involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures/study treatment that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol, the informed consent document and Investigator's Brochure (IB); and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures/treatment involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 8.4.2 NEW SAFETY INFORMATION REPORTING

The investigator will report NSI to the UNC IRB. The NSI report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents the NSI;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the NSI.

To satisfy the requirement for prompt reporting, NSIs will be reported using the following timeline:

- NSIs that are serious adverse events (SAEs) will be reported to the IRB and the DAIDS MO within 3 business days of the investigator becoming aware of the event.
- Any other NSIs will be reported to the IRB and to the DAIDS MO within 7 business days of the investigator becoming aware of the event.
- All NSIs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the NIH MO (or designee), and the Office for Human Research Protections (OHRP) within 30 business days of the IRB's review and determination that the report of the problem from the investigator imposed a safety risk.

### 8.4.3 REPORTING NEW SAFETY INFORMATION TO PARTICIPANTS

We would inform all study participants by letter or electronic messaging of any NSI if it is determined by the UNC IRB to merit such notice.

## 9 STATISTICAL CONSIDERATIONS

This is a phase I, single-site study to evaluate the safety of VRC07-523LS combined with VOR in HIV-infected individuals suppressed on ART. There are secondary analyses to measure the effect of this therapy on persistent HIV-1 infection. All eligible participants will receive the same treatment which includes two (2) VRC07-523LS infusions and twenty (20) doses of VOR 400 mg. Participants will continue their baseline ART regimen throughout the study.

### 9.1 STATISTICAL HYPOTHESES

**Hypothesis**
Combination therapy with VRC07-523LS administered by IV infusion in combination with multiple doses of VOR 400mg orally will be safe and well tolerated.

### 9.2 SAMPLE SIZE DETERMINATION

We will enroll up to 12 fully evaluable participants (who receive two cycles of VRC07-523LS and VOR) to examine the effect of adding VOR and VRC07-523LS to ART on persistent replication-competent HIV within resting CD4+ T cells.

Any participant who does not complete both series of VRC07-523LS and VOR and the leukapheresis in Step 4 for reasons other than a grade 3 or higher AE will be replaced, to ensure up to 12 evaluable participants for safety.

Since the trial will be stopped if two participants experience a study treatment-related toxicity of Grade 3 or higher, the criterion for safety is grade 3 or higher toxicity in no more than 1 of 12 participants in the study.

For n=12 participants, if there are no primary AEs, then the exact 95% 1-sided upper confidence limit (UCL) for the true AE rate will be 0.22. Thus, if no AEs are observed, one can confidently rule out event rates greater than 22%.

*All other analyses are therefore equally exploratory.*

Because a focus of the study is on safety and potential AEs, accrual will be staggered such that enrollment and treatment administration will include a maximum of 1 participant per week.

## 9.3 POPULATIONS FOR ANALYSES

All participants who receive at least one dose of study therapy will contribute to the safety analysis of this study.

## 9.4 STATISTICAL ANALYSES

### 9.4.1 GENERAL APPROACH

We plan a phase I, single-center study in participants with HIV-1 infection who are receiving ART. Baseline ART will be maintained throughout the study. HIV-1 infected participants with plasma HIV RNA stably below the limit of quantitation will be screened. After meeting all eligibility criteria and enrollment, all participants will undergo an initial evaluation of resting $CD4^+$T cells obtained via leukapheresis. A baseline measurement of the frequency of HIV-1 infection per million units (IUPM) in resting $CD4^+$ cells will be performed by QVOA.

In Step 2, all participants will receive one (1) IV infusion of VRC07-523LS 40mg/kg, followed by ten (10) doses of VOR 400 mg PO every 72 hours. This exact cycle of a single VRC07-523LS 40mg/kg infusion followed by ten (10) doses of VOR 400 mg PO every 72 hours is repeated in Step 3. Therefore all participants will receive a total of 2 IV infusions of VRC07-523LS and 20 doses of VOR 400mg PO over a 3 month period. Participants completing this protocol will receive no more than a total of 8,000 mg of VOR. For reference, participants who completed a prior multi-dose study (58) received a total of 10,000 mg of VOR without clear evidence of any durable drug-associated toxicity, and no AEs greater than Grade 1.

Following Step 3, a leukapheresis will be performed approximately 1- 4 weeks after the last dose of VOR to measure the frequency of HIV-1 infection (IUPM) by QVOA.

Each participant will be followed for approximately 26 weeks once Step 2 begins.

Formal interim analyses will be performed at 6 month intervals during the conduct of this study, and will be reviewed by an independent Safety Monitoring Committee (SMC). If an interim analysis has not yet been performed, the Committee will perform a preliminary review of accumulated safety data after 4 participants have completed the first series of combined treatment with VRC07-523LS and 10 doses of VOR. This review will be based on assessment of participant safety, and will serve as a basis for allowing enrollment to continue. The Committee also will oversee all subsequent analyses.

### 9.4.2 ANALYSIS OF THE PRIMARY SAFETY ENDPOINT

**Safety:**
For the primary safety analysis, AEs attributed to study treatment will be described through the end of study visit approximately 20 weeks after getting their first infusion at Day 0. All participants who have been exposed to at least one dose of study treatment will be included in this analysis.

Since the trial will be paused for SMC review if two participants experience a study treatment-related toxicity of Grade 3 or higher, the criterion for safety of this study is grade 3 or 4 toxicity in no more than 1 of 12 participants.

### 9.4.3 ANALYSIS OF THE OTHER ENDPOINT(S)

**Other Activity Endpoints:**

- **Change in the frequency of HIV infection per million resting CD4$^+$T cells (RCI) from baseline to after treatment with VRC07-523LS and VOR**

  We will analyze pre-VOR/VRC07-523LS and post- VOR/VRC07-523LS frequency of HIV infection per million resting CD4$^+$T cells using a non-parametric 2-sided sign test (supplemented by longitudinal regression modeling to estimate the magnitude of changes) to determine whether or not a significant decrease of IUPM is observed. With 12 participants, there will be 80% power to reject $H_0$ (change expected with ART alone) in favor of $H_A$ (greater change than expected with ART) if the true probability of observing a decrease in IUPM in a participant after VOR/VRC07-523LS is 0.93.

  This is based on a 2-sided alpha = 0.05 and the assumption that observed HIV infection frequency would decrease with probability 0.54 on ART alone after 6 months without intervention, based on the decay of IUPM seen on ART alone [Crooks 2015, Siliciano 2003].

  In addition to summarizing the number and proportion of participants who show decrease in IUPM after VOR/VRC07-523LS, we will describe the magnitude of the changes in decrease in IUPM after VOR/VRC07-523LS via the median fold-change and corresponding 95% confidence interval. We will also summarize the proportion of participants with >6-fold decreases; this magnitude change is rarely seen in participants on stable ART [9].

**Other Endpoints: Activity**

- **HIV-1 RNA by low level viremia assay measurement at baseline and after treatment with VRC07-523LS and VOR**

  The virologic analysis will include estimation of the low level viremia levels at pre-treatment (screening and entry) and separately at post-treatment. We assume that the probability would be 0.10 (10%) for a baseline (pre-entry, entry) detectable low level viremia ≥ 1 copy. The assumption that 10% of participants with a quantifiable low level viremia at screening will have low level viremia assay below the limit of detection at a pre-treatment measure is an estimate based on data from A5244 in which 6 of 50 (12%) enrolled participants had undetectable low

level of viremia at pre-entry and 5 of 51 (10%) at entry after having a screening low level of viremia ≥ 1 copy (59).

**Other Exploratory Analyses:**

- Following VOR/VRC07-523LS we will also explore whether there is a *depletion* of rc-RNA using the same statistical tests in the reverse (compare baseline rc-RNA to after two cycles of VOR/VRC07-523LS).

- To assess these within each individual participant (n of 1 analyses), we will use the non-parametric 2-sided Wilcoxon rank sum test to determine whether or not a statistically significant change in rc-RNA expression is observed, comparing rc-RNA levels measured in each of 24-36 replicate pools of 1 million resting $CD4^+$ cells. Pools with undetectable RNA will be considered as 0 copies and analyzed as the lowest rank in this rank-based statistical test.

  The pre-VOR rc-RNA expression will be determined as the median RNA copies over the individual pools of one million participant cells tested prior to VOR (setting undetectable RNA pools as 0 copies), and the post-VOR RNA expression level will be similarly determined. Changes in RNA expression will be evaluated by the exact sign test and the proportion of participants with increases versus decreases. Summaries of the magnitude of changes will be examined in terms of median fold-changes.

- We will also explore changes in the chromosomally integrated viral reservoir as measured by Q-PCR from baseline to post VOR/VRC07-523LS.

- We will also explore the change in frequency of viral envelope sequences detected in plasma or cells that are not recognized by VRC07-523LS from baseline to post VOR/VRC07-523LS.

- A 0.05 significance level will be used throughout, with no adjustment for multiple testing given the proof of concept nature of this study. Emphasis will be put on estimation with corresponding 95% confidence intervals to evaluate the scientific and biologic effect size. Individual-level data will be visualized in plots. Given the small sample size, exploratory analyses will have limited or no statistical power and findings should be interpreted with caution and assessed in a subsequent, larger study if the combined treatment is found to be safe and potentially efficacious. If the study is stopped at n=12 participants, statistical analyses will be limited to descriptive summaries and n of 1 analyses within each participant.

### 9.4.4 SAFETY ANALYSES

For the safety endpoint, we will describe all study treatment-related AEs through the end of study approximately 20 weeks after getting their first infusion at Day 0. AEs will be coded to the Medical Dictionary for Regulatory Activities (MedDRA). Events prior to treatment (e.g., due to study-related procedure) will be listed separately in an appendix to the final clinical study report. The following tables of AE data will be created to summarize the number and percent of participants who experience at least one event of each of the following types:

- All AEs
- Drug-related AEs by severity grade
- AEs by severity grade

- All SAEs (this may be a listing if there are few events)
- Drug-related SAEs
- Fatal AEs (this may be a listing if there are few events)
- AEs that result in study discontinuation
- AEs that lead to withdrawal of study drug
- AEs categorized as AESI and/or IREs
- AEs with severity grade 3 or greater
- Drug-related AEs with severity grade 3 or greater

All of these tables will display the number and percent of participants that experience the given event and will display events by System Organ Class (SOC) and Preferred Term (PT). Events will be displayed alphabetically for SOC and in descending order of overall PT incidence within each SOC.

#### 9.4.5 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

### 10.1.1 INFORMED CONSENT PROCESS

#### 10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

#### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The consent forms are UNC IRB - approved and the participant will be asked to read and review the document. The study investigator (or designee) and/or study coordinator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants are provided the opportunity to discuss the study with their family, primary care provider, or significant other or to just think about the study and its requirements prior to agreeing to participate. The participant signs the informed consent document prior to any procedures being done specifically for the study. Participants are informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants.

The informed consent process will be conducted and documented in the source document, and the consent form signed, before the participant undergoes any study-specific procedures. The study PI (or designee) or the research coordinator will inform participants that the quality of their medical care will not be adversely affected if they decline to participate in this study, thus emphasizing the protection of the rights and welfare of the participants.

### 10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided to the study participants, funding agency (NIH), the FDA (IND), the VRC (VRC07-523LS), Merck (Vorinostat) and UNC IRB. If the study is prematurely terminated or suspended, the study PI (or designee) will promptly inform study participants, the UNC IRB, and DAIDS and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy DAIDS, UNC IRB, and/or FDA.

### 10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the UNC IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the study PI, including but not limited to, medical records and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participants' contact information will be securely stored at the clinical study site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the UNC HIV Cure Center. This will not include the participants' contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical staff of the UNC HIV Cure Center and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

### 10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the UNC HIV Cure Center. After the study is completed, the de-identified, archived data will be stored in the UNC Cure Center Database, for use by the UNC HIV Cure Center researchers. Permission to transmit data to researchers outside the UNC HIV Cure Center Collaboratory will require review and approval by the UNC IRB. In some circumstances, we will need to obtain additional consent from participants to share samples collected for the purpose of this study.

With the participant's approval and as approved by the UNC IRB, de-identified biological samples will be stored at the UNC HIV Cure Center and/or the UNC Chapel Hill HIV/STD Laboratory Core. These samples could be used to research the causes of HIV cure for which individuals with HIV infection can greatly benefit. The UNC HIV Cure Research Laboratories will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the UNC HIV Cure Center Laboratory.

### 10.1.5 KEY ROLES AND STUDY GOVERNANCE

| **Protocol Principal Investigator** | **Grant Principal Investigator** |
|---|---|
| ***Cynthia Gay, MD, MPH*** | ***David Margolis, MD*** |

| | |
|---|---|
| *Associate Professor, Medical Director HIV Cure Center* | *Professor of Medicine, Microbiology & Immunology, and Epidemiology* |
| *University of North Carolina at Chapel Hill* | *University of North Carolina at Chapel Hill* |
| *130 Mason Farm Road, Suite 2112 Bioinformatics Building, Campus Box 7030* | *120 Mason Farm Road, 2060 Genetic Medicine Building, Campus Box 7042* |
| *Chapel Hill, NC 27599-7030* | *Chapel Hill, NC 27599-7042* |
| *919-843-2726* | *919-966-6388* |
| *cynthia_gay@med.unc.edu* | *dmargo@med.unc.edu* |

### 10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Safety Monitoring Committee (SMC) composed of individuals with the appropriate expertise, including a Biostatistician and an HIV Therapy clinician. Members of the SMC are independent from the study conduct and free of conflict of interest.

The SMC advises the study PI and protocol team for this Phase I study. The primary responsibility of the SMC is to monitor human subject safety. The SMC considers study-specific data as well as relevant background information about the disease, test agents, and target population under study.

During the trial the SMC will review:

- Real-time and cumulative safety data for evidence of study-related adverse events;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the trial data (such as protocol violations, losses to follow-up, etc.).
- Review the achievement of enrollment benchmarks

The SMC will receive monthly reports via email for review and comments. The SMC will be contacted directly via email (and possibly via teleconferencing) for any event or situation that impacts participant safety throughout the study and specified interventions or study participation will be suspended or terminated dependent on the response of the SMC.

**Safety Pause**

Administration of the study products and new enrollments will be paused by the PI according to the criteria noted below if any of the following occur:

a) Two or more participants experience a primary safety outcome measure that is a Grade ≥3 AE possibly related to study treatment (other than self-limited Grade 3 solicited reactogenicity AEs); or

b) One (or more) participant experiences a Serious Adverse Event (SAE) that is assessed as related to study product.

In the event of a pause, the Study Monitoring Committee (SMC) will be asked to review all safety data. Review will include the relation to study treatment of the event(s) thought by the core team to be a primary safety outcome. In the event of a pause, the FDA (IND) and the DAIDS Medical Officer (MO) will be promptly notified.

**Criteria for Resuming the Study**

Study product administration and enrollments would resume only if review of the AEs that caused the pause results in a recommendation to permit further study product administrations and study enrollments. The reviews to make this decision will occur as follows:

- Pauses for treatment-related SAEs: The DAIDS MO and the PI will consult with the FDA to conduct the review and make the decision to resume, amend, or close the study and will notify the IRB accordingly.
- Pauses for Grade 3 or higher treatment-related AEs: The DAIDS MO, with the PI and the Safety Monitoring Committee (SMC), will conduct the review and make the decision to resume, amend, or close the study for the Grade 3 or higher AEs that meet criteria for pausing the study. As part of the pause review, the reviewers will also advise on whether the study needs to be paused again for any subsequent events of the same type. The FDA and the IRB will be notified of Grade 3 or higher pause reviews and of the study protocol team decision.

### 10.1.7 CLINICAL MONITORING

To ensure the safety of participants in the study, compliance with applicable regulations, and to ensure accurate, complete, and reliable data, the study PI will keep records of laboratory tests, clinical notes, and participant medical records in the participant files as source documents for the study.

An independent study monitor will monitor the study on a regular basis throughout the study period according to the study monitoring plan. The study PI (or designee) will allocate adequate time for such monitoring activities. The study monitor periodically will conduct a review of a sample of the participant data recorded on source documents at the study site. The study PI (or designee) will also ensure that the monitor is given access to all the above noted study-related documents, source documents (regardless of media), and study-related facilities (e.g., IDS pharmacy, etc.), and has adequate space to conduct the monitoring visit. Queries may be raised if any datum is unclear or contradictory. The study PI and site study personnel must address all queries in a timely manner.

Participation as an Investigator in this study implies acceptance of the potential for inspection by the study Sponsor/Funder and its Representatives, US or non-US government regulatory authorities, IRB, and applicable compliance and quality assurance offices. The study PI (or designee) will permit study-related audits and inspections and will provide access to all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). The study PI will ensure the capability for inspections of applicable study-related facilities (e.g., IDS pharmacy, CTRC, etc.).

<u>Minimizing risk to participants</u>

Procedures to minimize risk to participants in the conduct of this study include: 1) informing participants about risks so they can recognize and report harms in partnership with the study team; 2) respecting local/national blood draw limits; 3) direct observation of participants after study treatment administration with VRC07-523LS and collection of information regarding side effects for several days post product administration; 4) having study staff properly trained in administering study procedures that may cause physical harm or psychologic distress, such as blood draws and infusions; and 5) providing study monitoring.

### 10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

UNC will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. A quality management plan was developed to describe the quality management program.

UNC follows Standard Operating Procedures (SOPs) for quality management. Clinical research files verify and insure that the clinical trial is conducted per protocol and that data is generated and biological specimens collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)). Data Quality is monitored per the data quality management plan with routine and specific research chart review.

The study staff will be educated on the protocol and training will be provided as needed to implement protocol procedures. The study data management team will be responsible for addressing QA issues (e.g., correcting procedures that are not in compliance with the protocol) and QC issues (e.g., correcting errors in data entry). Documentation, as required, will be maintained in the regulatory files.

UNC will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the funding sponsor, and inspection by local and regulatory authorities.

### 10.1.9 DATA HANDLING AND RECORD KEEPING

#### 10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The clinical research staff is responsible for data collection under the supervision of the site principal investigator (or designee). The study PI (or designee) is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hard copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a UNC School of Medicine Database, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and external quality checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

#### 10.1.9.2 STUDY RECORDS RETENTION

Per ICH guidelines, all essential documents, including source documents (regardless of media), signed ICFs, and laboratory test results, should be retained by the study PI (or designee) for at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since formal discontinuation of clinical development of the investigational products.

### 10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigators, or the study site staff. As a result of deviations, corrective actions will be developed and implemented promptly, when necessary.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the site PI (or designee) to use continuous vigilance to identify and report deviations at the annual renewal of the protocol, provided there is not impact on participant safety as a result of the deviation. All deviations must be addressed in study source documents. Protocol deviations are sent to the UNC IRB per their policies. The site PI is responsible for knowing and adhering to reviewing the IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

### 10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.
- NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov, if required.
- NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

### 10.1.12 CONFLICT OF INTEREST POLICY

The University of North Carolina at Chapel Hill recognizes that conflicts of interest will arise from the research enterprise, from technology transfer activities, and from the many facets of our investigators' professional activities. UNC seeks to identify and manage these conflicting relationships, restricting activities where necessary, to preserve transparency, independent decision-making, protection of research participants, and integrity of the educational experience. UNC's Conflict of Interest Program will have oversight over this study.

## 10.2 ABBREVIATIONS

| | |
|---|---|
| ACTG | AIDS Clinical Trials Group |
| ADA | Anti-Drug Antibody |
| ADCC | Antibody-Dependent Cell-Mediated Cytotoxicity |
| AE | Adverse Event |
| AESI | Adverse Events of Special Interest |
| AIA | Anti-Idiotypic Antibody |
| ALT | Alanine Aminotransferase |
| ANC | Absolute Neutrophil Count |
| ANCOVA | Analysis of Covariance |
| ART | Antiretroviral Therapy or combination ART |
| AST | Aspartate Aminotransferase |
| ATI | Analytical Treatment Interruption |
| BMI | Body Mass Index |
| Boosted-PI | Boosted Protease Inhibitor |
| BP | Blood Pressure |
| bNAbs | Broadly Neutralizing Antibodies |
| ca-RNA | CD4 T Cell-Associated HIV RNA |
| CFAR | Center for AIDS Research |
| CFR | Code of Federal Regulations |
| CKD-EPI | Chronic Kidney Disease - Epidemiology Collaboration Equation |
| CI | Confidence Interval |
| CLIA | Clinical Laboratory Improvement Amendments |
| CMP | Clinical Monitoring Plan |
| COC | Certificate of Confidentiality |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| CRS | Clinical Research Sites |
| DAIDS | Division of AIDS |
| DHHS | Department of Health and Human Services |
| DLT | Dose Limiting Toxicity |
| DOB | Date of Birth |
| DRE | Disease-Related Event |
| E/CIA | Enzyme Chemiluminescence Immunoassay |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Form |
| eGFR | estimated Glomerular Filtration Rate |
| EOS | End of Study |
| Fc-Rn | Fc-Receptor |

| | |
|---|---|
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FFR | Federal Financial Report |
| FSH | Follicle Stimulating Hormone |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| GWAS | Genome-Wide Association Studies |
| HBsAg | Hepatitis B Surface Antigen |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HDAC | Histone Deactylase |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| HPTN | HIV Prevention Trials Network |
| HSP | Human Subjects Protection |
| HVTN | HIV Vaccine Trials Network |
| IB | Investigator's Brochure |
| IC (F) | Informed Consent (Form) |
| ICH | International Conference on Harmonisation |
| ID | Infectious Diseases |
| IDS | Investigational Drug Services |
| IFN | Interferon |
| IGHID | International Global Health and Infectious Diseases |
| IL-2 | Interleukin 2 |
| IND | Investigational New Drug Application |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IRE | Immediate Reportable Events |
| ISO | International Organization for Standardization |
| IUD | Intrauterine Device |
| IUPM | Infectious Units per Million |
| IV | Intravenous |
| $K^+$ | Potassium |
| $kg/m^2$ | Kilogram per square meter |
| LDL | Low Density Lipoprotein |
| LRA | Latency Reversal Agent |
| LTFU | Lost To Follow Up |
| mAbs | Monoclonal Antibodies |
| MedDRA | Medical Dictionary for Regulatory Activities |
| meq | milliequivalents |
| $Mg^{++}$ | Magnesium |
| mm Hg | Millimeter of mercury |
| mg/kg | Milligram per kilogram |
| MOP | Manual of Procedures |
| MRN | Medical Record Number |
| NCT | National Clinical Trial |
| NIAID | National Institutes of Allergy & Infectious Diseases |
| NIH | National Institutes of Health |
| NIH IC | NIH Institute or Center |

| | |
|---|---|
| nm | Nanometer |
| NNRTI | Non-Nucleoside Reverse Transcriptase Inhibitor |
| NSI | New Safety Information |
| OHRP | Office for Human Research Protections |
| PHI Studies | Primary HIV Infections Studies |
| P | Pulse or heart rate |
| PI | Principal Investigator |
| PID | Participant Identifier Code |
| PK | Pharmacokinetic |
| PO | By mouth |
| PT | Prothrombin Time |
| PTT | Partial Thromboplastin Time |
| “q” or Q | every |
| Q-PCR | Quantitative–Polymerase Chain Reaction |
| QA | Quality Assurance |
| QC | Quality Control |
| QVOA | Quantitative Viral Outgrowth Assay |
| RNA | Ribonucleic Acid |
| RPR | Rapid Plasma Reagin |
| RR | Respiratory Rate |
| RSC | Regulatory Support Center |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SCA | Single Copy Assay |
| SID | Study Specific Identifier Code |
| SMC | Safety Monitoring Committee |
| SOE | Schedule of Events |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| T | Temperature |
| TAF | Tenofovir Alafenamide |
| TCR | Tissue Cross Reactivity |
| TDF | Tenofovir Disoproxil Fumarate |
| TEAE | Treatment Emergent Adverse Event |
| ULN | Upper Limit of Normal |
| UNC | University of North Carolina at Chapel Hill |
| US | United States |
| VOR | Vorinostat |
| VRC | Vaccine Research Center |
| VRC07-523LS | VRC-HIVMAB075-00-AB |

## 10.3 PROTOCOL AMENDMENT HISTORY

| Version | Date | Description of Change | Brief Rationale |
|---|---|---|---|
| Version 1.0 | 13 February 2018 | Initial Protocol | CSRC Review |
| Version 2.0 | 4 May 2018 | Amendments following the CSRC, FDA and UNC IRB reviews | UNC IRB approved on 5/29/18 |

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|---|---|---|---|
| Version 3.0 | 08 November 2018 | Increase in # participants to be enrolled (n=12); modification to Inclusion/Exclusion Criteria | Change in NIH funding; clarification of eligibility requirements |
| Version 4.0 | 09 May 2019 | Removed ex vivo and in vivo cell associated RNA response to Vorinostat | Advance of assay methodology to measure resting cell infection |
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