CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2a Study to Evaluate the Safety and Tolerability of a Regimen of Dual Anti-HIV Envelope Antibodies, VRC07-523LS and CAP256V2LS, in a Sequential Regimen with a TLR7 Agonist, Vesatolimod, in Early Antiretroviral-Treated HIV-1 Clade C-Infected Women
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	This is a non-IND study
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	~~Not Available~~ NCT05281510
Indication:	HIV-1 Infection
Protocol ID:	GS-US-382-5445
Contact Information:	The Medical Monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 18 December 2020 Amendment 1: 17 June 2021 Amendment 2: 26 August 2022 Amendment 3: 07 October 2022

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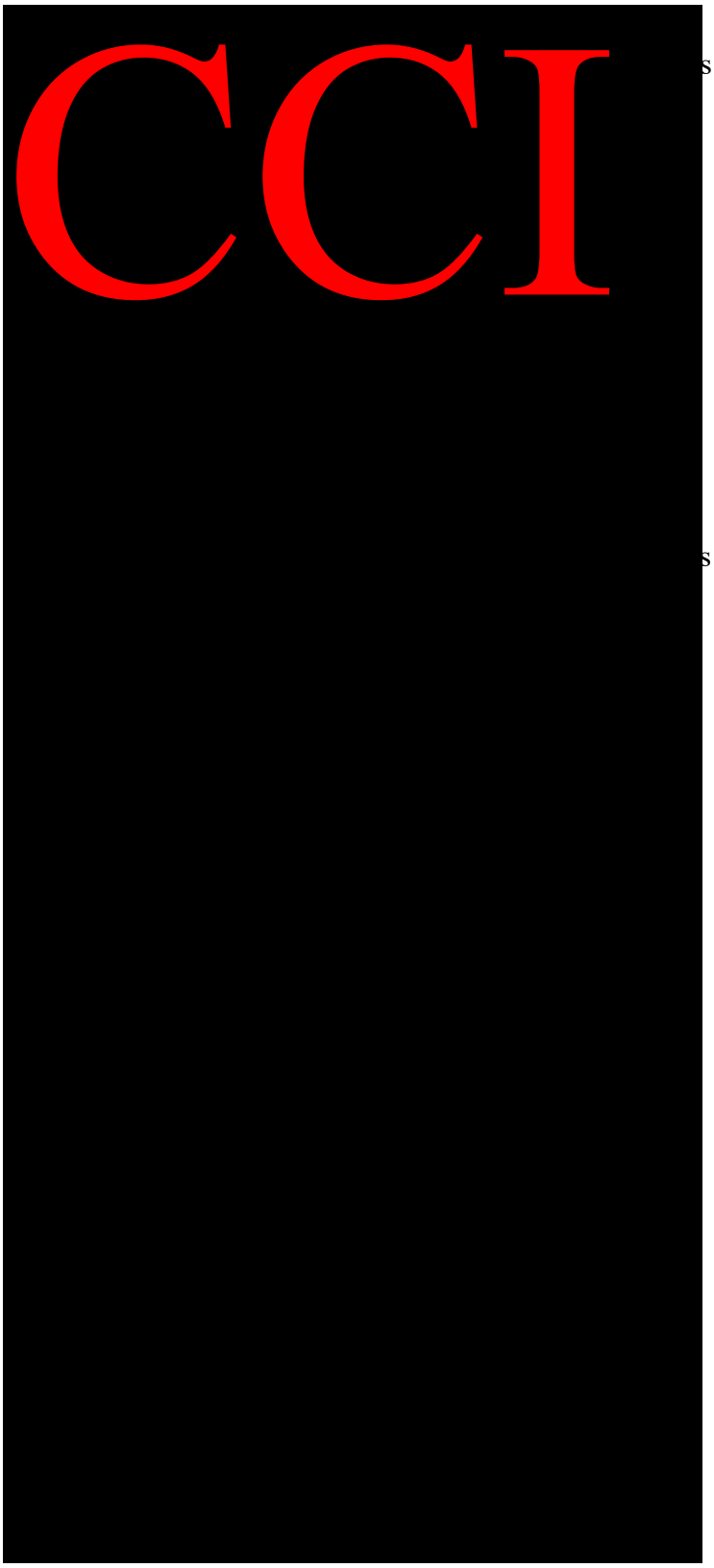
PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 2a Study to Evaluate the Safety and Tolerability of a Regimen of Dual Anti-HIV Envelope Antibodies, VRC07-523LS and CAP256V2LS, in a Sequential Regimen with a TLR7 Agonist, Vesatolimod, in Early Antiretroviral-Treated HIV-1 Clade C-Infected Women
IND Number:	This is a non-IND study
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	Not Available
Study Centers Planned:	Single center in South Africa
Objectives:	The primary objective of this study is as follows: • To evaluate the safety and tolerability of dual anti-HIV envelope monoclonal antibodies (mAbs), VRC07-523LS and CAP256V2LS, in a sequential regimen with a toll-like receptor (TLR)7 agonist, vesatolimod (VES), when administered in virologically suppressed HIV-1 Clade C-infected women on antiretroviral therapy (ART) and during analytical treatment interruption (ATI) The secondary objectives of this study are as follows: • To evaluate the pharmacokinetics (PK) of VRC07-523LS, CAP256V2LS, and VES • To evaluate whether VRC07-523LS and CAP256V2LS induce anti-VRC07-523LS and/or anti-CAP256V2LS antibodies • To evaluate the effect of VRC07-523LS and CAP256V2LS in a sequential regimen with VES on viral control or the need for resumption of ART following an ATI



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Study Design:

Number of Participants Planned:	Approximately 25 participants in total
Target Population:	Nonpregnant, nonlactating female adults recruited from the Females Rising through Education, Support, and Health (FRESH) acute HIV infection cohort, who have HIV-1 and have been virologically suppressed (HIV-1 RNA < 50 copies/mL) on ART for at least 12 consecutive months prior to screening. Two or less unconfirmed virologic elevations of ≤ 1000 copies/mL at nonconsecutive visits within 12 months are acceptable.
Duration of Treatment:	Participants will receive administration of study drugs for a maximum of 18 weeks.
Diagnosis and Main Eligibility Criteria:	Participants with HIV-1 Clade C who meet the following criteria: • Females recruited from the FRESH acute HIV infection cohort • Age ≥ 18 years • Plasma HIV-1 RNA levels < 50 copies/mL at the screening visit • Documented plasma HIV-1 RNA viral load must be < 50 copies/mL for 12 consecutive months prior to screening: o ≤ 2 detectable (≤ 1000 copies/mL) HIV-1 RNA measurements are acceptable o Determinations below the level of quantitation will be considered as detectable at the assay's threshold level • Documented history of viral sensitivity to VRC07-523LS or CAP256V2LS at the screening visit • ART selection and allowances: o On ART regimen for ≥ 12 consecutive months prior to screening. The following agents are allowed as part of the current ART regimen: nucleoside reverse-transcriptase inhibitors, raltegravir, bictegravir, dolutegravir, and rilpivirine.

  - A change in ART regimen ≤ 45 days prior to the prebaseline/Day −13 visit for reasons other than virologic failure (eg, tolerability, simplification, drug-drug interaction profile) is allowed. If the participant's ART regimen is changed, a plasma HIV-1 RNA level < 50 copies/mL at the prebaseline/Day −13 visit will be required to confirm eligibility.
  - Availability of a fully active alternative ART regimen, in the opinion of the investigator, in the event of discontinuation of the current ART regimen with development of resistance.
- Hemoglobin ≥ 10.0 g/dL
- White blood cells ≥ 2500 cells/μL
- Platelets ≥ 125,000/mL
- Absolute neutrophil counts ≥ 1000 cells/μL
- CD4+ T cell count ≥ 500 cells/μL
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin ≤ 2 × upper limit of normal
- Creatinine clearance ≥ 60 mL/min
- In women of childbearing potential:
  - Agreement to follow study contraceptive requirements
- Participants with coinfection and/or immunosuppression as described below will be excluded:
  - Autoimmune disease requiring ongoing immunosuppression (except in the case of mild autoimmune disease that only requires topical treatments)
  - Evidence of chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen OR positive hepatitis B core antibody and negative hepatitis B surface antibody)

- Evidence of current hepatitis C virus (HCV) infection (defined as positive hepatitis C antibody and HCV RNA > lower limit of quantitation)
    - positive anti-HCV antibody and negative HCV polymerase chain reaction results are acceptable
  - Documented history of pre-ART CD4+ T cell count nadir < 200 cells/μL (unknown pre-ART CD4+ T cell count nadir is acceptable)
  - History of opportunistic illness indicative of Stage 3 HIV
  - Acute febrile illness within 4 weeks prior to the first dose

Study Procedures/ Frequency:

Screening

Participants will be evaluated for eligibility. The screening visit assessments will include the following:

- Obtain written informed consent
- PBMC sample for testing of viral sensitivity to the VRC07-523LS and CAP256V2LS mAbs, if not previously conducted
- Blood and urine tests (hematology, serum chemistry, metabolic assessment, HIV-1 RNA, serum pregnancy, creatinine clearance, CD4+/CD8+ T cell counts, and urinalysis). Additional tests will include HBV and HCV serology
- 12-lead electrocardiogram (ECG)
- Complete physical examination, vital signs, height, body weight, and medical (including HIV) history
- Serum follicle-stimulating hormone test (for females < 54 years old who have ceased menstruating for ≥ 12 months, but are not permanently sterile or do not have documentation of ovarian hormonal failure)
- Documentation of participant agreement to follow study contraceptive requirements

- Documentation of HIV staging at detection using standard markers (eg, HIV-1 RNA, p24 antigen, fourth generation combination antigen/antibody enzyme-linked immunosorbent assay, HIV-1 Western blot), duration of viremia during acute HIV infection and peak HIV RNA

Eligible participants should return to the study center for prebaseline/Day −13 assessments within 5 weeks of the screening visit.

Prebaseline/Day −13 Assessments

The prebaseline/Day −13 visit is to be completed within 35 days of the screening visit. The prebaseline/Day −13 visit will include the following assessments:

- Review of inclusion/exclusion criteria to confirm participant eligibility
- Review of adverse events (AEs) and changes in concomitant medications
- Review medical history
- Symptom-directed physical examination as needed, and body weight
- Birth control will be checked and replaced, if required
- Urine pregnancy test
- Plasma HIV-1 RNA
- Blood and urine tests (hematology, serum chemistry, creatinine clearance, and urinalysis). Additional blood tests will also be taken for virology and biomarker analyses

Treatment Assignment

Obtain participant number and assign treatment to the participant in the interactive web response system. The participant number assignment and treatment assignment will be performed in clinic at the baseline/Day 0 visit, provided that all screening procedures have been completed and participant eligibility has been confirmed. If a participant's ART regimen is changed ≤ 45 days prior to

prebaseline/Day −13, plasma HIV-1 RNA < 50 copies/mL at prebaseline/Day −13 visit is required to confirm eligibility.

Period 1 (Days 0 to 28)

Participants will have up to 10 visits over 4 weeks.

Sentinel Dosing: Five participants will be enrolled first, to conduct visits and assessments up to Day 21. Upon review of the safety data and confirmation from an external data monitoring committee, up to a further 20 participants will be enrolled into Period 1.

The following assessments are to be completed:

- Dosing of VRC07-523LS and CAP256V2LS in a sequential regimen with VES:
  - Doses 1 to 3 of VES will be administered orally on baseline/Day 0, Day 14, and Day 28. One dose of VRC07-523LS and 1 dose of CAP256V2LS will be administered sequentially by intravenous (IV) infusions on Day 7.
  - Participants will continue to take their ART during this period (Days 0 to 28).
  - Fasted status and food consumption will be checked prior to dosing.
  - Participants will remain at the site for 24 hours after Dose 1 of VES, for at least 8 hours after Dose 2 of VES, and for at least 4 hours after Dose 3 of VES for monitoring. If participants experience significant influenza-like AEs (eg, moderate or severe pyrexia, chills, headache, myalgia, fatigue, malaise, joint pain) after the first 2 VES doses, or if dose is escalated to 8 mg, monitoring may be extended to > 4 hours for subsequent doses.
  - Participants will remain at the site for 8 hours after the infusions of VRC07-523LS and CAP256V2LS for monitoring.

If participants experience new or worsening symptoms, postdose safety monitoring should be extended.

- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature) at predose and frequent intervals following each scheduled dose of VES, VRC07-523LS, and CAP256V2LS:
  - **Dose 1 of VES**: Prior to administration and then at 1, 2, 4, 8, 12, 18, and 24 hours after administration. If the participant experiences new or worsening symptoms, evaluate for signs and symptoms of cytokine release syndrome (CRS), including vital signs.
  - **Dose 2 of VES:** Prior to administration and then at 1, 2, 4, and 8 hours after administration. If the participant experiences new or worsening symptoms, evaluate for signs and symptoms of CRS, including vital signs.
  - **Dose 3 of VES:** Prior to administration and then at 1, 2, and 4 hours after administration. If the participant experiences new or worsening symptoms, evaluate for signs and symptoms of CRS, including vital signs.
  - **VRC07-523LS and CAP256V2LS**: Prior to administration and at 1, 2, 4, and 8 hours after administration. If the participant experiences new or worsening symptoms, evaluate for signs and symptoms of CRS, including vital signs.
- Plasma HIV-1 RNA and Plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART will be performed at each weekly visit.
- Blood and urine safety monitoring (hematology, serum chemistry, creatinine clearance, and urinalysis) will be performed at all visits except Days 8 and 9. Additional blood samples will also be taken for PK, virology, and biomarker analyses at specified visits.
- CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio will be evaluated at a visit every 2 weeks.
- Body weight

- Urine pregnancy test at the baseline/Day 0 and Day 28 visits
- Birth control will be checked at every visit and replaced, if required.
- Symptom-directed physical examination will be performed at every visit.
- Adverse events and concomitant medications will be assessed at each visit. Participants will be reminded to report all symptoms, including flu-like symptoms (eg, fatigue, pyrexia, chills, myalgia, joint pain, or headache) or other unexpected symptoms.

Analytical treatment interruption eligibility will be assessed at Day 28, to determine whether the participant can proceed to Period 2.

Period 2 (Days 29 to 133)

Participants will have up to 18 visits over 15 weeks. The following assessments are to be completed:

- Dosing of VES:
  - Doses 4 to 10 of VES will be administered orally at Days 42, 56, 70, 84, 98, 112, and 126
  - Participants will remain at the site for at least 4 hours after dosing for monitoring. If participants experience significant influenza-like AEs (eg, moderate or severe pyrexia, chills, headache, myalgia, fatigue, malaise, joint pain) after the first 2 VES doses, monitoring may be extended to > 4 hours for subsequent doses.
  - No ART will be administered and ATI will start from Day 35.
  - Fasted status and food consumption will be checked prior to dosing

- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature) at predose and at frequent intervals following each scheduled dose:
  - **Doses 4 to 10 of VES**: Prior to administration and at 1, 2 and 4 hours after administration. If the participant experiences abnormal vital signs, new or worsening symptoms, evaluate for signs and symptoms of CRS, including vital signs.
- Plasma HIV-1 RNA and Plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART will be performed at Day 42 and at each visit every 2 weeks thereafter.
- Blood and urine safety monitoring (hematology, serum chemistry, creatinine clearance, and urinalysis) will be performed at Day 42 and at each visit every 2 weeks. Additional blood samples will also be taken for PK, virology, and biomarker analyses at required visits.
- CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio will be evaluated at Day 42 and each visit every 2 weeks.
- Body weight at Day 42 and at each visit every 2 weeks
- Urine pregnancy test at Day 42 and at each visit every 4 weeks
- Birth control will be checked at every visit and replaced, if required.
- Known HIV-1 seronegative sexual partners of enrolled study participants may be referred for HIV preexposure prophylaxis (PrEP) to decrease the risk of HIV transmission during ATI.
- Symptom-directed physical examination will be performed at every visit

- Adverse events and concomitant medications will be assessed at each visit. Participants will be reminded to report all symptoms, including flu-like symptoms (eg, fatigue, pyrexia, chills, myalgia, joint pain, or headache) or other unexpected symptoms

Period 3 (Days 134 to 336)

Participants will have up to 14 study visits every 2 weeks for a total of 29 weeks. At the end of Period 3, all participants will be required to complete an end-of-Period 3 visit prior to moving into Period 4.

No study drug (VES, VRC07-523LS, CAP256V2LS) or ART will be administered in this period.

The following assessments are to be completed:

- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature) at Day 147 and at each visit every 4 weeks
- Plasma HIV-1 RNA and plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART will be performed at a visit every 2 weeks
- CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio will be evaluated at Day 147 and at each visit every 4 weeks
- Blood and urine safety monitoring (hematology, serum chemistry, creatinine clearance, and urinalysis) will be performed at Day 147 and at each visit every 4 weeks. Additional blood samples will also be taken for PK, virology, and biomarker analyses at required visits.
- Body weight at Day 147 and at each visit every 4 weeks
- Urine pregnancy test at Day 147 and at each visit every 4 weeks
- Birth control will be checked at every visit and replaced, if required.
- Known HIV-1 seronegative sexual partners of enrolled study participants may be referred for HIV PrEP to decrease the risk of HIV transmission during ATI.

- Symptom-directed physical examination at Day 147 and at each visit every 4 weeks.
- Adverse events and concomitant medications will be assessed at each visit. Participants will be reminded to report all symptoms, including flu-like symptoms (eg, fatigue, pyrexia, chills, myalgia, joint pain, or headache) or other unexpected symptoms.

End-of-Period 3 Visit

This visit will be completed at the end of Period 3 or if ART restart criteria are met prior to starting Period 4A. The assessments will include AEs and concomitant medication review, blood tests, vital signs, symptom-directed physical examination, body weight, and a 12-lead ECG.

Period 4 (Days 337 to 413)

Participants who have remained virologically suppressed (plasma HIV-1 RNA < 50 copies/mL) or have not met the ART restart criteria by the end of Period 3 will continue in either Period 4A and restart ART for 12 weeks, or Period 4B and remain off ART for a 12-week ATI extension. The choice of Period 4A or 4B will be at the discretion of the participant and investigator.

Participants who meet the ART restart criteria prior to the end of Period 3 may also take part in Period 4A.

Participants will complete 6 study visits scheduled every 2 weeks over a 12-week period and will conclude with a separate end-of-study visit.

The following assessments are to be completed:

- Plasma HIV-1 RNA and plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART will be performed at a visit every 2 weeks during ART restart (Period 4A) and ATI extension (Period 4B)
- Blood safety monitoring (hematology, serum chemistry, creatinine clearance, and urinalysis) will be performed at Day 343 and at each visit every 4 weeks (Periods 4A and 4B). Additional blood samples will also be taken for PK, virology, and biomarker analyses at required visits

- CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio will be evaluated at Day 343 and at each visit every 4 weeks (Periods 4A and 4B)
- Urine pregnancy test at the first ART restart visit and every 4 weeks thereafter (Period 4A) and every 4 weeks during the ATI extension (Period 4B)
- Body weight at Day 343 and at each visit every 4 weeks (Periods 4A and 4B)
- Birth control will be checked at every visit and replaced, if required (Periods 4A and 4B).
- Symptom-directed physical examination at Day 343 and at each visit every 4 weeks (Periods 4A and 4B)
- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature) will be measured at Day 343 and at each visit every 4 weeks (Periods 4A and 4B)
- Known HIV-1 seronegative sexual partners of enrolled study participants may be referred for HIV PrEP to decrease the risk of HIV transmission during ATI (Period 4B only).
- Adverse events and concomitant medications will be assessed at each visit. Participants will be reminded to report all symptoms, including flu-like symptoms (eg, fatigue, pyrexia, chills, myalgia, joint pain, or headache) or other unexpected symptoms (Periods 4A and 4B).

Early Discontinuation from Study Drug and Follow-up Procedures

If a participant should discontinue study dosing as described in Section 6.9.1, they will be required to complete an early study drug discontinuation (ESDD) visit and every attempt should be made to keep the participant in the study and continue to perform study procedures. If the participant is unable to complete all scheduled procedures, for criteria other than those described for study discontinuation in Section 3.5., the participant should be followed by telephone for a further duration of time as described in Section 6.9.2.

If a participant has completed all study drug dosing but is unable to complete all subsequent visits at the study site, as scheduled in Periods 3 and 4, for criteria other than those described for study discontinuation in Section 3.5. for study discontinuation, the participant they should be followed by telephone for up for 250 days after mAb infusion. During follow up with telephone check-ups, participants should be followed every 4 weeks to monitor for AEs and retrieve urine pregnancy results (kits to be provided at the last study site visit and a positive urine pregnancy result will require confirmation with a serum pregnancy test at the study site). At the end of all follow-up monitoring, participants will undergo the end-of-follow-up visit at the study site.

End-of-Study Visit

The end-of-study visit will be completed for participants who have completed Period 4A or 4B. The assessments will include AEs and concomitant medication review, vital signs, symptom-directed physical examination, body weight, 12-lead ECG, creatinine clearance, hematology, serum chemistry, urine pregnancy test, urinalysis, and ATI remission tests.

ART Restart Criteria

Participants will receive ART in Periods 1 and 4A only. In Periods 2, 3, and 4B, participants will be in ATI and will restart ART if they have plasma HIV-1 RNA measurements of ≥ 1,000 copies/mL for 8 consecutive weeks and no drop of 0.3 $\log_{10}$ from previous week, or confirmed plasma HIV-1 RNA > 100,000 copies/mL, or a confirmed CD4+ T cell count < 350 cells/μL, or if a participant becomes pregnant, or per participant request, or at the discretion of the investigator or sponsor due to other clinical criteria. Once the first confirmed HIV-1 RNA value of ≥ 50 copies/mL is detected, this will trigger weekly testing to monitor the HIV-1 RNA measurements.

Additional Procedures

Additional blood sampling or procedures will be completed in all participants, unless otherwise specified as optional:

Pharmacokinetics

Plasma VES PK collections will be obtained relative to Dose 1 of VES at: predose (≤ 5 minutes prior to dosing), 1, 2, 4, 8, 12, 24 (Day 1), and 48 hours (Day 2) after dosing.

Serum VRC07-523LS PK collections will be obtained relative to VRC07-523LS infusion at: 0 hours (predose), end of infusion, 1, 2, 4, and 8 hours after end of infusion, and then at Days 8, 9, 14, 21, 28, 56, 84, 112, 133, 161, 189, 217, 245, 273, 301, 329, 343, 371, and 413.

Serum CAP256V2LS PK collections will be obtained relative to CAP256V2LS infusion at: 0 hours (predose), end of infusion, 1, 2, 4, and 8 hours after end of infusion, and then at Days 8, 9, 14, 21, 28, 56, 84, 112, 133, 161, 189, 217, 245, 273, 301, 329, 343, 371, and 413.

Plasma dolutegravir PK collections will be obtained at: Days 56, 84, 112, 133, 161, 189, 217, 245, 273, 301, 329, and for participants in Period 4B only Days 343, 371, and 413.

Immunogenicity (Anti-VRC07-523LS and Anti-CAP256V2LS assessments)

Blood samples for detection of serum anti-VRC07-523LS and anti-CAP256V2LS antibodies will be collected at the following timepoints: prebaseline/Day −13, Days 28, 56, 84, 112, 133, 161, 189, 217, 245, 273, 301, 329, 343, 371, and 413.

Pharmacodynamics and Immunology

Whole blood messenger RNA (mRNA) expression (including ISGs) at: prebaseline/Day −13, within 1 hour before Doses 1, 5, and 10 of VES and 1 day after Doses 1, 5, and 10 of VES, end-of-Period 3 visit, and if completing Period 4B only, the end-of-study visit.

Change in HIV-specific antibody profiling using plasma samples at: prebaseline/Day −13, within 1 hour before Doses 1 and 10 of VES, 7 days after Doses 1 and 10 of VES, end-of-Period 3 visit, and the end-of-study visit.

Prebaseline soluble proteins in TruCulture® Whole Blood Culture System (Day –13).

Changes in the levels of soluble proteins (cytokines, chemokines, and inflammatory markers) at: prebaseline/Day −13, within 1 hour before Doses 1, 5, and 10 of VES, 1 day and 7 days after Doses 1, 5, and 10 of VES, end-of-Period 3 visit, and the end-of-study visit.

PBMC immune cell frequency, activation and phenotyping at: prebaseline/Day −13, within 1 hour before Doses 1, 5, and 10 of VES, 1 day and 7 days after Doses 1, 5, and 10 of VES, end-of-Period 3 visit, and the end-of-study visit.

HIV-specific T cell responses from PBMC by intracellular cytokine staining at: prebaseline/Day −13, 7 days after Doses 1, 5, and 10 of VES, end-of-Period 3 visit, and the end-of-study visit.

Participants who sign an additional consent will have the following optional samples taken:

Human leucocyte antigen genotype, TLR7, and Fc gamma receptors (FcgR) single nucleotide polymorphism (SNP) at: prebaseline/Day −13.

Lymph node and/or GALT biopsies at prebaseline/Day −13, Week 21 (beginning of Period 3), end-of-Period 3 visit, and the end-of-study visit will be used for some or all of the following tests: immune cell frequency, activation, and phenotype, gene expression, and HIV-specific T cell response evaluation.

Virology

Plasma viremia will be assessed throughout the study Periods 1, 2, 3, and 4.

Whole blood derived PBMC samples will be used to assess changes in latent HIV-1 reservoir at prebaseline/Day −13, Week 21 (beginning Period 3), end-of-Period 3 visit, and end-of-study visit.

Whole blood derived plasma and PBMC samples will be used to assess changes in active HIV-1 reservoir at prebaseline/Day −13, Days 0, 2, 56, 57, 126, 127, 128, end-of-Period 3 visit, and end-of-study visit.

Whole blood derived PBMC samples will be used to assess for viral sensitivity to VRC07-523LS and CAP256V2LS mAbs at screening, Week 21 (beginning Period 3), end-of-Period 3 visit, and end-of-study visit.

In case of viral rebound at any time point during the study, plasma virus will be tested for resistance to VRC07-523LS, CAP256V2LS, and baseline ART.

Participants who sign an additional consent will have the following optional samples taken:

Immune cell isolates from lymph node and/or GALT biopsies will be assessed for changes in active and latent HIV-1 reservoir at prebaseline/Day −13, Week 21 (beginning of Period 3), end-of-Period 3 visit, and the end-of-study visit

Procedure Definitions and Specifications

HIV-1 RNA will be performed by a validated assay with a lower limit of quantitation of at least 50 copies/mL.

Hematology panel includes: complete blood count with differential and platelets, CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio.

Serum chemistry panel includes: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, creatine kinase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, and uric acid.

Urinalysis includes dipstick.

Serum and urine pregnancy tests are performed only on female participants of childbearing potential. A positive urine result will be confirmed with a serum pregnancy test.

Known HIV-seronegative male partners to the female study participants may be referred for HIV PrEP to decrease the risk of HIV transmission during ATI.

Test Product, Dose, and Mode of Administration:	• VRC07-523LS, 20 mg/kg, IV infusion over 30 minutes • CAP256V2LS, 20 mg/kg, IV infusion over 30 minutes • Vesatolimod, 6 mg (3 × 2 mg tablets) or 8 mg (4 × 2 mg tablets), administered orally under fasted conditions
Reference Therapy, Dose, and Mode of Administration:	• Not applicable
Criteria for Evaluation:	
Safety:	Adverse events and clinical laboratory tests
Efficacy:	Time to viral rebound (confirmed ≥ 50 copies/mL and ≥ 200 copies/mL) following ATI Plasma viral load set-point following ATI Viral load at the end of ATI Time to ART resumption following ATI
Immunogenicity:	Proportion of participants with positive anti-VRC07-523LS or anti-CAP256V2LS antibodies
Pharmacokinetics:	PK parameters for VES in plasma will include C_{max}, T_{max}, C_{last}, T_{last}, AUC_{inf}, AUC_{last}, AUC_{exp}, $t_{1/2}$, CL/F, and V_z/F. PK parameters for VRC07-523LS and CAP256V2LS in serum will include C_{max}, T_{max}, C_{last}, T_{last}, AUC_{inf}, AUC_{last}, AUC_{exp}, $t_{1/2}$, CL, V_{ss}, and V_z. Plasma concentrations of dolutegravir may be analyzed
Pharmacodynamics and Immunology:	Induction of cytokines, chemokines, inflammatory markers, mRNA transcript (including ISGs), immune activation in response to VES, VRC07-523LS, and CAP256V2LS may be analyzed. TLR7 genotype may be analyzed
Statistical Methods:	Safety: • The incidences of treatment-emergent AEs and treatment-emergent laboratory abnormalities will be summarized.

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Sample Size:

The sample size in this study is determined based on practical considerations and empirical experience with similar types of studies. No sample size and power calculation was performed. Up to 25 participants will provide a preliminary assessment of descriptive safety, efficacy and PK.

This study will be conducted in accordance with the guidelines of Good Clinical Practice including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration of drug versus time curve of the drug
ACTG	AIDS Clinical Trials Group
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATI	analytical treatment interruption
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AV	atrioventricular
BCRP	breast cancer resistance protein
BLQ	below the limit of quantitation
BMD	bone mineral density
BUN	blood urea nitrogen
C_{28d}	concentration 28 days postdose
C_{84d}	concentration 84 days postdose
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CBC	complete blood count
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
CHB	chronic hepatitis B
CHF	congestive heart failure
CL	Clearance following intravenous administration
CL/F	Clearance following extravascular administration
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
CK	creatine kinase
CRF	case report form
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board

EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ER	emergency room
ESDD	early study drug discontinuation
EVM	elipovimab
FAS	Full Analysis Set
FcgR	Fc gamma receptors
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in the first second of expiration
FRESH	Females Rising through Education, Support, and Health
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
Gilead	Gilead Sciences
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HLA	human leucocyte antigen
IB	investigator's brochure
IC_{50}	50% inhibitory concentration
IC_{80}	80% inhibitory concentration
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IFN	interferon
IL	interleukin
IM	intramuscular
IND	investigational new drug
IRB	institutional review board
ISG	interferon-stimulated gene
ITAC	inducible T cell alpha chemoattractant
IUD	intrauterine device
IV	intravenous(ly)
IWRS	interactive web response system
L	leucine

LLN	lower limit of normal
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
NA	not applicable
NK	natural killer
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PrEP	preexposure prophylaxis
PWH	people with HIV-1
GLPS	Global Patient Safety
Q1	first quartile
Q3	third quartile
QTc	QT interval corrected for heart rate
RBC	red blood cell
RBC/HPF	red blood cells per high power field
RNA	ribonucleic acid
S	serine
SAD	single ascending dose
SAE	serious adverse event
SAHPRA	South African Health Products Regulatory Authority
SC	subcutaneous(ly)
SD	standard deviation
SDV	source data verification
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SHIV	simian-human immunodeficiency virus
SNP	single nucleotide polymorphism
SOP	standard operating procedure
SSRs	special situation reports
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
TLR	toll-like receptor

ULN	upper limit of normal
UNAIDS	United Nations Programme on HIV/AIDS
US	United States
VES	vesatolimod
VR	virologic rebound
V_z	volume of distribution of the drug after intravenous administration

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus type-1 (HIV-1) infection is a life-threatening and serious disease that is of major public health interest around the world. A 2021 report by the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 79.3 million people have been infected with HIV since the start of the epidemic, contributing to 36.3 million deaths from AIDS-related illnesses {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2021}. Despite extensive prevention and treatment efforts, South Africa remains an epicenter of the HIV pandemic where young women carry a high burden of disease with persistent high HIV incidence and prevalence. Untreated infection leads to deterioration in immune function and death. Although antiretroviral therapy (ART) has been associated with a dramatic decrease in AIDS-related morbidity and mortality {Palella 1998}, {Mocroft 1998}, {Sterne 2005}, there is still an urgent medical need to develop new therapies and approaches to eradicate HIV. Current therapy is associated with challenges with tolerability, long-term adherence and safety, drug-drug interactions, and expense. Persistent HIV infection may also be associated with psychosocial stigma. Despite the availability of chronic treatment, morbidity and mortality due to HIV infection remain high due to the latent HIV reservoir, which may contribute to ongoing inflammation-driven disease. Persistent viral reservoirs fuel rebound viremia when treatment ceases. Thus, the discovery and development of therapeutic interventions that can eradicate or control HIV reservoirs, leading to long-term ART-free remission or HIV cure, is a major priority.

Following entry into the target cell, HIV-1 stably integrates into the host genome, thus establishing the basis for latent infection and the main barrier to HIV cure. Neither the host immune system nor ART can eliminate transcriptionally inactive virus. Therefore, adjunctive therapies that efficiently reactivate (“activate”) virus out of this latent reservoir to enable its destruction (“eliminate”) may be required for viral eradication. This activation strategy has been tested in clinical studies of latency reversal agents such as histone deacetylase inhibitors and toll-like receptor (TLR) 9 agonists {Sogaard 2015, Vibholm 2017}.

One challenge of HIV curative efforts is the lack of a fully validated biomarker for the detection of the latent HIV-1 reservoir. This can be overcome by measuring the time to viral rebound and/or new viral load set-points following analytical treatment interruption (ATI). While the AIDS Clinical Trials Group (ACTG) has reported that certain measures of the HIV reservoir may be correlated with time to viral rebound {Li 2016}, ATI remains the most accurate endpoint to evaluate the efficacy of “activate and eliminate” interventions and can be conducted safely in participants {Bar 2016}.

Cohorts of acutely treated people with HIV provide an ideal opportunity to evaluate novel HIV cure interventions with ATI, maximizing the chances of effectively achieving durable control without ART {Dihel 2001}. In fact, initiation of ART during acute HIV infection can reduce the size and dissemination of the viral reservoir {Chun 2007}, thereby potentially facilitating viremic control after ATI. Additionally, early ART initiation results in decrease in viral diversification and preservation of immune function and in some individuals, leads to long-term viral remission after withdrawal of treatment {Saez-Cirion 2013}.

It is postulated that a combination of therapies exerting viral activation and engagement of the host immune system will be necessary to have a demonstrable effect on reducing the HIV-1 reservoir. Combining multiple agents, such as immunomodulators and monoclonal antibodies (mAbs) could therefore provide a multipronged approach to viral control. Given the enormous genetic diversity of HIV-1, the use of multiple mAbs may be required to ensure adequate coverage of circulating strains. Recently, in vitro studies have demonstrated that a combined use of mAbs, simultaneously targeting different epitopes of the virus, results in an improved neutralization breadth and potency. In addition, a combination of mAbs reduces the selective immune pressure created by the virus and thus prevent viral escape mutants.

VRC07-523LS, is a highly potent and broadly neutralizing HIV-1 human mAb targeted against the HIV-1 cluster of differentiation 4 (CD4) binding site, engineered from an antibody isolated from a participant whose immune system controlled the virus without ART. This antibody is characterized by high neutralization potency in vitro and prolonged half-life, which correlates with improved protection against simian-human immunodeficiency virus (SHIV) infection in vivo in animal studies, making it an ideal candidate for clinical application against HIV-1 infection in humans in therapeutic settings. Clinical studies are ongoing.

CAP256V2LS is an engineered variant of CAP256-VRC26.25, a highly potent broadly neutralizing mAb isolated from a South African participant with HIV-1 Clade C enrolled in the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 002 acute HIV infection study. The neutralization breadth of CAP256-VRC26.25 makes it particularly well suited as a complementary mAb with antibodies targeting a different epitope. Furthermore, this mAb provided 100% protection against SHIV challenges in macaque experiments {McLellan 1996}. Clinical studies are ongoing.

Vesatolimod (VES) is a TLR7 agonist currently in clinical development for the treatment and remission of HIV-1 infection. Vesatolimod has been shown to induce interferon-stimulated gene (ISG) messenger RNA (mRNA) expression and production of cytokines and chemokines, and to induce activation of CD4+ and cluster of differentiation 8 (CD8)+ T lymphocytes in people with HIV-1 (PWH) virologically suppressed on ART. The ability of VES to increase the cytotoxic activity of HIV-specific T lymphocytes and activate phagocytic cells, improving antibody-dependent cell-mediated cytotoxicity in vitro, suggests that its immunomodulatory effect could enhance the antiviral activity of mAbs. In fact, in rhesus macaque studies, sequential regimens including TLR7 agonists and either therapeutic vaccination or mAbs have led to SHIV ART-free viral control {Borducchi 2016, Borducchi 2018b}.

This study will evaluate the safety, tolerability, pharmacokinetics (PK), and effect of dual anti-HIV envelope mAbs, VRC07-523LS and CAP256V2LS, in a sequential regimen with a TLR7 agonist, VES, in virologically suppressed women with HIV-1 Clade C on ART and during ATI.

1.2. Investigational Medicinal Products

1.2.1. Nonclinical Studies of Vesatolimod

1.2.1.1. General Information on Vesatolimod

Vesatolimod is an orally administered TLR7 agonist in development for the treatment of HIV infection. Data in vitro have shown that VES is a potent and selective TLR7 receptor agonist with > 30-fold selectivity for TLR7 (32-fold based on half-maximal effective concentration and 81-fold based on minimum effective concentration) over TLR8, with no detectable stimulation of other human TLRs at concentrations up to 100 μM.

1.2.1.2. Nonclinical Pharmacology of Vesatolimod

Nonclinical data in mice and in chimpanzees chronically infected with hepatitis B virus (HBV) demonstrated that oral administration of VES induce a type I interferon (IFN)-dependent innate response in the liver, as measured by induction of ISGs, in the absence of concomitant serum detectable levels of IFN-α (ie, a presystemic response) {Fosdick 2013}, {Lanford 2013}.

In a rhesus macaque model of chronic SHIV infection, treatment with VES demonstrated the ability to enhance the benefits of treatment with a broadly neutralizing antibody, PGT121 {Borducchi 2018a}. Treatment of ART-suppressed SHIV-infected rhesus macaques with VES induced transient increases in cytokine levels and activation of CD4+ T cells, CD8+ T cells, and natural killer (NK) cells. Viral DNA in lymph node biopsies was reduced in the VES and PGT121 combination-treated monkeys, but not in animals receiving VES alone. Following ART discontinuation, the combination treatment group showed the greatest increase in days to viral rebound and number of animals that did not rebound (5 of 11 in combination versus 2 of 11 with PGT121 alone). In animals with sustained ART-free control, depletion of CD8/NK cells did not lead to rebound. Collectively, these results demonstrate that the replication competent viral reservoir was reduced to extremely low levels or eliminated. This study demonstrates that therapeutic administration of VES in combination with a neutralizing anti-HIV envelope antibody can lead to viral remission in a subset of SHIV-infected rhesus macaques in the absence of ART.

For further information on VES, refer to the investigator's brochure (IB) for VES, including information on the following:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology

1.2.2. Nonclinical Studies of CAP256V2LS

1.2.2.1. General Information on CAP256V2LS

CAP256V2LS is an engineered variant of CAP256-VRC26.25, a highly potent broadly neutralizing mAb isolated from a South African participant with HIV-1 Clade C enrolled in the CAPRISA 002 acute HIV infection study {Doria-Rose 2016}. CAP256V2LS differs from its parent by 3 amino acids found in 2 locations: a mutation of lysine to alanine, which prevents proteolytic cleavage by cellular proteases during Chinese hamster ovary cell culture in the CDRH3 region (CAP256V2LS IB Edition 1); and the methionine to leucine (L) and asparagine to serine (S) mutations (referred to as the LS mutation) in the C-terminus of the heavy chain Fc region, which increase the antibody binding affinity for the neonatal Fc receptor (FcRn) resulting in an extended half-life of human antibodies in vivo {Ko 2014},{Gaudinski 2018}.

1.2.2.2. Nonclinical Pharmacology and Pharmacokinetics of CAP256V2LS

CAP256V2LS neutralized 63% of the multiclade 208-pseudovirus panel with high potency, a median 50% inhibitory concentration (IC_{50}) of 0.001 µg/mL and 80% inhibitory concentration (IC_{80}) of 0.004 µg/mL.

In human FcRn transgenic mice and rhesus macaques, CAP256V2LS displays a PK profile similar to other anti-HIV-1 antibodies. In mice, the average serum half-life for CAP256V2LS was calculated to be 7.7 days with a range of 6.2 to 8.5 days. In rhesus macaques, the average half-life was calculated to be 14.3 days for the intravenous (IV) route and 9.9 days for the subcutaneous (SC) route.

For further information on CAP256V2LS, refer to the IB for CAP256V2LS, including information on the following:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology

1.2.3. Nonclinical Studies of VRC07-523LS

1.2.3.1. General Information on VRC07-523LS

VRC07-523LS, is a highly potent and broadly neutralizing HIV-1 human mAb targeted against the HIV-1 CD4 binding site. The predecessor, VRC01 mAb, was originally discovered in a participant with HIV-1 for more than 15 years and whose immune system controlled the virus without ART {Wu 2012}.

The VRC07 (wild-type) heavy chain was identified by deep sequencing based on its similarity to the VRC01 mAb and paired with the VRC01 (wild-type) light chain {Rudicell 2014}, {Kwon 2012}. The LS mutations increase the binding affinity for the FcRn, resulting in increased recirculation of functional immunoglobulin G and therefore increasing plasma half-life {Ko 2014}, {Zalevsky 2010}

1.2.3.2. Nonclinical Pharmacology and Pharmacokinetics of VRC07-523LS

VRC07-523LS was found to be 5- to 8-fold more potent than VRC01, with a median IC_{50} of 0.046 μg/mL (breadth 96%, 50 μg/mL cutoff) and an IC_{80} of 0.229 μg/mL (breadth 95%, 50 μg/mL cutoff) of HIV-1 pseudoviruses representing the major circulating HIV-1 clades.

In cynomolgus macaques administered 10 mg/kg of VRC07-523LS, the half-life of VRC07-523LS was determined to be approximately 10 to 12 days for the IV route and approximately 14 days for the SC route.

For further information on VRC07-523LS, refer to the IB for VRC07-523LS, including information on the following:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology

1.2.4. Clinical Studies of Vesatolimod

1.2.4.1. Studies in Participants with HIV-1 Infection

As of March 2022, 63 virologically suppressed adults with HIV-1 were dosed with VES in the following Phase 1b Gilead clinical studies:

- GS-US-382-1450: A Phase 1b, Randomized, Blinded, Placebo-Controlled Dose-Escalation Study of the Safety and Biological Activity of VES in HIV-1-Infected, Virologically Suppressed Adults
- GS-US-382-3961: A Phase 1b, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of VES in Antiretroviral-Treated HIV-1-Infected Controllers
- GS-US-420-3902: A Phase 1b, Randomized, Blinded, Placebo-Controlled, Staggered, Single and Multiple Ascending Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of GS-9722, Administered Alone or in Combination with Vesatolimod, in Virologically Suppressed HIV-1 Infected Subjects on ART

Details on the primary objectives, study design, study and control drug regimens, number of participants by treatment, study status, and key findings for these clinical studies are provided below. Vesatolimod is also being dosed in an external study (AELIX-003 [National Clinical Trial number NCT04364035]) either alone or in combination with other investigational agents. Additionally, VES is planned to be dosed in the following studies.

Study GS-US-382-1587: A Phase 1, Open-label, Multicohort Study to Evaluate the Impact of Inhibitors and Inducers of Cytochrome P450 Enzyme (CYP)3A and/or P-glycoprotein (P-gp) on the Pharmacokinetics (PK) of Vesatolimod (VES) in Virologically Suppressed Adults With HIV-1 on Antiretroviral Therapy (ART)

1.2.4.1.1. Study GS-US-382-1450

Study Design

This Phase 1b, randomized, double-blind, placebo-controlled, dose-escalation study was conducted to evaluate the safety and biological activity of VES with the following dose cohorts: Cohort 1 (1 mg), Cohort 2 (2 mg), Cohort 3 (4 mg), Cohort 4 (6 mg), Cohort 5 (8 mg), Cohort 6 (3 doses of 10 mg followed by 7 doses of 12 mg). Three optional cohorts (Cohorts 7, 8, and 9) were not conducted.

For each cohort, 8 participants were randomized in a 6:2 ratio to receive VES or placebo.

Participants received a total of either 6 doses in Cohorts 1 to 3 or 10 doses in Cohorts 4 to 6, administered once every other week. Vesatolimod was administered with a meal in Cohorts 1 to 4, and under fasted conditions in Cohorts 5 and 6. Participants continued with their existing ART regimen throughout the whole study. After all participants in a cohort received at least 3 doses (Cohorts 1 to 3) or 5 doses (Cohorts 4 to 6), a Safety Evaluation Committee reviewed safety data from that cohort, including adverse events (AEs) and clinical laboratory results before approving the opening of enrollment in the next cohort.

The study is now complete.

Participant Disposition and Baseline Characteristics

Overall, 48 participants were enrolled. Eight participants were dosed in each of 6 cohorts with doses up to 12 mg (based on the assigned cohort). Participants had a median age of 47 years and 89.6% were male. All participants had HIV-1 RNA levels < 50 copies/mL at baseline.

Administration of VES at doses of 1, 2, 4, 6, 8, 10, or 12 mg did not lead to consistent increases in viremia from baseline.

Virology Results

The following participants had plasma HIV-1 RNA ≥ 50 copies/mL in the VES or placebo groups:

- 1 participant in the placebo group had an HIV-1 RNA level peak at 1040 copies/mL 7 days after Dose 3 and returned to < 50 copies/mL 17 days after Dose 3
- 1 participant in the placebo group had an HIV-1 RNA level of 81 copies/mL 2 days after Dose 5 and returned to < 50 copies/mL 4 days after Dose 5
- 1 participant in the VES 4 mg group had HIV-1 RNA levels of 60 copies/mL 4 days after Dose 4 and returned to < 50 copies/mL 7 days after Dose 4, and 69 copies/mL 7 days after Dose 5 and returned to < 50 copies/mL 14 days after Dose 5

- 1 participant in the placebo group had HIV-1 RNA levels peak at 2430 copies/mL 7 days after Dose 6 and returned to < 50 copies/mL 14 days after Dose 6, another peak at 112 copies/mL 2 days after Dose 7 and returned to < 50 copies/mL 14 days after Dose 7, another peak at 78 copies/mL 7 days after Dose 8 and returned to < 50 copies/mL 16 days after Dose 8, and a range of 64 to 98 copies/mL from 7 to 76 days after Dose 10

Administration of VES at doses of 1, 2, 4, 6, 8, 10, or 12 mg did not lead to consistent increases from baseline median plasma viremia.

There were no statistically significant differences between any VES dose groups and placebo group in the number of participants with HIV-1 RNA ≥ 50 copies/mL at any time after each dose (Dose 1 to Dose 10)

There were no statistically significant differences in median maximum change from baseline in plasma HIV-1 RNA for all doses compared to placebo with the exception of VES 8 mg ($P = 0.0289$). There were no statistically significant differences in change from baseline between any VES dose groups and placebo group for active or latent HIV-1 reservoir {Riddler 2020}.

Pharmacokinetics and Pharmacodynamics

Across all cohorts, VES was administered for up to 10 doses, every other week.

Vesatolimod PK in PWH was similar to VES PK in healthy volunteers and participants.

Increases in AUC_{last}, AUC_{inf}, and C_{max} were generally dose proportional following single-dose administration of VES across the doses of 1 to 12 mg in PWH. The median T_{max} ranged from 1 to 3 hours postdose, and median $t_{1/2}$ ranged from 9 to 19 hours across the dose levels evaluated. As no accumulation of VES is anticipated based on the observed half-life, the PK parameters observed after the first dose are representative of chronic exposure following every other week dosing.

The evaluated pharmacodynamic (PD) markers (cytokine, ISG markers, and lymphocyte activation) were induced following dosing with VES in PWH. The cytokine markers with the greatest fold increases in serum following dosing with VES were interleukin (IL)-1ra and IFN-α, which showed maximal 3.67-fold and 8.81-fold increases from baseline, respectively, in the VES 12 mg group. Overall, absolute levels of IFN-α production were low. All ISGs assessed in this study were induced in a generally dose-dependent fashion following administration of VES 4 mg or more, with the greatest inductions in the 8 mg group at 21.18-fold, 8.42-fold, and 10.50-fold increases for ISG-15, 2'-5'-oligoadenylate synthetase 1, and MX Dynamin Like GTPase 1, respectively. The VES dose required to elicit an ISG response (VES ≥ 4 mg) was lower than that required for any substantial detection of serum IFN-α. Activation of the subpopulation of CD4+ CD38+ human leucocyte antigen (HLA) DR+ T cells and CD8+ CD38+ HLA-DR+ T cells was generally in a dose-dependent fashion in participants who received VES at doses of at least 6 mg. Activation of NK cells (CD69+) was achieved at VES doses of 8 and 12 mg.

Safety Results

Overall, 32 of 48 participants (66.7%) reported at least 1 AE during the study. No Grade 4 AEs were reported in the study. No deaths were reported and there were no discontinuations from study drug due to AEs. The most frequently reported (≥ 25% of participants in any VES group) treatment-emergent AEs included: fatigue, nausea, myalgia, nasal congestion, and upper respiratory tract infection. These flu-like symptoms are not unexpected given the mechanism of action of VES. One participant (16.7%) in the VES 2 mg group experienced a Grade 3 AE of abdominal pain lower (unrelated to study drug). The same participant experienced a serious adverse event (SAE) during the study (diverticulitis); the SAE was not considered by the investigator to be related to study drug. Eleven participants experienced AEs (eg, headache, fatigue, myalgia) that were considered by the investigator to be related to study drug. Refer to the IB for details.

Three participants experienced Grade 3 or 4 laboratory abnormalities: 1 participant in the 8 mg group (Grade 4 creatine kinase increase associated with strenuous exercise and Grade 3 aspartate aminotransferase [AST] increase) and 2 participants in the 10/12 mg group (1 participant had Grade 4 creatine kinase increase and 1 participant had Grade 3 creatine kinase increase, both were associated with strenuous exercise).

Conclusion

This study demonstrated the following:

- Multiple VES doses from 1 to 12 mg were well tolerated.
- Immune stimulation was evident at VES doses ≥ 4 mg.
- There were no consistent elevations in plasma HIV-1 RNA to ≥ 50 copies/mL compared with placebo.
- Increases in plasma exposure (as measured by AUC_{inf}, AUC_{last}, and C_{max}) were generally dose proportional following single-dose administration of VES at doses of 1 to 12 mg.

1.2.4.1.2. Study GS-US-382-3961

This Phase 1b randomized, double-blind, placebo-controlled study with a single cohort of HIV-1 controllers on ART with a history of pre-ART plasma HIV-1 RNA between 50 and ≤ 5000 copies/mL was conducted to evaluate the safety and efficacy of VES. The study was conducted in 3 periods. In Period 1, 25 participants were randomized 2:1 to receive VES (17 participants) or placebo-to-match (8 participants), while continuing ART. Randomization was stratified by pre-ART viral load (≥ 50 to < 2000 copies/mL or ≥ 2000 to ≤ 5000 copies/mL) at screening. In addition, 3 participants from the 8 mg cohort in Study GS-US-382-1450 rolled over to Study GS-US-382-3961 after completing VES dosing. All participants received up to 10 doses of their assigned study treatment administered orally once every 14 days. In Period 2, all participants discontinued both ART and VES during an ATI and were monitored for rebound in HIV-1 plasma viremia for 24 weeks with close observation and follow up. Participants who

restarted ART during Period 2 due to virologic rebound completed ART reinitiation visits, and then post-ART resuppression visits monthly for 6 additional months. Participants who completed 24 weeks of ATI without restarting ART moved onto Period 3. In Period 3, participants could either restart ART (along with post-ART resuppression visits for 6 additional months) or remain off ART for an additional 24 weeks after the first 24 weeks of ATI were completed, if low viral loads were maintained.

Study GS-US-382-3961 opened for screening on 09 March 2017. All participants completed dosing of VES (4 to 8 mg intraparticipant dose escalation) or placebo (Period 1), and underwent ATI (Period 2), or restarted ART per protocol (Periods 2 or 3).

Participant Disposition and Baseline Characteristics

The Full Analysis Set (FAS) for Study GS-US-382-3961 consisted of 25 participants. The median age was 45 years and 84.0% of participants were male. Median baseline HIV-1 RNA level was 1.28 $\log_{10}$ copies/mL and 24 of 25 participants had HIV-1 RNA < 50 copies/mL. Median CD4 T lymphocyte count was 755/μL and 92.0% of participants had a CD4 cell count ≥ 500/μL.

Virology Results

The effect of VES on change from baseline in HIV-1 RNA was assessed at multiple postdose timepoints throughout the study. There was no consistent induction of plasma viremia during VES or placebo dosing pre-ATI. During the ATI period, increases in plasma HIV-1 RNA were generally lower in participants receiving VES compared with those receiving placebo. Vesatolimod was associated with a longer period of viral suppression following ATI compared with placebo. The median (first quartile [Q1], third quartile [Q3]) time to viral rebound (≥ 50 copies/mL) was 4.3 (3.1, 6.1) weeks for the VES group compared with 4.0 (3.0, 4.2) weeks for the placebo group ($P = 0.035$). For rebound to ≥ 200 copies/mL, the median (Q1, Q3) time to viral rebound was 5.1 (4.1, 6.3) weeks for the VES group compared with 4.1 (3.8, 4.6) weeks for the placebo group ($P = 0.024$). Five participants in the VES group had no virologic rebound (≥ 50 copies/mL) for 6 or more weeks. One of these participants (VES 6 mg) did not rebound to ≥ 50 copies/mL until 15 weeks after ATI. This participant did not rebound to ≥ 200 copies/mL until 28 weeks after ATI. All participants in the placebo group had virologic rebound within 5 weeks of stopping ART.

For VES, median pre-ART viral set-point was 3.23 log10 copies/mL and median viral set-point following ATI was 2.78 $\log_{10}$ copies/mL. The median plasma viral set-point change was -0.37 log10 copies/mL ($P = 0.022$ compared with the pre-ART viral set-point). For placebo, median pre-ART viral set-point was 3.05 $\log_{10}$ copies/mL and median viral set-point following ATI was 2.85 $\log_{10}$ copies/mL. The median plasma viral set-point change was -0.28 log10 copies/mL ($P = 0.38$ compared with the pre-ART viral set-point). Median peak viral load during ATI was 4.21 $\log_{10}$ copies/mL and 3.97 $\log_{10}$ copies/mL for VES and placebo, respectively ($P = 0.67$). Peak viral load was reached faster in the placebo group (largest median change at ATI Visit 6) compared with the VES group (largest median change at ATI Visit 9). The active HIV-1 reservoir was evaluated by measuring change in plasma HIV-1 RNA via Single Copy Assay during the dosing period and no consistent changes were observed after VES or placebo

dosing. The latent HIV-1 reservoir was evaluated by Intact Proviral DNA Assay (IPDA) and Inducible Virus Production Assay (IVPA). No consistent change was observed following VES or placebo dosing by IVPA or total HIV DNA measured by IPDA. However, a significant decrease in the estimated frequency of cells harboring intact HIV DNA measured by IPDA was observed in the VES group ($P = 0.046$) but not in the placebo group. The delayed viral rebound was associated with lower intact proviral DNA at the end of VES treatment {Riddler 2021, SenGupta 2021}.

Pharmacokinetics/Pharmacodynamics Results

Vesatolimod PK following administration of 4 mg or 6 mg was similar to that observed previously (Studies GS-US-243-0101 and GS-US-382-1450). Mean exposure (AUC and C_{max}) following administration of VES 8 mg was numerically higher than previously observed following administration of VES 8 mg or 12 mg (Studies GS-US-243-0101 and GS-US-382-1450); this may be due to the small number of participants in this group (N = 3).

The evaluated PD markers (cytokine, ISG markers, and lymphocyte activation) were induced following dosing with VES in PWH. The cytokine markers with the greatest fold increases in serum following dosing with VES were IP-10 and IFN-α. Overall, absolute levels of IFN-α production were low and comparable to previous studies of VES. There was a 4.11-fold maximal mean increase from baseline in IL-1RA observed 1 day after the 10th VES dose. There was a 6.02-fold maximal mean increase from baseline in IP-10 observed 1 day after the 10th VES dose. There was a 3.45-fold maximal mean increase from baseline in inducible T cell alpha chemoattractant (ITAC) observed 1 day after the 10th dose of VES. There was a 62.57-fold maximal mean increase from baseline in IFN-α observed 1 day after the fourth dose of VES.

All ISGs assessed in this study were induced with the greatest mean inductions of 19.71-fold, 7.44-fold, and 10.29-fold increases for ISG-15, OAS-1, and MX1, respectively. IL-1RA, IP10, and ITAC decreased to baseline levels 7 days after each dosing cycle, while IFN-α decreased to baseline levels by Day 1 of the next VES dose. An increase in the activation of T cells, DCs (CD54+pDC), monocytes (CD14+CD16+), T cells (CD4+HLA-DR+CD38+ and CD8+HLA-DR+CD38+) and NK cells (CD69+CD56+CD16+, CD69+CD56dimCD16- and CD69+CD56brCD16dim) was observed 1 and 3 days following dosing with VES, which returned to baseline 13 days after each dose.

Safety Results

Adverse events were reported in 22 of 25 participants (88.0%) as follows: VES 4 mg, 2 of 2 participants (100.0%); VES 4/6 mg, 3 of 4 participants (75.0%); VES 6 mg, 5 of 5 participants (100.0%); VES 6/8 mg, 3 of 3 participants (100.0%); VES 8 mg, 3 of 3 participants (100.0%); and placebo, 6 of 8 participants (75.0%). No deaths, study drug-related SAEs, pregnancies, or AEs leading to discontinuation of study drug were reported. The most common AEs in the VES group (occurring in > 2 participants) were headache and nausea (5 participants each), chills (4 participants), and sinusitis, arthralgia, fatigue, lymphadenopathy, and pyrexia (3 participants each). The most common AEs in the placebo group (occurring in > 1 participant) were headache (3 participants) and sinusitis (2 participants). Nine participants (53%) who received VES and 1 participant (13%) who received placebo experienced study drug-related AEs. The majority of

the VES-related AEs were mild, transient influenza-like symptoms: 2 participants with fatigue, 3 participants with chills, 2 participants with pyrexia, 3 participants with headache, and 3 participants with lymphadenopathy. One participant who received VES had Grade 3 AEs of gout, arthralgia, and sciatica exacerbation occurring on Days 102, 109, and 113, respectively (between Doses 8 and 9), that were considered study drug-related, as well as an unrelated Grade 3 AE of viral gastroenteritis. One participant who received VES had a Grade 2 SAE of chronic gastritis that was not considered related to study drug. There were no Grade 3 or 4 AEs or SAEs reported in the placebo group.

Overall 19 of 25 participants (76.0%) had any graded laboratory abnormality as follows: VES 4 mg, 2 of 2 participants; (100.0%); VES 4/6 mg, 4 of 4 participants (100.0%); VES 6 mg, 4 of 5 participants (80.0%); VES 6/8 mg, 1 of 3 participants (33.3%); VES 8 mg, 2 of 2 participants (100.0%); and placebo, 6 of 8 participants (75.0%). The majority of laboratory abnormalities were Grade 1 or 2 in severity. One participant with a history of diabetes who received VES had transient Grade 3 nonfasting hyperglycemia, and Grade 3 glycosuria. No Grade 4 laboratory abnormalities were observed. There were no treatment-emergent graded abnormalities in platelets or lymphocytes.

Conclusions

This study demonstrated that:

- Multiple doses of VES (up to 8 mg) were well tolerated.
- Time to viral rebound after ATI was modestly increased with VES compared with placebo, and viral set-point was decreased from pre-ART levels with VES.
- Compared with VES exposures observed in previous studies at the same doses, VES exposures at 4 mg and 6 mg were similar, while VES exposure at 8 mg was numerically higher in this study.

The induced ISG expression, induced cytokine release, and activated immune cells observed in this study were potentially due to an augmented antiviral immune response.

1.2.4.1.3. Study GS-US-420-3902

This Phase 1b randomized, double-blinded, placebo-controlled, staggered single ascending dose (SAD) and multiple ascending dose (MAD) study was conducted to evaluate the safety, tolerability, and PK of EVM, an HIV-1 broadly neutralizing antibody (bNAb), administered alone or in combination with VES in virologically suppressed PWH. This study was designed to evaluate EVM as a single agent (Cohorts 1 to 4), and in combination with VES (Cohorts 5 to 8). Following completion of screening and Day −1 procedures, eligible participants were randomized in a 3:1 ratio per cohort to receive either EVM or placebo (either alone or in combination with VES). Following completion of enrollment and dosing in Cohort 5, Gilead decided to terminate Study GS-US-420-3902; accordingly, no participants were enrolled in Cohorts 6 to 8. Cessation of this clinical study was not the result of any safety concerns related to EVM or VES. Gilead completed follow-up visits for participants in Cohort 5 prior to closing the study.

In Cohorts 1 to 4, participants received either EVM or placebo. In the SAD Cohorts 1 and 2, a single IV dose of 150 mg or 500 mg, respectively, was administered. In the MAD Cohorts 3 and 4, five IV doses of 150 mg or 500 mg, respectively, were administered, a single dose every other week. In Cohort 5, participants received 6 mg VES orally administered alone for the first dose (Day 1) followed by 150 mg of EVM coadministered intravenously with 6 mg of VES orally once every other week for 4 doses. Final results from Cohort 5, in which participants received EVM in combination with VES, are presented below.

The study is now complete.

Participant Disposition and Baseline Characteristics

Overall, 42 participants were randomized (8 participants in each of the Cohorts 1 to 4 and 10 participants in Cohort 5). Of these, 39 participants completed study drug treatment and 39 participants completed the study. In Cohort 5, 10 participants were randomized, and 7 participants completed study drug treatment. The age range in Cohort 5 was 28 to 64 years, inclusive, and all the participants were male. All participants had HIV-1 RNA < 50 copies/mL. The median (Q1, Q3) baseline HIV-1 RNA value was 1.28 (1.28, 1.28) $\log_{10}$ copies/mL.

Virology Results

Overall, no median changes from baseline in plasma HIV-1 RNA were observed across treatment groups during the study, with the exception of a transient median (Q1, Q3) increase from baseline at Day 28 in participants in Cohort 5 who received VES 6 mg + placebo (0.11 [0.00, 0.23] $\log_{10}$ copies/mL [n = 2]). This median increase was attributable to 1 participant who had a quantifiable plasma HIV-1 RNA level < 50 copies/mL on Day 28 and was not clinically significant. No clinically relevant changes from baseline in CD4 and CD8 cell counts or CD4 percentage were observed across treatment groups, and no participant met the criteria for confirmed virologic rebound or resistance testing during the study.

Pharmacokinetics/Pharmacodynamics Results

Co-administration of EVM and VES did not appear to impact the PK of either study drug.

Safety Results

Co-administration of EVM and VES was generally safe and well tolerated in virologically suppressed people with HIV-1 on ART. In Cohort 5, most AEs were Grade 1 or 2 in severity. One participant who received VES 6 mg + EVM 150 mg had a Grade 1 AE of SARS CoV 2 test positive, which was considered not related to study drug and led to premature discontinuation of study drug. No Grade 4 AEs, Stage 3 HIV-related opportunistic illnesses, deaths, or pregnancies were reported during the study.

One participant in Cohort 5 who received VES 6 mg + EVM 150 mg had Grade 2 increased creatine kinase (1992 U/L) on Day 14 and Grade 4 increased creatine kinase (7391 U/L) on Day 17, which were attributed to exercise by the investigator and resolved by Day 22.

There were no clinically relevant findings in vital signs, oxygen saturation, or electrocardiogram (ECGs).

External Clinical Studies With Vesatolimod

Based on preliminary data communicated to Gilead from the ongoing externally sponsored clinical study investigating the safety of VES with HIV-1 vaccines in participants who started ART in early stages of HIV-1 infection (AELIX-003; National Clinical Trial number NCT04364035), no new safety signals have been identified with administration of VES to date.

1.2.4.2. Studies in Healthy Participants and Participants with Chronic Hepatitis B and C Virus

Five Phase 1 clinical studies (GS-US-420-5372, GS-US-243-0101, GS-US-243-0102, GS-US-283-0102, and GS-US-283-0106), 2 Phase 2 clinical studies (GS-US-283-1059, GS-US-283-1062), and 1 registry study (GS-US-283-0110) have been completed in which 59 healthy participants, 42 participants with hepatitis C virus (HCV), 162 viremic participants with chronic hepatitis B (CHB), and 230 participants with HBV (189 virologically suppressed and 41 treatment-naive participants) were dosed with VES. Vesatolimod was initially developed to provide participants with CHB infection with a finite duration, curative treatment option. However, no significant declines in HBV DNA, hepatitis B surface antigen (HBsAg) levels, or HBsAg loss were detected through the program. Therefore, due to the lack of efficacy, VES is no longer being investigated in the CHB therapeutic area. Safety data from the program are included in the IB to provide additional context for AEs.

1.2.4.2.1. Study GS-US-420-5372

Study GS-US-420-5372 was a Phase 1, randomized, blinded, placebo-controlled, single-center, multiple-dose study of EVM in combination with VES with staggered dose escalations and adaptive VES dose selection.

A total of 5 cohorts were planned for evaluation in this study, of which 2 cohorts were optional. Only a single dose of study treatment (EVM 250 mg with VES 8 mg or EVM 250 mg with placebo for VES) was received by 4 participants in Cohort 1 of the study. Cohorts 2 through 5 were not initiated and the study was terminated after completion of study assessments in the 4 participants in Cohort 1, as an SAE considered related to study treatment by the investigator was reported in 1 participant.

Overall, AEs were reported in 3 of the 4 participants, of which all except one were Grade 1 in severity. No deaths were reported during the study. A Grade 3 SAE of cytokine release syndrome (CRS) was reported on Day 1 in 1 participant who received EVM with VES; this Grade 3 SAE was considered related to the study treatment and led to discontinuation of study treatment for this participant and termination of study treatment for the other 3 participants. This participant had myalgias, back pain, tachycardia, fever, chills, nausea, and vomiting 6 hours after receiving study treatment. The participant was also hypotensive; therefore, IV fluid and solumedrol were administered to stabilize the blood pressure. Approximately 2 hours after the onset of symptoms, the participant had another episode of hypotension and was treated with IV solumedrol prior to being transported to the hospital. At the hospital, the participant was normotensive, tachycardic, febrile, and hypoxic. Physical examination showed no rash, normal conjunctiva, moist oral mucosa, normal breath sounds, and no swelling. The participant received acetaminophen for fever and supplemental oxygen by nasal canula for hypoxia with resolution.

Venous lactic acid was elevated above the laboratory reference range and the participant was admitted to the hospital for observation. The SAE of CRS resolved, and laboratory values for the participant returned to baseline without additional intervention; the participant was discharged from the hospital on Day 3. The SAE was considered related to study treatment by the investigator and study treatment was withdrawn.

Although this SAE was reported as Grade 3 by the investigator, according to the NCI CRS grading this SAE was consistent with Grade 2 as the associated hypotension responded to fluids {Shimabukuro-Vornhagen 2018}. The participant did not require vasopressors and was discharged from the hospital 2 days after the SAE occurred. No other SAEs or AEs leading to premature discontinuation of study treatment were reported, and no other AEs were considered related to study treatment.

Preliminary assessment of cytokines including those associated with CRS (eg, IL-1, IL-6, granulocyte-macrophage colony-stimulating factor [GM-CSF], MCP-1, macrophage inflammatory protein-1 [MIP-1], IP-10 and IFN-γ) did not show elevated baseline or on-treatment levels for the study participant with CRS relative to the other participants. Analysis of serum taken at baseline from the participant with the SAE of CRS showed a unique biomarker profile with higher E-selectin (a marker of vascular inflammation) and lower Factor VII than the other participants at baseline (though within normal ranges), as well as higher acute elevation of IFN-α and ISGs after treatment with EVM and VES. The participant with the SAE of CRS tested positive for cocaine use at an outpatient visit on Day 57. It is unclear whether chronic cocaine use contributed to higher baseline vascular inflammation or greater risk for CRS. No other SAEs or AEs leading to premature discontinuation of study treatment were reported, and no other AEs were considered related to study treatment. The only AE reported in > 1 participant was constipation (1 participant in each treatment group).

1.2.5. Clinical Studies of CAP256V2LS

First-in-human studies (VRC 611 in healthy participants and CAPRISA 012B in both healthy participants and participants with HIV) are ongoing. As of 04 January 2021, 37 HIV-negative participants have been enrolled into the CAPRISA 012B study and no participants have been enrolled in the VRC 611 study. Emerging data from these 2 studies will inform on dose selection for this study.

1.2.5.1. VRC 611

The VRC 611 Phase 1 study, entitled “A Phase I Safety and Pharmacokinetics Study to Evaluate a Human Monoclonal Antibody (mAb) VRC-HIVMAB0102-00-AB (CAP256V2LS) Administered Via Subcutaneous and Intravenous Injection in Healthy Adults” is being conducted at the VRC Vaccine Evaluation Clinic in the National Institutes of Health Clinical Center in the United States (US). This study will include 2 dosing regimens with CAP256V2LS administered as a single dose at 5 mg/kg SC or 5 mg/kg IV (N = 5 per cohort). Safety, PK, and formation of antidrug antibodies will be evaluated throughout the study.

1.2.5.2. CAPRISA 012B

The South African Phase 1 study, CAPRISA 012B, entitled "A Phase I Dose-Escalation Study of the Safety, Tolerability and Pharmacokinetics of a Human Monoclonal Antibody, CAP256V2LS (VRC-HIVMAB0102-00-AB) Administered Intravenously to HIV-Negative and HIV-Positive Women or Subcutaneously Alone and in Combination with VRC07-523LS and/or PGT121 to HIV-Negative Women in South Africa," is being conducted, in parallel to VRC 611, under the South African Health Products Regulatory Authority (SAHPRA).

A total of 66 women, aged 18 to 45 years, will enroll into the study at the CAPRISA eThekwini Clinical Research Site in Durban, South Africa. Groups 1a, 1b, 2, 3, and 4 will consist of HIV-negative women (N = 52), while Group 1c and 1d will enroll HIV-positive women (N = 14) who have not yet started ART. Safety and PK will be evaluated throughout the study. No SAEs have been reported in this study thus far.

This Phase 1 double-blinded, randomized placebo-controlled trial in South African women is currently ongoing with only blinded interim safety data available. As of 23 August 2021, 42 HIV-negative participants have been enrolled into the CAPRISA 012B study.

Overall, reported reactogenicity events ranged from mild to severe and all reactogenicity events resolved within the 3-day reactogenicity assessment period. Solicited local reactions were reported by 14 out of 42 participants (33%) with 10 (24%) experiencing mild tenderness, 9 (21%) experiencing pain (8 mild in severity, 1 moderate), 5 (12%) experiencing swelling/induration (1 mild in severity, 2 moderate, 1 severe), and 2 (5%) experiencing moderate redness/erythema. In the combination group 3a, 2 participants experienced solicited local reactions that occurred at the injection site attributed to the VRC07-523LS/placebo injection. In the combination group 3b, 4 participants experienced solicited local reactions that occurred at the injection site and were attributed to the VRC07-523LS/placebo injection.

Solicited systemic reactions were reported by 40 out of 42 participants (95%) including 90 participants (86%) experiencing headache, 28 participants (67%) experiencing chills, 17 participants (40%) experiencing nausea, 20 participants (48%) experiencing malaise and/or fatigue, 14 participants (33%) experiencing arthralgia, 10 participants (24%) experiencing raised temperature, 7 participants (17%) experiencing vomiting, and 11 participants (26%) experiencing myalgia. The majority of systemic symptoms were mild to moderate in severity. Three events were reported as severe: 1 (2%) participant with severe headache and 2 (5%) participants with severe chills and 1 (2%) participant reported severe malaise and/or fatigue.

There have been no infusion reactions during study drug administration. There were 76 unsolicited AEs reported in 37 out of 42 (88%) participants, of which 50 events were attributed as related to study drug. All events attributed to study injection have resolved to date.

Common events attributed to study drug included:

There were 8 lymphocytopenia events observed in 8 participants, of which 2 were mild (Grade 1 range, 600 to < 650 cells/mm^3), 2 were moderate (Grade 2 range, 500 to < 600 cells/mm^3), 2 events were severe (Grade 3 range, 350 to < 500 cells/mm^3), and 2 were graded potentially life threatening (Grade 4 range, < 350 cells/mm^3). There were 10 proteinuria events observed in 9 participants, of which 7 were mild and 3 were moderate in severity. There were 8 events of

increased AST observed in 8 participants, all of which were mild in severity. There were 6 events of increased alanine aminotransferase (ALT) observed in 7 participants, of which 6 were mild and 1 was moderate in severity.

The 2 related Grade 3 AEs of transient decline in lymphocyte counts were observed in 1 participant who received CAP256V2LS at 5 mg/kg SC without hyaluronidase and 1 participant who received CAP256V2LS at 20 mg/kg SC with hyaluronidase. The 2 related Grade 4 AEs of transient decline in lymphocyte counts were both observed in participants who received either a combination of CAP256V2LS 10 mg/kg and VRC07-523LS 10 mg/kg, or a placebo, with hyaluronidase. These events occurred at Day 1 post study drug administration and resolved by Day 3 to Day 7. Lymphocytopenia in these participants was accompanied by transient nongradable total white blood cell increases due to neutrophilia and transient nongradable decreases in eosinophils and monocytes in these participants occurring Day 1 post study drug administration that also rapidly resolved by Day 3. One participant with severe lymphocytopenia also had Grade 1 transient thrombocytopenia (122,000 cells/mm^3) on Day 3 that resolved the same day. There were no other hematologic abnormalities and no clinical signs or symptoms in any of these participants. Gradable lymphocytopenia events were not associated with route of administration, dosage, or hyaluronidase.

The transient decline in lymphocyte counts observed during conduct of the trial prompted a protocol-specified study pause by the principal investigators and a Data Safety Monitoring Board (DSMB) meeting was convened. After review of the data and consultation with expert hematologists, the DSMB concluded that the transient laboratory abnormality did not seem to be a safety concern, as occurrences of transient declines in lymphocyte count have been observed in animal studies and human studies following the administration of monoclonal antibodies {Brinkman 2011, Buysmann 1996, Dettmar 2012, Hansel 2010, Schulz 2007, Soler 2009} and all participants were clinically stable and remain well to date. The DSMB also agreed with the CAPRISA team recommendation to inform participants about this observation, and to further investigate the transient lymphocytopenia in future participants. The DSMB advised that the trial resume with recommendations in place.

There were no SAEs and AEs did not result in study drug discontinuation in any participant. There have been no suspected unexpected serious adverse reactions (SUSARs) reported to the SAHPRA.

For updated clinical information on CAP256V2LS, please refer to the IB for CAP256V2LS.

1.2.6. Clinical Studies of VRC07-523LS

The clinical experience with VRC07-523LS is derived from 15 clinical studies (3 completed and 12 ongoing with preliminary data) conducted in the US, the Republic of South Africa, and/or Switzerland. Cumulatively (as of October 2020 based on the data presented in the VRC07-523LS IB), VRC07-523LS has been administered by IV, SC, or intramuscular (IM) infusion/injection, either individually or in combination with other HIV mAbs of different HIV-1 envelope epitope specificity, to approximately 230 HIV-uninfected adults and 28 adults with HIV, and 22 HIV-1-exposed infants. Overall, single-dose regimens of VRC07-523LS ranging from 1 to 40 mg/kg IV or 5 to 10 mg/kg SC; or repeat-dose regimens ranging from 2.5 to 30 mg/kg IV,

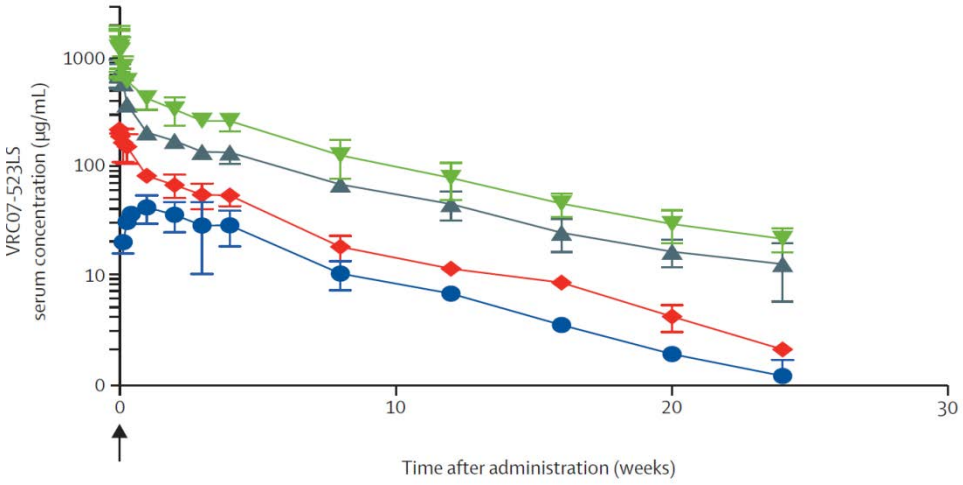
2.5 to 10 mg/kg SC, or 2.5 mg/kg IM; have generally been well tolerated in all adult populations examined. The limited data in the 22 HIV-1-exposed infants administered VRC07-523LS (maximum 100 mg per dose) by SC injection has shown it was well tolerated. No SAEs related to VRC07-523LS have been reported in any studies as of 14 October 2020.

Preliminary data obtained from 9 viremic adults with HIV-1 enrolled in Study VRC 607/A5378, have shown a majority of participants (8 of 9) administered a single IV dose of VRC07-523LS at 40 mg/kg achieved a 1.2$\log_{10}$ or greater decrease in viral load 7 days postinfusion {Kippax 2019}.

Safety summaries for clinical studies of VRC07-523LS are presented in the VRC07-523LS IB.

Pharmacokinetic data from Study VRC605, in which VRC07-523LS was administered IV as a single dose of 1, 5, 20, or 40 mg/kg in healthy participants are presented in Figure 1 (blue, red, gray, and green lines, respectively) and Table 1 {Gaudinski 2018}. VRC07-523LS C_{max} and C_{Day84} increased in a dose-proportional manner across the dose range of 1 to 40 mg/kg. T_{max} occurred within 0.04 to 0.7 days (1 to 16 hours), and the mean (SD) $t_{1/2}$ following IV administration was approximately 38 (12) days (Figure 1, Table 1). The PK of VRC07-523LS in aviremic HIV-positive participants is similar to that observed in healthy volunteers (data not shown).

Figure 1. Serum PK Following Single Dose IV Administration of 1, 5, 20, or 40 mg/kg VRC07-523LS



IV = intravenous; PK = pharmacokinetics(s)

Table 1. Serum PK Parameters Following Single Dose IV Administration of 1, 5, 20, or 40 mg/kg VRC07-523LS

Dose (mg/kg)	C_{max} (µg/mL)	T_{max} (days)	AUC_{inf} (µg•day/mL)	C_{28d} (µg/mL)	C_{84d} (µg/mL)	$t_{1/2}$ (days)
1	47 (16)	0.7 (0.5)	1381 (325)	14 (7.5)	3.8 (0.7)	48 (26)
5	240 (35)	0.04 (0.02)	4551 (904)	57 (11)	12 (1.8)	32 (1.1)
20	869 (190)	0.3 (0.4)	13,748 (1853)	148 (28)	44 (14)	45 (5.2)
40	1630 (644)	0.04 (0.02)	25,517 (5097)	272 (52)	85 (30)	42 (5.1)

IV = intravenous; PK = pharmacokinetics
Data are presented as mean (standard deviation).
Source: {Gaudinski 2019}

1.3. Rationale for This Study

Despite the extensive advances made in the treatment of chronic HIV-1 infection, control and/or eradication of the latent HIV-1 reservoir is still needed to achieve sustained viral remission or a functional cure that abrogates the requirement for lifelong ART. To this end, strategies to target latent virus have been tested in a number of clinical studies, but none have resulted in long-lasting virologic remission. The immune modulator VES and mAb constitute a promising candidate regimen given the preclinical evidence that it can lead to enhanced SHIV control in the absence of ART, both in terms of time to rebound and number of animals demonstrating sustained control. CD8 depletion in animals with sustained viral control did not lead to immediate rebound, indicating the latent SHIV reservoir was reduced to extremely low levels or eliminated. In the subsequent studies, the combination of VES with the mAb PGT121 led to sustained viral control after ART cessation in 33% to 50% of animals, whereas all control animals rebounded {Barouch 2020}. Additionally, VES resulted in a modest, but significant delay in time to viral rebound and decrease in viral load set-point in a clinical study of VES in HIV viremic controllers (PWH whose pre-ART plasma HIV-1 RNA was between 50 to ≤ 5000 copies/ml).

These results suggest a promising path toward reduction of HIV reservoirs and ultimately finite therapies for HIV-1 infection via a combination of TLR agonists and mAbs on ART. To test this concept, clinical trials combining immune modulators (eg, TLR9 agonist, lefitolimod) with anti-HIV mAbs (eg, 3BNC117 and 10-1074) in PWH are ongoing without any safety signals to date (NCT03837756).

Clinically, 6 mg and 8 mg VES appears to be safe in healthy volunteers and participants with HIV infection on ART. The next goal is to measure the efficacy of VES in a sequential regimen with mAbs in reducing and/or controlling the HIV-1 reservoir. Measurement of the time to viral rebound and/or new viral set-point following ATI is the most definitive method for evaluating HIV-1 cure interventions. The ACTG and other groups have demonstrated the safety of ATI in chronically-infected PWH, despite the risk associated with viral rebound to high levels. Additionally, the safety of ATI has been demonstrated in cohorts from acutely treated participants in Spain and Thailand {Julg 2019}, {Li 2016}, {Bar 2016}. Therefore, studying "activate and eliminate" interventions in the setting of an ATI in these participants could potentially provide useful information and maximize the chances of sustained viral load rebound in the absence of ART.

The primary objective of this study is to evaluate the safety and tolerability of dual anti-HIV envelope mAbs, VRC07-523LS and CAP256V2LS, in a sequential regimen with a TLR7 agonist, VES, when administered in virologically-suppressed women with HIV-1 Clade C on ART and during ATI. The secondary objectives of this study are to evaluate the PK of VRC07-523LS, CAP256V2LS, and VES, to assess the induction of anti-VRC07-523LS and/or anti-CAP256V2LS antibodies, and to assess potential viral control or the need for resumption of ART following an ATI. This pair of antibodies (VRC07-523LS and CAP256V2LS) was chosen due to the predicted complementary targeting of HIV-1 Clade-C envelope regions (CD4 binding site and V2 loop, respectively). CCI [redacted]

1.4. Rationale for Dose Selection

1.4.1. Rationale for Dose Selection of Vesatolimod

Dose selection for VES is supported by the available PK, safety, and PD data from the completed Study GS-US-382-1450 and Study GS-US-382-3961 in ART-suppressed PWH, as well as the completed Study GS-US-243-0101 in healthy volunteers (for further information, please refer to the VES IB). The results from these studies indicate that VES is generally well tolerated up to 12 mg administered as a single dose or multiple doses, given every 2 weeks. As a TLR7 agonist, VES is expected to activate its receptor on plasmacytoid dendritic cells or B cells and stimulate the production of cytokines. Therefore, AEs related to influenza-like symptoms may be expected. When administered alone in ART-suppressed PWH and in healthy volunteers, VES up to 8 mg is well tolerated, with mild and infrequent influenza-like AEs (eg, fatigue, headache), whereas individuals receiving VES at the 10 mg dose or higher more frequently experienced influenza-like AEs. The VES starting dose selected for this study is 6 mg, with the option for intraparticipant dose escalation to 8 mg at the third VES administration (Day 28), pending safety and tolerability of the 6 mg dose in each participant, with close safety monitoring. Participants who escalate to 8 mg VES may remain on 8 mg VES, or de-escalate to 6 mg VES, pending safety and tolerability of the 8 mg VES dose in that participant. Participants who de-escalate to 6 mg VES would remain on 6 mg VES for the remainder of the study. The proposed dose range of 6 mg to 8 mg VES is expected to provide exposures associated with activity, as evidenced by induction of ISGs and cellular activation observed at VES doses of 4 to 12 mg.

1.4.2. Rationale for Dose Selection of CAP256V2LS

The dose of 20 mg/kg for CAP256V2LS was selected based on the PK and safety of the ongoing Study CAPRISA 012B. Following the 20 mg/kg IV dose, antibody levels in Periods 1 and 2 are anticipated to provide antiviral activity, while in Period 3, antibody levels are anticipated to decline below therapeutic concentrations (as defined as approximately 100-fold higher than in

vitro IC_{50}), allowing the assessment of viral control potentially resulting from HIV reservoir reduction and/or immunologic control.

1.4.3. Rationale for Dose Selection of VRC07-523LS

Dose selection for VRC07-523LS is supported by PK and safety data from the completed Study VRC605 and the ongoing Study VRC607. In these studies, IV administration of VRC07-523LS single dose up to 40 mg/kg has been shown to be safe and well tolerated. The proposed dose of 20 mg/kg IV administered on Day 7 is predicted to provide concentrations of VRC07-523LS > 20 µg/mL through the end of Period 2 (Week 19); 20 µg/mL VRC07-523LS is approximately 100-fold higher than the in vitro IC_{80}, corresponding to a predicted > 80% neutralization coverage of sensitive HIV viruses {Gaudinski 2019}. In Period 3, VRC07-523LS concentrations are predicted to be subtherapeutic (< 20 µg/mL), allowing the assessment of viral control potentially resulting from HIV reservoir reduction and/or immunologic control.

1.5. Risk/Benefit Assessment for the Study

Based on the current available clinical data, potential risks associated with VES include transient influenza-like symptoms, such as chills, pyrexia, aches, and headache and CRS. In completed and ongoing studies of VES, the majority of the influenza-like symptoms have been mild and transient. One healthy volunteer who received 1 dose of VES 8 mg coadministered with EVM 250 mg experienced a Grade 3 SAE of CRS that was considered related to VES, leading to treatment and observation in the hospital followed by full recovery (Section 1.2.1). The other 3 participants receiving this regimen did not experience SAEs. Co-administration of EVM and VES 6 mg was generally safe and well tolerated in virologically-suppressed people with HIV-1 on ART. In this study, VES will not be coadministered on the same day as VRC07-523LS and CAP256V2LS, but rather separated by at least 7 days. Furthermore, these antibodies are not known to have off-target binding and have not been engineered with the same Fc-enhancement mutations as EVM, further lowering the risk of toxicity. There is no known or expected overlapping safety risk with VES, VRC07-523LS, and CAP256V2LS. However, it is possible that administration of VES in the presence of detectable plasma concentrations of VRC07-523LS and CAP256V2LS may transiently increase the risk of inflammatory events (see below). Additionally, as VES-related AEs are more common following Doses 1 and 2, enhanced monitoring after the first 2 doses of VES is proposed with adaptive monitoring thereafter. Participants will be monitored on site following study drug administration, and an external data monitoring committee (DMC) will evaluate safety data after the first 5 participants have reached Day 21. Nonclinical studies have reported findings of thrombocytopenia, hematologic effects, and hepatic injury. Hematologic effects or hepatic injury have not been observed in clinical studies. At the 12 mg dose level of VES in healthy volunteers (Study GS-US-243-0101), nongraded nonclinically significant decreases in platelet counts were observed in some participants, which resolved within 2 days without intervention. Treatment-emergent platelet decreases have not been observed at doses up to 12 mg in PWH in Study GS-US-382-1450 or in Study GS-US-382-3961. Safety laboratory values, including complete blood count and chemistry panels, will be regularly monitored throughout the study.

Intravenous administrations of VRC07-523LS to approximately 161 adults have been well tolerated. Observed local reactogenicity events have been of low frequency, and have included mild pain/tenderness, bruising, swelling, localized erythema, and mild paresthesia at the site of infusion that resolved within a few minutes to a few hours after the study drug administration. Most participants reported no systemic reactogenicity symptoms with VRC07-523LS IV administration; when observed, systemic symptoms were mostly mild, less frequently of moderate severity, started 1 to 3 days after study drug administration, and lasted 1 to 2 days. The most commonly reported symptoms following IV administration have been malaise, myalgia, headache, nausea, and joint pain. All other drug-related AEs have been of low frequency and mild or moderate in severity, and have resolved with no residual effects.

Among the approximately 161 participants who have received VRC07-523LS IV, 12 participants have experienced 16 infusion reaction episodes, including 1 participant who experienced an infusion reaction with all 3 administrations. Observed infusion reactions developed within 1 hour of infusion and were Grade 1 or 2 in severity, with symptoms typical of those observed with administration of other mAbs: fever, rigors, back pain, abdominal pain, nausea, flushing, pruritus, and changes in heart rate and blood pressure {Gaudinski 2018, Patel 2012}. No participants required treatment with epinephrine or steroids and were treated symptomatically. Three participants discontinued drug administrations due to an infusion reaction. For the remaining participants who experienced infusion-related reactions, VRC07-523LS dosing continued at a reduced infusion rate per protocol with no increase in severity of symptoms observed with subsequent infusions.

Clinical studies of CAP256V2LS are ongoing. As of 23 August 2021, 40 HIV-negative participants received CAP256V2LS in the CAPRISA012B study. There were no SAEs and AEs did not result in study drug-drug discontinuation in any participant. There have been no SUSARs reported to SAHPRA.

There were 8 transient lymphocytopenia events observed in 8 participants, ranging from Grade 1 to 4 in severity. These events occurred at Day 1 post study drug administration and resolved by Day 3 to Day 7. There were no clinical signs or symptoms and no other clinically relevant hematologic abnormalities in these participants. There have been no infusion reactions during study drug administration.

To date, the transient laboratory abnormalities do not represent a safety concern, as occurrences of transient declines in lymphocyte count have been observed in animal studies and human studies following the administration of many monoclonal antibodies.

Participants will be monitored on site following study drug administration, and safety laboratory values, including complete blood count and chemistry panels, will be regularly monitored throughout the study.

Typically, the side effects of mAbs are mild to moderate and may include local reactions at the injection site (including pain, redness, bruising, swelling) and systemic reactions such as fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia, or chest pain. When infused IV, infusion-related events most commonly occur within hours of initiation of mAb administration. Infusion-related reactions are common with licensed therapeutic mAbs, and typical symptoms include mild fevers, rigors, backpain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, or changes in pulse rate and blood pressure {Patel 2012}. Infusion-related reactions are managed by temporarily stopping the infusion, administering histamine blockers and restarting the infusion at a slower rate {Vogel 2010}.

Clinical use of mAbs that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infections {Hansel 2010}; however, this is not expected to be a risk for a mAb targeted to a viral antigen.

Less commonly, administration of mAbs may cause severe immune reactions such as acute anaphylaxis, CRS, serum sickness, and the generation of antidrug antibodies. These reactions are rare and more often associated with mAbs targeted to human proteins or with the use of mouse or chimeric mAbs that would have a risk of human antimouse antibodies {Hansel 2010}. In this regard, CAP256V2LS and VRC07-523LS are expected to have a low risk of such side effects since they are directed against a viral antigen and are of human in origin.

Published experience with other human mAbs directed against cell surface targets on lymphocytes shows that infusion of a mAb may be associated with cytokine release, causing a reaction known as CRS {Bugelski 2012}.In contrast to the mild infusion reactions described above, CRS is rare and mechanistically associated with indiscriminate activation of immune cells leading to a cytokine storm characterized by severe headaches, low back pain, nausea, vomiting, diarrhea, fever, disseminated intravascular coagulation, and other symptoms of critical illness including respiratory and renal failure requiring intensive care treatment.

Delayed allergic reactions to other mAbs that include a serum sickness type of reaction characterized by urticaria, fever, lymph node enlargement, and joint pains, typically occur several days after mAb exposure and are more commonly associated with chimeric types of mAbs {Hansel 2010}.

To mitigate the risk of infusion-related reactions, anaphylaxis, CRS, and serum sickness, intensive clinical monitoring will occur during the course of the study. Anaphylactoid and infusion-related reactions, including fevers, chills, rigors, changes in blood pressure, bronchospasm, and other AEs, will be closely monitored. Furthermore, sentinel dosing will occur, thereby limiting the numbers of participants exposed and the number of additional participants who may enroll and initiate study drug therapy.

Potential risks of ATI include rebound of plasma HIV-1 viremia to > 50 copies/mL, which may result in the development of HIV-1 resistance mutations, decrease in CD4+ T cell count, symptoms of retroviral syndrome, and transmission of virus to other individuals.

To mitigate these risks, plasma viral load and CD4+ T cell count will be measured frequently during ATI, and ART will be promptly reinitiated according to the protocol-defined algorithm. Participants will also be monitored for AEs, and ART will be reinitiated if these are judged (by the investigator and/or sponsor) to be related to the ATI. The initial selection of participants who have a documented detection during acute HIV infection and timing of ART initiation, durable viral suppression for at least 12 consecutive months prior to the screening visit, and the availability of a fully active alternative ART regimen, in the event of discontinuation of the current ART regimen with development of resistance, will further minimize the risks of ATI.

Potential benefits include reduction of the latent HIV-1 viral reservoir, enhanced immune control of virus producing cells, and finally the combination of these effects on HIV-1 viral control (measured as plasma virus rebound and viral load set-point) in the absence of ART. There are no direct benefits to participants participating in this study.

During a pandemic, additional potential risks to the conduct of the study may include adequate study drug availability, interruptions to the study visit schedule, and adherence to protocol-specified treatment regimen, safety monitoring or laboratory assessments. Refer to Appendix 7 for further details on the risks and risk mitigation strategy.

Considering the above, the benefit-risk balance for this study is considered positive.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of dual anti-HIV envelope mAbs, VRC07-523LS and CAP256V2LS, in a sequential regimen with a TLR7 agonist, VES, when administered in virologically suppressed HIV-1 Clade C-infected women on ART and during ATI

The secondary objectives of this study are as follows:

- To evaluate the PK of VRC07-523LS, CAP256V2LS, and VES
- To evaluate whether VRC07-523LS and CAP256V2LS induce anti-VRC07-523LS and/or anti-CAP256V2LS antibodies
- To evaluate the effect of VRC07-523LS and CAP256V2LS in a sequential regimen with VES on viral control or the need for resumption of ART following an ATI.

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3. STUDY DESIGN

3.1. Endpoints

The primary endpoints of this study are as follows:

- The proportion of participants with treatment-emergent AEs
- The proportion of participants with treatment-emergent graded laboratory abnormalities

The secondary endpoints of this study are as follows:

Virology/Efficacy

- Time to viral rebound (confirmed ≥ 50 copies/mL and ≥ 200 copies/mL) following ATI
- The change in plasma viral load set-point following ATI
- Viral load at the end of ATI
- Time to ART resumption following ATI

Pharmacokinetics

- PK parameters for VES in plasma will include Cmax, Tmax, Clast, Tlast, AUCinf, AUClast, AUCexp, t1/2, CL/F, and Vz/F.
- PK parameters for VRC07-523LS and CAP256V2LS in serum will include Cmax, Tmax, Clast, Tlast, AUCinf, AUClast, AUCexp, t1/2, CL, Vss, and Vz.

Immunogenicity

- The proportion of participants with positive anti-VRC07-523LS or anti-CAP256V2LS antibodies

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3.2. Study Design

This is an open-label, single-center, single-arm study to evaluate a sequential regimen of dual mAbs, VRC07-523LS and CAP256V2LS with a TLR7 agonist, VES, in participants from the Females Rising through Education, Support, and Health (FRESH) cohort.

The FRESH cohort consists of women with HIV-1 Clade C in Durban, South Africa, who were initiated on ART immediately after detection of HIV-1 RNA and are virologically suppressed on ART.

Participants will attend study visits and undergo assessments over 4 periods for a maximum of 60 weeks. During Periods 1 and 2, participants will be evaluated weekly at a minimum and during Periods 3 and 4, every 2 weeks at a minimum. Vesatolimod will be dosed orally, every 2 weeks, for a total of 10 doses during Periods 1 and 2. Participants will receive a first dose of VES alone in Period 1 prior to single, sequential infusions of VRC07-523LS and CAP256V2LS administration 1 week later.

Figure 2. Study Schema

Screening[a]	Prebaseline	Period 1[b]	Period 2[c]	Period 3[d]	End-of-Period 3 Visit[e]	Period 4[f]	ESDD and Follow-Up Procedure[g]	End-of-Study Visit[h]
		Continue ART	ATI from Day 35	ATI		4A–(ART restart[i]) or 4B (ATI Extension[j])		
≤ 35 days	Day −13	Days 0-28	Days 29-133	Days 134-336		Days 337-413		
		VES Doses 1-3[k]	VES Doses 4-10[k]	No Dosing		No Dosing		
		VRC07-523LS and CAP256V2LS Doses[l]						

ART = antiretroviral therapy; ATI = analytical treatment interruption; VES = vesatolimod

a Screening must occur 35 days prior to prebaseline/Day −13 visit.

b During Period 1, participants will have a study visit every week at a minimum over 4 weeks. Participants will continue to take their ART during this period.

c During Period 2, participants will have a study visit every week at a minimum over 15 weeks. No VRC07-523LS and CAP256V2LS dose to occur in this period. No ART will be administered and ATI will start from Day 35. If the ART restart criteria are met, the participant may stop Period 2, complete the end-of-Period 3 visit, and restart ART in Period 4A.

d During Period 3, participants will have a study visit every 2 weeks over 28 weeks. No study drug (VES, VRC07-523LS, or CAP256V2LS) will be administered in this period. No ART will be administered, and ATI will continue. If the ART restart criteria are met, the participant may stop Period 3, complete the end-of-Period 3 visit, and restart ART in Period 4A.

e The visit will be completed at the end of Period 3 or if ART restart criteria are met prior to starting Period 4A.

f Participants who have remained virologically suppressed (plasma HIV-1 RNA < 50 copies/mL) or have not met the ART restart criteria by the end of Period 3 will continue into Period 4. The option will be available for either Period 4A, restart of ART for 12 weeks, or Period 4B, to remain off ART for a 12-week ATI extension. The choice of Period 4A or 4B will be at the discretion of the participant and investigator. Participants who meet the ART restart criteria prior to the end of Period 3 may also take part in Period 4A. No study drug (VES, VRC07-523LS, and CAP256V2LS) will be administered in this period.

g If a participant should discontinue study dosing as described in Section 6.9.1, they will be required to complete an early study drug discontinuation (ESDD) visit and every attempt should be made to keep the participant in the study and continue to perform study procedures. If the participant is unable to complete all scheduled procedures, for criteria other than those described for study discontinuation in Section 3.5., the participant should be followed by telephone for a further duration of time as described in Section 6.9.2. If a participant has completed all study drug dosing but is unable to complete all subsequent visits at the study site, as scheduled in Periods 3 and 4, for criteria other than those described for study discontinuation in Section 3.5. for study discontinuation, the participant they should be followed by telephone for up for 250 days after mAb infusion. During follow up with telephone check-ups, participants should be followed every 4 weeks to monitor for AEs and retrieve urine pregnancy results (kits to be provided at the last study site visit and a positive urine pregnancy result will require confirmation with a serum pregnancy test at the study site). At the end of all follow-up monitoring, participants will undergo the end-of-follow-up visit at the study site.

i Participants who restart ART in Period 4A will complete 6 study visits scheduled every 2 weeks over a 12-week period.

j Participants who opt to remain off ART and complete the ATI extension will complete 6 study visits scheduled every 2 weeks over a 12-week period.

k VES dose administration to occur at baseline/Day 0 and then every 2 weeks up to Dose 10.

l VRC07-523LS and CAP256V2LS sequential dose administration to occur only once at Day 7.

During Period 1, VRC07-523LS, CAP256V2LS, and VES will be administered together with ART.

Sentinel Dosing: Participants will be enrolled and dosed in a staggered fashion, with a sentinel group consisting of 5 participants conducting Period 1 visits and assessments up to Day 21 first. The safety data of the first 5 participants will be reviewed by an external DMC, and upon confirmation, up to a further 20 participants will be enrolled into Period 1.

During Period 2, the participants will be administered VES and discontinue ART to start ATI with weekly plasma virus monitoring at each study visit.

In Period 3, no treatment (VES, VRC07-523LS, CAP256V2LS, or ART) will be administered, participants will continue ATI and plasma virus levels will be monitored.

At the end of Period 3 or if ART restart criteria are met prior to starting Period 4A, participants will be required to complete an end-of-Period 3 visit.

In Period 4, participants who have remained virologically suppressed (plasma HIV-1 RNA < 50 copies/mL) or have not met the ART restart criteria by the end of Period 3 will continue in either Period 4A and restart ART for 12 weeks, or in Period 4B and remain off ART for a 12-week ATI extension. The choice of Period 4A or 4B will be at the discretion of the participant and investigator.

If the ART restart criteria are met prior to the end of Period 3, participants may also receive ART for 12 weeks in Period 4A.

At the end of Period 4, all participants will complete an end-of-study visit.

If a participant should discontinue study dosing as described in Section 6.9.1, they will be required to complete an early study drug discontinuation (ESDD) visit and every attempt should be made to keep the participant in the study and continue to perform study procedures. If the participant is unable to complete all scheduled procedures, for criteria other than those described for study discontinuation in Section 3.5, the participant should be followed by as described in Section 6.9.2.

If a participant has completed all study drug dosing but is unable to complete all subsequent visits at the study site, as scheduled in Periods 3 and 4, for criteria other than those described for study discontinuation in Section 3.5, the participant should be followed by telephone for up for 250 days after mAb infusion.

During follow up with telephone check-ups, participants should be followed every 4 weeks to monitor for AEs and retrieve urine pregnancy results (kits to be provided at the last study site visit and a positive urine pregnancy result will require confirmation with a serum pregnancy test at the study site).

At the end of all follow-up monitoring, participants will undergo the end-of-follow-up visit at the study site..

ART Restart Criteria: Participants will receive ART in Periods 1 and 4A only. In Periods 2, 3, and 4B, participants will be in ATI and will restart ART if they have plasma HIV-1 RNA measurements of ≥ 1,000 copies/mL for 8 consecutive weeks and no drop of 0.3 $\log_{10}$ from the previous week, or confirmed plasma HIV-1 RNA > 100,000 copies/mL, or a confirmed CD4+ T cell count < 350 cells/μL, or if a participant becomes pregnant, or per participant request, or at the discretion of the investigator or sponsor due to other clinical criteria. Once the first confirmed HIV-1 RNA value of ≥ 50 copies/mL is detected, this will trigger weekly testing to monitor the HIV-1 RNA measurements.

Known HIV-seronegative male partners to the female study participants may be referred for HIV preexposure prophylaxis (PrEP) to decrease the risk of HIV transmission during ATI.

3.3. Study Treatments

Participants will receive a single, sequential infusion of VRC07-523LS and CAP256V2LS in combination with a total of 10 VES doses received every 2 weeks during Periods 1 and 2. Participants will receive the first dose of VES alone and VRC07-523LS and CAP256V2LS will be administered 1 week later. Participants will continue their prescribed ART regimen during Period 1, and may restart ART in Period 4A, upon conclusion of Period 3 or if the ART restart criteria are met during Periods 2, 3, and 4B.

3.4. Duration of Treatment

Participants will receive study drugs, VRC07-523LS, CAP256V2LS, and VES, for a maximum of 18 weeks during Periods 1 and 2. Participants who have remained virologically suppressed (plasma HIV-1 RNA < 50 copies/mL) or have not met the ART restart criteria by the end of Period 3 (maximum 43 weeks ATI [Periods 2 and 3]) will continue in either Period 4A and restart ART for 12 weeks, or Period 4B and remain off ART for a 12-week ATI extension.

3.5. Protocol-specific Discontinuation Criteria

- Intercurrent illness, unacceptable toxicity, or toxicity that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree and/or compromises the participant's ability to continue in the study or is considered to not be in the participant's best interest
- Participant request to discontinue for any reason
- Participant noncompliance
- Discontinuation of the study at the request of Gilead Sciences (Gilead), a regulatory agency, or an institutional review board (IRB) or independent ethics committee (IEC)

3.6. End of Study

The end of study will be the last participant's last observation (or visit).

3.7. Poststudy Care

After a participant has completed/terminated their participation in the study, long-term care for the participants will remain the responsibility of their primary treating physician.

3.8. Source Data

The source data for this study will be obtained from participants clinical/hospital records, interactive web response system (IWRS), central laboratory, local laboratory, and specialty laboratory.

3.9. Biomarker Testing

3.9.1. Biomarker Samples to Address the Study Objectives

The following biological specimens will be collected from all participants who have provided consent to participate in this study and may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response (including efficacy and/or AEs) and dosage selection, and to better understand the biological pathways, biology of HIV or related diseases, and/or the validation of a companion diagnostic for HIV cure. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to specify prospectively all tests that may be done on the specimens provided. The specific analyses will include but may not be limited to the biomarkers and assays listed below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of study to remove tests no longer indicated and/or to add new tests based upon new state of the art knowledge.

Samples will be collected to measure biomarkers that may include but will not be limited to:

Blood specimens will be collected (> 1 time) at prebaseline/Day −13, baseline, 1-day and 7-day after VES, at various time points during the study (please see Appendix 2, Study Procedures Table), end-of-Period 3 visit, and at the end-of-study visit for the isolation of PBMCs and plasma/serum for analyzing immune cell activation/phenotype, HIV-specific T cell responses, soluble protein (cytokines, chemokines, and inflammatory markers), CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio, and HIV-specific antibody profiling. Blood samples will be collected at prebaseline/Day −13 to evaluate soluble proteins in the TruCulture® Whole Blood Culture System.

From participants who provide additional consent, lymph node and GALT biopsies will be taken for some or all of the following tests: immunophenotyping, viral reservoir measurements, gene expression analysis and glycosylation profile analysis (depending on viable cells isolated).

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of study or per country requirements.


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4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 25 participants will be enrolled in the study.

4.1.1. Participant Replacement

Participants who discontinue before the end of study will not be replaced.

4.2. Inclusion Criteria

Participants must meet *all* of the following inclusion criteria to be eligible for participation in this study:

1) Females recruited from the FRESH acute HIV infection cohort
2) Age ≥ 18 years
3) Plasma HIV-1 RNA levels < 50 copies/mL at the screening visit
4) On ART regimen for ≥ 12 consecutive months prior to the screening visit
    a. The following agents are allowed as part of the current ART regimen: nucleoside reverse-transcriptase inhibitors, raltegravir, bictegravir, dolutegravir, and rilpivirine.
    b. A change in ART regimen ≤ 45 days prior to the prebaseline/Day −13 visit for reasons other than virologic failure (eg, tolerability, simplification, drug-drug interaction profile) is allowed. If the participant's ART regimen is changed, a plasma HIV-1 RNA level < 50 copies/mL at the prebaseline/Day −13 visit will be required to confirm eligibility.
    c. Availability of a fully active alternative ART regimen, in the opinion of the investigator, in the event of discontinuation of the current ART regimen with development of resistance
5) Have all the following laboratory values at the screening visit:
    a. Hemoglobin ≥ 10.0 g/dL
    b. White blood cells ≥ 2500 cells/µL
    c. Platelets ≥ 125,000/mL
    d. Absolute neutrophil counts ≥ 1000 cells/µL
    e. CD4+ T cell count ≥ 500 cells/µL
    f. ALT, AST, and bilirubin ≤ 2 × upper limit of normal (ULN)
    g. Creatinine clearance ≥ 60 mL/min using Cockcroft-Gault formula {Cockcroft 1976}
        1) Female Estimated Creatinine Clearance = [(140 − age in years) × (weight in kg)]/[72 × (serum creatinine in mg/dL)] × 0.85
6) Women of childbearing potential to have documentation of agreement to follow study contraceptive requirements as outlined in Appendix 5

7) Documented plasma HIV-1 RNA viral load must be < 50 copies/mL for 12 consecutive months prior to screening:
   a. ≤ 2 detectable HIV-1 RNA measurements that must be ≤ 1000 copies/mL at nonconsecutive visits within 12 months are acceptable
   b. Determinations below the level of quantitation will be considered as detectable at the assay's threshold level
8) In the judgment of the investigator, be in good general health, based on review of the results from a screening visit (to include physical examination, measurement of vital signs, resting 12-lead electrocardiogram [ECG] and routine clinical laboratory testing), performed no more than 28 days prior to study drug administration
9) Must be willing and able to comply with all study requirements and available to complete the study schedule of assessments
10) Documented history of viral sensitivity to VRC07-523LS or CAP256V2LS at the screening visit

4.3. Exclusion Criteria

Participants who meet *any* of the following exclusion criteria are not eligible to be enrolled in this study:

1) Positive serum pregnancy test
2) Nursing females
3) Participants with coinfection and/or immunosuppression as described below:
   a. Autoimmune disease requiring ongoing immunosuppression (except in the case of mild autoimmune disease that only requires topical treatments)
   b. Evidence of chronic HBV infection (defined as positive HBsAg OR positive hepatitis B core antibody and negative hepatitis B surface antibody)
   c. Evidence of current HCV infection (defined as positive hepatitis C antibody and HCV RNA > lower limit of quantitation [LLOQ])
      - positive anti-HCV antibody and negative HCV polymerase chain reaction results are acceptable
   d. Documented history of pre-ART CD4+ T cell count nadir < 200 cells/µL (unknown pre-ART CD4+ T cell count nadir is acceptable)
   e. History of opportunistic illness indicative of Stage 3 HIV as referenced in Appendix 6
   f. Acute febrile illness within 4 weeks prior to the first dose
4) Have current alcohol or substance abuse judged by the investigator to potentially interfere with participant's compliance or participant's safety
5) Have poor venous access that limits phlebotomy

6) Have been treated with systemic steroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months prior to screening or are expected to receive these agents during the study (eg, corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies)

7) Have previous or current receipt of humanized or human mAbs, or polyclonal immunoglobulin

8) Have previous history of an antidrug antibodies response to a therapeutic agent

9) Have previous receipt of an HIV vaccine

10) Received any vaccine or immunomodulatory medication within 4 weeks prior to screening. Elective vaccination (eg, flu shot, hepatitis A or B vaccine) during the course of the study will require prior approval from the sponsor

    a. COVID-19 vaccinations are allowed, with the requirement that they should not be administered within 5 days of receiving IMP

11) Have a history of any of the following:

    a. Significant serious skin disease, such as but not limited to rash, food allergy, eczema, psoriasis, or urticaria

    b. Significant drug sensitivity or drug allergy (such as anaphylaxis or hepatoxicity). Any history of anaphylaxis and related symptoms such as hives, respiratory difficulty, or angioedema

    c. Known hypersensitivity to the study drugs, metabolites, or formulation excipients

    d. Previous or current history of bleeding disorder, platelet disorder including unexplained acute or chronic thrombocytopenia

    e. Autoimmune diseases including type 1 diabetes mellitus

12) Have current Class C AIDS-defining condition

13) Have any serious or active medical or psychiatric illness (including depression) that, in the opinion of the investigator, would interfere with participants treatment, assessment, or compliance with the protocol. This would include renal, cardiac, hematological, hepatic, pulmonary (including chronic asthma), endocrine (including diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders other than HIV-1 infection, active infection, or malignancy that are clinically significant or requiring treatment

14) Participation in any other clinical study (including observation studies) without prior approval from the sponsor is prohibited while participating in this study

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Treatment Assignment

It is the responsibility of the investigator to ensure that the participants are eligible for the study prior to enrollment. Participants will be assigned a screening number at the time of consent.

Treatment assignment in the interactive voice/web response system will be performed in clinic at the baseline/Day 0 visit, provided that all other screening procedures have been completed and participant eligibility has been confirmed. If a participant's ART regimen is changed ≤ 45 days prior to prebaseline/Day −13, plasma HIV-1 RNA < 50 copies/mL at prebaseline/Day −13 visit is required to confirm eligibility. Once a participant number has been assigned, it will not be reassigned to any other participant.

5.2. Description and Handling

5.2.1. Formulation

Vesatolimod, 2 mg tablets, are round, biconvex, plain-faced, and film-coated white. Vesatolimod tablets contain the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

VRC07-523LS is a sterile, aqueous buffered solution filled into 10 mL single-dose glass vials. Each vial contains a volume of 6.25 ± 0.1 mL or 2.25 ± 0.1 mL at a concentration of 100 ± 10 mg/mL in formulation buffer composed of 50 mM histidine, 50 mM sodium chloride, 5% sucrose, and 2.5% sorbitol at pH 6.8.

CAP256V2LS is a sterile aqueous buffered solution filled into 10 mL single-dose glass vials. Each vial contains 6.25 ± 0.1 mL at a concentration of 100 ± 10 mg/mL in formulation buffer composed of 20 mM sodium phosphate, 100 mM sodium chloride, 75 mM L-arginine HCl, 3% (w/w) sucrose, and 0.01% (w/v) polysorbate 80 at pH 7.0.

5.2.2. Packaging and Labeling

Vesatolimod tablets are packaged in white, high-density polyethylene bottles. Each bottle contains 3 tablets or 4 tablets, silica gel desiccant, and polyester packing material. Each bottle is capped with a child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

VRC07-523LS drug product is aseptically filled into 10 mL single-dose glass vials, stoppered, and sealed.

CAP256V2LS drug product is aseptically filled into 10 mL single-dose glass vials, stoppered, and sealed.

Study drug(s) to be distributed to centers in South Africa shall be labeled to meet applicable requirements of the SAHPRA and/or other local regulations

5.2.3. Storage and Handling

Vesatolimod tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Keep the bottles tightly closed.

VRC07-523LS vials should be stored at −35°C to −15°C as indicated on the product label until use. VRC07-523LS vials stored at clinical sites should be in a qualified, continuously monitored, temperature-controlled freezer with temperature excursions between −45°C to −10°C is acceptable.

CAP256V2LS vials should be stored at −35°C to −15°C as indicated on the product label until use. CAP256V2LS vials stored at clinical sites should be in a qualified, continuously monitored, temperature-controlled freezer. Each vial is intended strictly for single use; refreeze and reuse after thaw should be avoided.

Until dispensed to the participants, the study drug should be stored in a securely locked area, accessible only to authorized site personnel. To ensure proper product identification, the drug products should be stored in the containers in which they are supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling the study drug.

5.3. Dosage and Administration

On dosing days, VES (6 mg [3 × 2 mg tablets] for Doses 1 and 2; 6 mg [3 × 2 mg tablets] or 8 mg [4 × 2 mg tablets] for Doses 3-10 per discussion with and approval from the Gilead medical monitor based on safety and tolerability of prior doses) should be administered orally by a participant with approximately 240 mL of water on an empty stomach (ie, no food or liquids except water for at least 2 hours prior to dosing; overnight fasting is preferable). Participants will not be allowed to consume water 1 hour before and 2 hours after dosing, except for the 240 mL administered with VES. Participants should remain fasted without food until 2 hours after dosing. Participants will be asked to provide information on food consumption and total fasting time prior to dosing.

There are no fasting requirements on VRC07-523LS and CAP256V2LS dosing days:

- VRC07-523LS, 20 mg/kg, IV infusion over 30 minutes
- CAP256V2LS, 20 mg/kg, IV infusion over 30 minutes

Supportive medications, including but not limited to antihistamines (such as diphenhydramine), acetaminophen (paracetamol), and steroids, will be available in the clinic settings during the IV infusions.

Study drug infusion may be slowed and/or discontinued if an infusion-related adverse reaction occurs. Symptom severity will be evaluated, and supportive medications will be provided as clinically indicated. Study drug infusion may be resumed upon symptom resolution. If the symptoms, in the judgment of the investigator and the medical monitor, compromise the ability to continue study-specific procedures or are considered to not be in the participant's best interests, the infusion will be permanently discontinued.

5.4. Prior and Concomitant Medications

Due to potential for interference with VRC07-523LS or CAP256V2LS mAb binding or activity, CCR5 inhibitors (maraviroc), fusion inhibitors, and mAb HIV entry inhibitors (Trogarzo) are prohibited from use during this study.

No clinical drug-drug interaction studies have been conducted with VES. Based on nonclinical data, VES is predominantly metabolized by cytochrome P450 enzyme (CYP)3A with minor contribution of CYP2C8 and CYP2D6 and was shown to be a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Vesatolimod plasma exposure may increase or decrease on co-administration with CYP3A/P-gp/BCRP inhibitors or inducers.

ART agents known to inhibit or induce CYP3A/P-gp/BCRP are excluded from use in this study. Due to the potential for a PK-mediated drug-drug interaction, the following agents are NOT allowed as part of the current ART regimen: HIV protease inhibitors (including low-dose ritonavir), cobicistat-containing regimens, elvitegravir, efavirenz, etravirine, and nevirapine.

Concomitant use of herbal/natural supplements with VES may result in PK interactions resulting in alterations in exposure of VES. Administration of VES with grapefruit juice or Seville orange juice may result in higher exposures to VES. Participants will refrain from consumption of grapefruit juice, grapefruits, and Seville orange juice from enrollment to the end of Period 2.

Medications that are prohibited or to be used with caution are listed in Table 2; this table is not exhaustive. Administration of any of the disallowed medications listed in Table 2 must be discontinued at least **14** days prior to the prebaseline/Day −13 and through completion of Period 2 or the ESDD visit.

Any medications not on the list must be reviewed with the sponsor prior to enrollment and during the study treatment period.

Vitamins and/or acetaminophen (paracetamol) and/or ibuprofen and/or hormonal contraceptive medications are exceptions and are allowed during the study period. No immunomodulatory concomitant medications are allowed within 4 weeks prior to screening.

At clinically achieved plasma concentrations, VES is not expected to be a perpetrator of systemic drug-drug interactions.

Table 2. Medications Prohibited

Drug Class	Agents Disallowed
Acetyl-coenzyme A acetyltransferase inhibitor	Avasimibe
Angiotensin-converting enzyme inhibitors	Captopril
Analeptic	Modafinil, lomitapide
Angiotensin II inhibitors	Telmisartan
Anti-anginals	Ranolazine
Anti-arrhythmics	Amiodarone, dronedarone, quinidine
Antibiotics	Azithromycin, clarithromycin, erythromycin, nafcillin, telithromycin
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital, oxcarbazepine, cenobamate
Antidepressants	Fluvoxamine, nefazodone, venlafaxine, ziprasidone, paroxetine
Antidiabetics	Pioglitazone
Antiepileptics	Divalproex
Antiemetics	Aprepitant, casopitant
Antifungals	Caspofungin, ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, clotrimazole
Antimigraine	Rimegepant
Antimycobacterials	Rifampin, rifapentine
Beta-blockers	Carvedilol, talinolol
Calcium channel blockers	Amlodipine, diltiazem, felodipine mibefradil, nicardipine, nifedipine, nitrendipine, verapamil
Diuretics	Conivaptan
Endothelin receptor antagonists	Bosentan
Gonadotropin-releasing hormone receptor antagonist	Elagolix
Herbal/natural supplements	St John’s wort, echinacea, gingko, milk thistle, Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Histamine-2 receptor antagonists	Cimetidine, ranitidine
3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors	Atorvastatin
Immunosuppressants	Cyclosporine, rapamycin, sirolimus, tacrolimus
Systemic corticosteroids	All agents, including dexamethasone
Systemic chemotherapeutic (antineoplastic) agents	All agents

a Use of complementary or alternative medicines is prohibited at least 14 days prior to baseline/Day 0 through the end of the follow up.

Should participants have a need to initiate treatment with any concomitant medication, the Gilead medical monitor must be consulted prior to initiation of the new medication. In instances where a medication is initiated prior to discussion with the sponsor, the investigator must notify Gilead as soon as he/she is aware of the use of the medication.

5.5. Accountability for Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to participants must be returned to the site.

Each study site must keep accountability records that capture:

- The date received and quantity of study drug
- The date, participant number, and the amount of study drug dispensed
- The date, quantity of used and unused study drug returned, along with the initials of the person recording the information

5.5.1. Investigational Medicinal Product Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform drug accountability during an on-site monitoring visit.

6. STUDY PROCEDURES

The study procedures to be conducted for each participant enrolled in the study are presented in tabular form in Appendix 2a and Appendix 2b and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify Gilead or the contract research organization.

6.1. Participant Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any time.

Rescreening may be allowed. Investigators must consult with the Gilead medical monitor and receive approval prior to re-screening a participant.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Participants will be screened within 35 days prior to prebaseline/Day −13 to determine eligibility for participation in the study. The following will be performed and documented at the screening visit:

- Obtain written informed consent
- Obtain medical history including route and estimated duration of HIV-1 infection, history of HIV-1 disease-related events, ART history for at least 12 consecutive months prior to screening, and prior concomitant medications within 35 days of the screening visit
- Obtain HIV staging at detection using standard markers (eg, HIV-1 RNA, p24 antigen, fourth generation combination antigen/antibody enzyme-linked immunosorbent assay, HIV-1 Western blot), duration of viremia during acute HIV infection and peak HIV RNA
- Complete physical examination, including vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature)
- Body weight and height
- Obtain urine for urinalysis
- Obtain blood samples for:
    - Plasma HIV-1 RNA
    - Serum pregnancy test (females of childbearing potential only). If the test is positive, the participants will not be enrolled

- Serum follicle-stimulating hormone test (for females < 54 years old who have ceased menstruating for ≥ 12 months, but are not permanently sterile or do not have documentation of ovarian hormonal failure)
- Chemistry profile: alkaline phosphatase (ALP), AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, creatine kinase (CK), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
- Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, high-density lipoprotein, direct low-density lipoprotein, and triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments
- Hematology profile: complete blood count (CBC) with differential and platelet count
- Creatinine clearance according to the Cockcroft-Gault formula:

  Female Estimated Creatinine Clearance = [(140 − age in years) × (weight in kg)] / [72 × (serum creatinine in mg/dL)] × 0.85
- CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio
- HBV serology
- HCV serology
- PBMC sample for testing of viral sensitivity to the VRC07-523LS and CAP256V2LS mAbs, if not previously conducted

- 12-lead ECG
- Documentation of participant agreement to follow study contraceptive requirements as outlined in Appendix 5

Participants who meet all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 5 weeks of the screening visit for the prebaseline/Day −13 assessments.

From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-mandated procedures on the AEs electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be considered medical history. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Prebaseline/Day −13 Assessments

The prebaseline/Day −13 visit is to be completed within 35 days of the screening visit. The following evaluations are to be completed at the prebaseline/Day −13 visit:

- Review of inclusion/exclusion criteria to confirm participant eligibility
- Review of AEs and changes in concomitant medications
- Review of medical history
- Symptom-directed physical examination as needed
- Body weight
- Obtain blood samples for:
    - Plasma HIV-1 RNA
    - Chemistry profile: ALP, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
    - Hematology profile: CBC with differential and platelet count
    - Creatinine clearance according to the Cockcroft-Gault formula:

      Female Estimated Creatinine Clearance = [(140 − age in years) × (weight in kg)] / [72 × (serum creatinine in mg/dL)] × 0.85
    - Whole blood ISG mRNA panel
    - Anti-VRC07-523LS and anti-CAP256V2LS antibody profiling from serum
    - HIV-specific antibody profiling using plasma
    - Soluble proteins (cytokines, chemokines, and inflammatory markers)
    - Prebaseline soluble proteins in the TruCulture® Whole Blood Culture System
    - PBMC sample for immune cell frequency, activation, and phenotyping
    - PBMC sample for HIV-specific T cell responses
    - PBMC sample for latent HIV-1 reservoir
    - Plasma sample for active HIV-1 reservoir
    - PBMC sample for active HIV-1 reservoir

- From participants who provide additional consent, HLA genotype, TLR7, and FcgR SNP samples will be collected for pharmacogenetic research.

- From participants who provide additional consent, lymph node and/or GALT (GALT obtained by rectosigmoid biopsy) tissue collection (within window of ± 5 days) for some or all the following tests:

  - Immune cell frequency, activation, and phenotype, gene expression, and HIV-specific T cell response evaluation (PD and immunology)

  - HIV-1 reservoir measurements (virology)

- Obtain urine collection for:

  - Urinalysis

  - Urine pregnancy test (females of childbearing potential only). A positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the participant will not be able to participate.

- Birth control will be checked and replaced, if required

6.2.3. Treatment Assignment

Obtain participant number and assign treatment to the participant in the IWRS. The participant number assignment and treatment assignment will be performed in clinic at the baseline/Day 0 visit, provided that all screening procedures have been completed and participant eligibility has been confirmed.

If a participant's ART regimen is changed ≤ 45 days prior to prebaseline/Day −13, plasma HIV-1 RNA < 50 copies/mL at prebaseline/Day −13 visit is required to confirm eligibility. Once a participant number has been assigned, it will not be reassigned to any other participant.

6.3. Treatment Assessments–Period 1

Participants will have up to 9 visits over 4 weeks. Dosing of VRC07-523LS and CAP256V2LS will occur in a sequential regimen with VES.

Doses 1 to 3 of VES will be administered orally on baseline/Day 0, Day 14, and Day 28. For Dose 3 only, 6 mg [3x2 mg tablets] or 8 mg [4x2 mg tablets]) will be administered per discussion with and approval from the Gilead medical monitor based on safety and tolerability of prior doses.

One dose of VRC07-523LS and 1 dose of CAP256V2LS will be administered sequentially by IV infusions on Day 7.

Participants will remain at the site for monitoring for 24 hours after Dose 1 of VES, for at least 8 hours after Dose 2 of VES, and for at least 4 hours after Dose 3 of VES. If participants experience significant influenza-like AEs (eg, moderate or severe pyrexia, chills, headache, myalgia, fatigue, malaise, joint pain) after the first 2 VES doses, or if dose is escalated to 8 mg, monitoring may be extended to > 4 hours for subsequent doses. For VRC07-523LS and CAP256V2LS, participants will remain on site for at least 8 hours after infusion on Day 7 for monitoring. If participants experience new or worsening flu-like symptoms, postdose safety monitoring should be extended.

Fasted status and food consumption will be checked prior to dosing.

Participants will continue to take their ART during this period (Days 0 to 28).

Sentinel Dosing:

Five participants will be enrolled first, to conduct visits and assessments up to Day 21. Upon review of the safety data and confirmation from an external DMC, up to a further 20 participants will be enrolled into Period 1.

Table 3. Period 1 Study Visits and Study Drug Administration

Period 1									
Week	**-**	**-**	**-**	**1**	**-**	**-**	**2**	**3**	**4**
Day	**Baseline/0**	**1**	**2**	**7**	**8**	**9**	**14**	**21**	**28**
VES Dose	1						2		3
VRC07-523LS and CAP256V2LS Dose				1					
ART (Days 0 to 28)									

ART = antiretroviral therapy

6.3.1. Treatment Assessments–Baseline/Day 0

The following assessments are to be completed at the baseline/Day 0 visit. The investigator must confirm eligibility before proceeding with the baseline/Day 0 visit.

Participants must complete all study procedures before being administered study drug.

- Symptom-directed physical examination
- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature) at predose and then at 1, 2, 4, 8, 12, and 18 hours after VES administration
- Body weight

- Obtain blood samples for:
  - Plasma HIV-1 RNA
  - Plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART
  - Chemistry profile: ALP, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
  - Hematology profile: CBC with differential and platelet count
  - Creatinine clearance according to the Cockcroft-Gault formula:

    Female Estimated Creatinine Clearance = [(140 − age in years) × (weight in kg)]/[72 × (serum creatinine in mg/dL)] × 0.85
  - Plasma sample for active HIV-1 reservoir
  - PBMC sample for active HIV-1 reservoir
  - Whole blood ISG mRNA panel
  - Soluble proteins (cytokines, chemokines, and inflammatory markers)
  - HIV-specific antibody profiling using plasma
  - CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio
  - PBMC sample for immune cell frequency, activation, and phenotyping
  - Plasma VES PK collection: Predose (≤ 5 minutes prior to dosing), 1, 2, 4, 8, and 12 hours after Dose 1 of VES
- Obtain urine collection for:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive at baseline/Day 0, study drug will not be dispensed. A positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the participant will not be able to participate.
- Birth control will be checked and replaced, if required.
- Adverse events and changes in concomitant medications will be assessed and recorded. Participants will be reminded to report all symptoms, including flu-like symptoms (eg, fatigue, pyrexia, chills, myalgia, joint pain, or headache) or other unexpected symptoms.

6.3.2. Treatment Assessments–Days 1 to 28

All study visits are to be completed within ± 3 days of the protocol-specified visit date (based on the Day 0 visit) except for the Day 7 visit, and study procedures are to be completed within ± 2 hours of the protocol-specified time point.

At the Day 28 visit and prior to moving into Period 2, each participant will be assessed to determine whether the criteria to start ATI has been met as described in Section 6.3.3.

The following assessments are to be completed at every visit, unless otherwise specified.

- Symptom-directed physical examination
- Body weight
- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature) at:
  - Dose 1 of VES 24 hours after administration **(Day 1)**
  - VRC07-523LS and CAP256V2LS infusions prior to administration and at 1, 2, 4, and 8 hours after administration **(Day 7)**
  - Dose 2 of VES prior to administration and at 1, 2, 4 and 8 hours after administration **(Day 14)**
  - Dose 3 of VES prior to administration and at 1, 2 and 4 hours after administration **(Day 28)**
  - If the participant experiences new or worsening symptoms, evaluate for signs and symptoms of CRS, including vital signs
- Obtain blood samples for:
  - Plasma HIV-1 RNA **(Day 7 and each weekly visit thereafter)**
  - Plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART **(Day 7 and each weekly visit thereafter)**
  - Chemistry profile: ALP, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid **(all visits except Days 8 and 9)**
  - Hematology profile: CBC with differential and platelet count **(all visit days except Days 8 and 9)**
  - Creatinine clearance according to the Cockcroft-Gault formula **(all visits except Days 8 and 9):**

Female Estimated Creatinine Clearance = [(140 − age in years) × (weight in kg)]/[72 × (serum creatinine in mg/dL)] × 0.85

- Anti-VRC07-523LS and anti-CAP256V2LS antibody profiling from serum **(Day 28)**
- HIV-specific antibody profiling using plasma **(Day 8)**
- Whole blood ISG mRNA panel **(Day 1)**
- Soluble proteins (cytokines, chemokines, and inflammatory markers) **(Days 1 and 8)**
- CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio **(Days 14 and 28)**
- PBMC sample for immune cell frequency, activation, and phenotyping **(Days 1 and 8)**
- PBMC sample for HIV-specific T cell responses **(Day 8)**
- Plasma sample for active HIV-1 reservoir **(Days 1 and 2)**
- PBMC sample for active HIV-1 reservoir **(Days 1 and 2)**
- Plasma VES PK collections **(Day 1 and 2 [24 and 48 hours after VES Dose 1 at baseline/Day 0])**
- Serum VRC07-523LS PK collections **(0 hours [predose], end of infusion, 1, 2, 4, and 8 hours after end of infusion on Day 7 and then at Days 8, 9, 14, 21, and 28)**
- Serum CAP256V2LS PK collections **(0 hours [predose], end of infusion, 1, 2, 4, and 8 hours after end of infusion on Day 7, and then at Days 8, 9, 14, 21, and 28)**

- Obtain urine collection for:
  - Urinalysis **(all visits except Days 8 and 9)**
  - Urine pregnancy testing; a positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the participant will discontinue from study drug **(Day 28)**
- Birth control will be checked and replaced, if required.
- Ongoing eligibility assessment prior to the participant being administered study drug on site **(Days 7, 14, and 28)**
- Adverse events and changes in concomitant medications will be assessed and recorded. Participants will be reminded to report all symptoms, including flu-like symptoms (eg, fatigue, pyrexia, chills, myalgia, joint pain, or headache) or other unexpected symptoms.

6.3.3. ATI Eligibility Criteria

At the Day 28 visit and prior to the Period 2 Day 35 visit, participants will be assessed to determine whether the criteria necessary to begin ATI are met. All of the following criteria must be met for a participant to begin ATI (Period 2):

- Viral load < 50 copies/mL
- CD4+ T cell count > 400 cells/μL
- Negative urine pregnancy test
- Participant has received VRC07-523LS, CAP256V2LS, and at least 3 of the 10 scheduled doses of VES.
- Participant confirms agreement to request their partners to use condoms throughout the ATI period.

The initiation of ATI (Period 2) may be postponed for up to 4 weeks after the last VES dose for participants to meet the above requirements. If a participant develops any other acute event during this time that may require treatment before the participant starts the ATI (Period 2), the investigator should consult with the medical monitor. The investigator may delay the initiation of the ATI (Period 2), after consultation with the medical monitor, for up to a further 4 weeks if it is determined that the participant may proceed to ATI (Period 2) once the acute event has been treated successfully. The investigator should consult with the medical monitor to determine if repeat assessments should be performed to re-confirm the participant's eligibility for the ATI (Period 2).

Participants who do not meet the requirements for ATI (Period 2) will complete an ESDD visit within 3 days of informing the investigator/site and may undergo early discontinuation of study follow up and procedures as described in Section 6.9.2.

6.4. Treatment Assessments–Period 2

Participants will have up to 18 visits over 15 weeks. Doses 4 to 10 of VES will be administered orally on Day 42, Day 56, Day 70, Day 84, Day 98, Day 112, and Day 126.

For Doses 4 to 10, 6 mg [3x2 mg tablets] or 8 mg [4x2 mg tablets]) will be administered per discussion with and approval from the Gilead medical monitor based on safety and tolerability of prior doses.

Participants will remain at the site for monitoring for at least 4 hours after VES dosing. If participants experience significant influenza-like AEs (eg, moderate or severe pyrexia, chills, headache, myalgia, fatigue, malaise, joint pain) after the first 2 VES doses, monitoring may be extended to > 4 hours for subsequent doses. Fasted status and food consumption will be checked prior to dosing.

No ART will be administered and ATI will start from Day 35.

If the ART restart criteria are met, the end-of-Period 3 visit (Section 6.5.2) will be completed and the participant may begin Period 4A.

Table 4. Period 2 Study Visits and Study Drug Administration

	Period 2																	
Week	**5**	**6**	**7**	**8**	**-**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**-**	**-**	**19**
Day	**35**	**42**	**49**	**56**	**57**	**63**	**70**	**77**	**84**	**91**	**98**	**105**	**112**	**119**	**126**	**127**	**128**	**133**
VES Dose		4		5			6		7		8		9		10			
VRC07-523LS and CAP256V2LS Dose	No dosing																	
ATI (Days 35 to 133)																		

ATI = analytical treatment interruption; VES = vesatolimod
Every Period 2 study visit is based on the Day 0 visit + the number of postponement days required to confirm ATI eligibility in Period 1, if applicable

6.4.1. Treatment Assessments–Days 29 to 133

The following assessments are to be completed at every visit, unless otherwise specified. All study visits are to be completed within ± 3 days of the protocol-specified visit date (based on the Day 0 visit + the number of postponement days required to confirm ATI eligibility in Period 1, if applicable), and study procedures are to be completed within ± 2 hours of the protocol-specified time point. Symptom-directed physical examination

- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature) at:
  - Doses 4 to 10 of VES prior to administration and at 1, 2, and 4 hours after administration **(Day 42 and at each visit every 2 weeks thereafter)**
  - If the participant experiences new or worsening symptoms, evaluate for signs and symptoms of CRS, including vital signs
- Body weight (Day 42 and at each visit every 2 weeks thereafter)
- Obtain blood samples for:
  - Plasma HIV-1 RNA **(Day 42 and at each visit every 2 weeks thereafter)**
    - If a confirmed rebound of ≥ 50 copies/mL occurs, the test should be completed weekly

- Plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART **(Day 42 and at each visit every 2 weeks thereafter)**

- Chemistry profile: ALP, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid **(Day 42 and at each visit every 2 weeks thereafter)**

- Hematology profile: CBC with differential and platelet count **(Day 42 and at each visit every 2 weeks thereafter)**

- Creatinine clearance according to the Cockcroft-Gault formula **(Day 42 and at each visit every 2 weeks thereafter):**

  Female Estimated Creatinine Clearance = [(140 − age in years) × (weight in kg)]/[72 × (serum creatinine in mg/dL)] × 0.85

- Anti-VRC07-523LS and anti-CAP256V2LS antibody profiling from serum **(Days 56, 84, 112, and 133)**

- HIV-specific antibody profiling using plasma **(Days 126 and 133)**

- Whole blood ISG mRNA panel **(Days 56, 57, 126, and 127)**

- Soluble proteins (cytokines, chemokines, and inflammatory markers) **(Days 56, 57, 63, 126, 127, and 133)**

- CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio **(Days 42, 56, 70, 84, 98, 112, 126, and 133)**

- PBMC sample for immune cell frequency, activation, and phenotyping **(Days 56, 57, 63, 126, 127, and 133)**

- PBMC sample for HIV-specific T cell responses **(Days 63 and 133)**

- Serum VRC07-523LS PK collection **(Days 56, 84, 112, and 133)**

- Serum CAP256V2LS PK collection **(Days 56, 84, 112, and 133)**

- Plasma dolutegravir PK collection **(Days 56, 84, 112, and 133)**

- Plasma sample for active HIV-1 reservoir **(Days 56, 57, 126, 127, and 128)**

- PBMC sample for active HIV-1 reservoir **(Days 56, 57, 126, 127, and 128)**

- Obtain urine collection for:
  - Urinalysis **(Day 42 and at each visit every 2 weeks thereafter)**
  - Urine pregnancy testing; a positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the participant will discontinue from study drug **(Day 42 and at each visit every 4 weeks thereafter)**
- Birth control will be checked and replaced, if required.
- Ongoing eligibility assessment prior to the participant being administered study drug on site **(Days 42, 56, 70, 84, 98, 112, and 126)**
  - Known HIV-1 seronegative sexual partners of enrolled study participants may be referred for HIV PrEP to decrease risk of HIV transmission during ATI.
- Adverse events and changes in concomitant medications will be assessed and recorded. Participants will be reminded to report all symptoms, including flu-like symptoms (eg, fatigue, pyrexia, chills, myalgia, joint pain, or headache) or other unexpected symptoms

6.5. Posttreatment Assessments–Period 3

Participants will have up to 14 study visits every 2 weeks for a total of 29 weeks.

No study drug (VES, VRC07-523LS, or CAP256V2LS) will be administered during this period.

No ART will be administered during this period and ATI will continue. If the ART restart criteria are met, the participant will stop Period 3, complete the end-of-Period 3 visit (Section 6.5.2), and may restart ART in Period 4A.

Upon completion of Period 3, all participants will be required to complete an end-of-Period 3 visit prior to moving into Period 4.

Table 5. Period 3 Study Visits and Study Drug Administration

	Period 3													
Week	**21**	**23**	**25**	**27**	**29**	**31**	**33**	**35**	**37**	**39**	**41**	**43**	**45**	**47**
Day	**147**	**161**	**175**	**189**	**203**	**217**	**231**	**245**	**259**	**273**	**287**	**301**	**315**	**329**
VES Dose	No dosing													
VRC07-523LS and CAP256V2LS Dose	No dosing													
ATI (Days 134 to 336)														

Every Period 3 study visit is based on the Day 0 visit + the number of postponement days required to confirm ATI eligibility in Period 1, if applicable

6.5.1. Treatment Assessments–Days 134 to 336

The following assessments are to be completed at every visit, unless otherwise specified. All study visits are to be completed within ± 3 days of the protocol-specified visit date (based on the Day 0 visit + the number of postponement days required to confirm ATI eligibility in Period 1, if applicable), and study procedures are to be completed within ± 2 hours of the protocol-specified time point.

- Symptom-directed physical examination (Day 147 and at each visit every 4 weeks thereafter)
- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature) (Day 147 and at each visit every 4 weeks thereafter)
- Body weight (Day 147 and at each visit every 4 weeks thereafter)
- Obtain blood samples for:
  - Plasma HIV-1 RNA
    - If a confirmed rebound of ≥ 50 copies/mL occurs, the test should be completed weekly
  - Plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART
  - Chemistry profile: ALP, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid **(Day 147 and at each visit every 4 weeks thereafter)**
  - Hematology profile: CBC with differential and platelet count **(Day 147 and at each visit every 4 weeks thereafter)**
  - Creatinine clearance according to the Cockcroft-Gault formula **(Day 147 and at each visit every 4 weeks thereafter)**:

    Female Estimated Creatinine Clearance = [(140 − age in years) × (weight in kg)] / [72 × (serum creatinine in mg/dL)] × 0.85
  - Anti-VRC07-523LS and anti-CAP256V2LS antibody profiling from serum **(Days 161, 189, 217, 245, 273, 301, and 329)**
  - CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio **(Day 147 and at each visit every 4 weeks thereafter)**

  - PBMC sample for latent HIV-1 reservoir **(Day 147)**
  - PBMC sample for testing of viral sensitivity to the VRC07-523LS and CAP256V2LS mAbs **(Day 147)**
  - Serum VRC07-523LS PK collection **(Days 161, 189, 217, 245, 273, 301, and 329)**
  - Serum CAP256V2LS PK collection **(Days 161, 189, 217, 245, 273, 301, and 329)**
  - Plasma dolutegravir PK collection **(Days 161, 189, 217, 245, 273, 301, and 329)**
- From participants who provide additional consent, lymph node and/or GALT (GALT obtained by rectosigmoid biopsy) tissue collection (within window of ± 5 days) will be taken at **Day 134** for some or all of the following tests:
  - Immune cell frequency, activation, and phenotype, gene expression and HIV-specific T cell response evaluation (PD and immunology)
  - HIV-1 reservoir measurements (virology)
- Obtain urine collection for:
  - Urinalysis **(Day 147 and at each visit every 4 weeks thereafter)**
  - Urine pregnancy testing; a positive result will be confirmed with a serum pregnancy test. **(Day 147 and at each visit every 4 weeks thereafter)**
- Birth control will be checked and replaced, if required.
- Known HIV-1 seronegative sexual partners of enrolled study participants may be referred for HIV PrEP to decrease risk of HIV transmission during ATI.
- Adverse events and changes in concomitant medications will be assessed and recorded. Participants will be reminded to report all symptoms, including flu-like symptoms (eg, fatigue, pyrexia, chills, myalgia, joint pain, or headache) or other unexpected symptoms.

At the end of Period 3, all participants will be required to complete an end-of-Period 3 visit prior to moving into Period 4.

6.5.2. End of Period 3 Visit

Participants who complete Period 3 or meet the ART restart criteria will be required to complete an end-of-Period 3 visit 1 week after their last visit (to be completed within ± 1 day of the protocol-specified visit date [based on the Day 0 visit + the number of postponement days required to confirm ATI eligibility in Period 1, if applicable]). All participants will complete the following procedures:

- Symptom-directed physical examination
- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature)

- Body weight
- Review of AEs and changes in concomitant medications
- 12-lead ECG
- Obtain blood samples for:
  - Plasma HIV-1 RNA
  - Plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART
  - HIV-specific antibody profiling using plasma
  - Whole blood ISG mRNA panel
  - Soluble proteins (cytokines, chemokines, and inflammatory markers)
  - CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio
  - PBMC sample for testing of viral sensitivity to the VRC07-523LS and CAP256V2LS mAbs
  - PBMC sample for immune cell frequency, activation, and phenotyping
  - PBMC sample for HIV-specific T cell responses
  - PBMC sample for latent HIV-1 reservoir
  - PBMC sample for active HIV-1 reservoir
  - Plasma sample for active HIV-1 reservoir
- From participants who provide additional consent, lymph node and/or GALT (GALT obtained by rectosigmoid biopsy) tissue collection (within window of ± 5 days) for some or all of the following tests:
  - Immune cell frequency, activation and phenotype, gene expression and HIV-specific T cell response evaluation (PD and immunology)
  - HIV-1 reservoir measurements (virology)

6.6. Posttreatment Assessments–Period 4

Participants who have remained virologically suppressed (plasma HIV-1 RNA < 50 copies/mL) or have not met the ART restart criteria at the end of Period 3 will continue into Period 4. The option will be available for either Period 4A, restart of ART for 12 weeks, or Period 4B, to remain off ART for a 12-week ATI extension. The period will begin after end of Period 3 Visit

to the end-of-study visit. The choice of Period 4A or 4B will be at the discretion of the participant and investigator.

Participants who meet the ART restart criteria prior to the end of Period 3 may also take part in Period 4A. The first Period 4A visit will require a urine pregnancy test. The ART restart criteria are:

- Plasma HIV-1 RNA measurements of ≥ 1,000 copies/mL for 8 consecutive weeks AND no drop of 0.3 $\log_{10}$ from the previous week
  - — Once the first confirmed HIV-1 RNA value of ≥ 50 copies/mL is detected, this will trigger weekly testing to monitor the HIV-1 RNA measurements,

OR

- Confirmed plasma HIV-1 RNA > 100,000 copies/mL

OR

- If a confirmed CD4+ T cell count < 350 cells/μL

OR

- If a participant becomes pregnant

OR

- ART may also be reinitiated during ATI per participant request, or at the discretion of the investigator, or sponsor due to other clinical criteria

Participants who restart ART in Period 4A will complete 6 study visits scheduled every 2 weeks over a 12-week period.

Participants who opt to remain off ART in Period 4B for the ATI extension will complete 6 study visits scheduled every 2 weeks over a 12-week period. If the participant's HIV-1 RNA remains at < 50 copies/mL throughout Period 4B, additional procedures may be required at the end-of-study visit.

No study drug (VES, VRC07-523LS, or CAP256V2LS) will be administered in this period.

Table 6. Periods 4A and 4B Study Visits and Study Drug Administration

Periods 4A & 4B						
Week	**49**	**51**	**53**	**55**	**57**	**59**
Day	**343**	**357**	**371**	**385**	**399**	**413**
VES Dose	No dosing					
VRC07-523LS and CAP256V2LS Dose	No dosing					
4A: ART Restart 4B: ATI Extension Days 337 to 413						

VES = Vesatolimod, Every Period 4 study visit is based on the Day 0 visit + the number of postponement days required to confirm ATI eligibility in Period 1, if applicable

6.6.1. Treatment Assessments–Days 337 to 413

The following assessments are to be completed at every visit for Periods 4A and 4B, unless otherwise specified. All study visits are to be completed within ± 3 days of the protocol-specified visit date (based on the Day 0 visit + the number of postponement days required to confirm ATI eligibility in Period 1, if applicable), and study procedures are to be completed within ± 2 hours of the protocol-specified time point.

- Symptom-directed physical examination (**Day 343 and at each visit every 4 weeks thereafter)**
- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature) (**Day 343 and at each visit every 4 weeks thereafter**)
- Body weight (**Day 343 and at each visit every 4 weeks thereafter**)
- Obtain blood samples for:
  - Plasma HIV-1 RNA
    - Period 4A: If a confirmed rebound of ≥ 50 copies/mL occurs, the test should be completed at each scheduled visit until the end-of-study visit
    - Period 4B: If a confirmed rebound of ≥ 50 copies/mL occurs, the test should be completed weekly until ART restart criteria are met or the end-of-study visit
  - Plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART
  - Chemistry profile: ALP, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid (**Day 343 and at each visit every 4 weeks thereafter**)
  - Hematology profile: CBC with differential and platelet count (**Day 343 and at each visit every 4 weeks thereafter**)
  - Creatinine clearance according to the Cockcroft-Gault (**Day 343 and at each visit every 4 weeks thereafter**):

    Female Estimated Creatinine Clearance = [(140 − age in years) × (weight in kg)]/[72 × (serum creatinine in mg/dL)] × 0.85
  - CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio (**Day 343 and at each visit every 4 weeks thereafter**)

  - Serum VRC07-523LS PK collection (**Days 343, 371, and 413**)
  - Serum CAP256V2LS PK collection (**Days 343, 371, and 413**)
  - Plasma dolutegravir PK collection (**Days 343, 371, and 413**) **[Period 4B only]**
  - Anti-VRC07-523LS and anti-CAP256V2LS antibody profiling from serum **(Days 343, 371, and 413)**

- Obtain urine collection for:
  - Urinalysis **(Day 343 and at each visit every 4 weeks thereafter)**
  - Urine pregnancy testing; a positive result will be confirmed with a serum pregnancy test **(At the first ART visit/Day 343 and at each visit every 4 weeks thereafter)**

- Birth control will be checked and replaced, if required.

- Known HIV-1 seronegative sexual partners of enrolled study participants may be referred for HIV PrEP to decrease risk of HIV transmission during ATI **(Period 4B only)**.

- Adverse events and changes in concomitant medications will be assessed and recorded. Participants will be reminded to report all symptoms, including flu-like symptoms (eg, fatigue, pyrexia, chills, myalgia, joint pain, or headache) or other unexpected symptom.

6.7. Posttreatment Assessments–Early Study Drug Discontinuation Visit

Participants who prematurely discontinue study drug prior to completing the infusions of the VRC07-523LS and CAP256V2LS, or all 10 doses of VES, as described in Section 6.9.1, Criteria for Discontinuation of Study Drug, will complete an ESDD visit within 3 days of informing the investigator/site.

At the ESDD visit, any evaluations showing abnormal results indicating that there is a possible or probable causal relationship with the study drug should be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

The following assessments will be performed at the ESDD visit:

- Symptom-directed physical examination
- Review of AEs and changes in concomitant medications
- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature)
- Body weight

- Obtain blood samples for:
  - Plasma HIV-1 RNA
  - Plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART
  - Chemistry profile: ALP, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
  - Hematology profile: CBC with differential and platelet count
  - Creatinine clearance according to the Cockcroft-Gault:

    Female Estimated Creatinine Clearance = [(140 − age in years) × (weight in kg)]/[72 × (serum creatinine in mg/dL)] × 0.85
  - Whole blood ISG mRNA panel
  - Soluble proteins (cytokines, chemokines, and inflammatory markers)
  - CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio
- Obtain urine collection for:
  - Urinalysis
  - Urine pregnancy testing; a positive result will be confirmed with a serum pregnancy test.
    - Urine pregnancy kits will be provided to participants who completed the VRC07-523LS and CAP256V2LS infusion for monitoring as described in Section 6.9.2

6.8. End-of-Study Visit

The end-of-study visit will occur for participants who have completed Period 4A or 4B. The visit will occur 1 week after completion of the last Period 4 visit. For the purpose of scheduling the end-of-study visit, a ± 3 day window may be used based on the based on the Day 0 visit + the number of postponement days required to confirm ATI eligibility in Period 1, if applicable.

The ART reinitiation after the end-of-study visit will be up to the participant's health care provider discretion.

The following assessments will be performed at the end-of-study visit:

- Symptom-directed physical examination
- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature)
- Body weight
- Review of AEs and changes in concomitant medications
- 12-lead ECG
- Obtain urine collection for:
  - Urinalysis
  - Urine pregnancy testing; a positive result will be confirmed with a serum pregnancy test
- Obtain blood samples for:
  - Plasma HIV-1 RNA
  - Plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART
  - Chemistry profile: ALP, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
  - Hematology profile: CBC with differential and platelet count
  - CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio
  - Creatinine clearance according to the Cockcroft-Gault formula:

    Female Estimated Creatinine Clearance = [(140 − age in years) × (weight in kg)]/72 × (serum creatinine in mg/dL)] × 0.85
- The following additional ATI remission tests will be required:
  - HIV-specific antibody profiling using plasma
  - Whole blood ISG mRNA panel
  - Soluble proteins (cytokines, chemokines, and inflammatory markers)
  - PBMC sample for testing of viral sensitivity to the VRC07-523LS and CAP256V2LS mAbs
  - PBMC sample for immune cell frequency, activation, and phenotyping
  - PBMC sample for HIV-specific T cell responses

- PBMC sample for latent HIV-1 reservoir
- PBMC sample for active HIV-1 reservoir
- Plasma sample for active HIV-1 reservoir
- From participants who provide additional consent, lymph node and/or GALT (GALT obtained by rectosigmoid biopsy) tissue collection (within window of ± 5 days) for some or all of the following tests:
  - Immune cell frequency, activation and phenotype, gene expression, and HIV-specific T cell response evaluation (PD and immunology)
  - HIV-1 reservoir measurements (virology)

6.9. Assessments for Early Discontinuation from Study

If a participant should discontinue study dosing as described in Section 6.9.1, they will be required to complete an early study drug discontinuation (ESDD) visit and every attempt should be made to keep the participant in the study and continue to perform study procedures. If the participant is unable to complete all scheduled procedures, for criteria other than those described for study discontinuation in Section 3.5, the participant should be followed by telephone as described in Section 6.9.2.

If a participant has completed all study drug dosing but is unable to complete all subsequent visits at the study site, as scheduled in Periods 3 and 4,for criteria other than those described for study discontinuation in Section 3.5, the participant should be followed by telephone for 250 days after mAb infusion.

At the end of all follow-up monitoring, participants will undergo the end-of-follow-up visit at the study site.

6.9.1. Criteria for Discontinuation of Study Drug

Study drug may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the participant may resume study dosing at the discretion of the investigator
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the participant's best interest
- Participant request to discontinue for any reason
- Participant noncompliance
- Pregnancy during the study; refer to Appendix 5

- Discontinuation of the study at the request of Gilead, a regulatory agency or an IRB or IEC
- Participant receives study drug(s) and experiences 1 or more AE or laboratory abnormality as follows:
    - ≥ Grade 3 treatment-emergent AE (including new finding of splenomegaly, mucosal petechiae or purpura on physical examination or CRS) judged by the investigator as at least possibly related to study drug, OR
    - ≥ Grade 3 confirmed laboratory abnormality (including a confirmed significant drop in platelets to < 50,000/mm^3 and/or confirmed drop of 50% from baseline), unless there is a clear and obvious physiologic explanation for the events (eg, blood in urine occurring in a menstruating female, CK elevation after strenuous exercise, or triglyceride elevation that is nonfasting) judged by the investigators as at least possibly related to study drug, OR
    - A persistent (≥ 72 hours) ≥ Grade 2 pyrexia considered related to study drug by the investigator, OR
    - Any SAE considered at least possibly related to study drug

6.9.2. Follow Up and Procedures After Early Discontinuation of Study Drug

After early discontinuation of study drug, for criteria other than those described in Section 3.5 every attempt should be made to keep the participant in the study and continue to perform planned study procedures. Antiretroviral therapy may be restarted at the discretion of the investigator. If participant is unable to complete all scheduled procedures, the participant should undergo the following follow-up procedures:

- If a participant discontinues study drug after having received VES alone, the participant should be followed for 30 days after the last VES dose, to monitor for AEs.
    - The participant will complete the ESDD visit within 3 days of informing the investigator/site. Participants should then be followed with a telephone check-up at 14 days after the last VES dose to monitor for AEs. The end of the monitoring period will be 30 days after the last VES dose and participants will undergo the end-of-follow-up visit at the study site.
- If a participant discontinues study drug after having received CAP256V2LS and VRC07-523LS, and before ATI is initiated, the participant should not start ATI and should be followed for 250 days after mAb infusion.
    - The participant will complete the ESDD visit within 3 days of informing the investigator/site. Participants should be followed with telephone check-ups after the ESDD visit every 4 weeks thereafter to monitor for AEs and retrieve urine pregnancy results. At the end of the monitoring period, participants will undergo the end-of-follow-up visit at the study site.
        - A positive urine pregnancy result will require confirmation with a serum pregnancy test at the study site.

- If a participant discontinues study drug after having received CAP256V2LS and VRC07-523LS, and after ATI is initiated, the participant should undergo the following procedures:

  - If ART is reinitiated, the participant should be followed for 250 days after mAb infusion. An ESDD visit will be completed within 3 days for the last study drug dose. Participants should continue the study visit schedule and undergo all other planned study-related procedures. If participants are not able to attend the visit, participants may then be followed with telephone check-ups every 4 weeks thereafter to monitor for AEs and retrieve urine pregnancy results. At the end of the monitoring period, participants will undergo the end-of-follow-up visit at the study site.

    - A positive urine pregnancy result will require confirmation with a serum pregnancy test at the study site.

  - If ART is not reinitiated (ATI is continued), an ESDD visit will be completed within 3 days of informing the investigator/site and the participant should continue the study visit schedule and undergo all other planned study-related procedures.

- If a participant experiences any AE or reports any unexpected symptoms during telephone check-ups, an unscheduled visit should be arranged to perform the following:

  - Symptom-directed physical examination

  - Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature)

  - Symptom-directed acquisition of blood and urine samples

Participants may be followed with weekly on-site visits until the AE has been treated successfully. Telephone check-ups every 4 weeks will resume thereafter, as applicable.

6.9.3. Follow Up and Procedures After Treatment Completion

If a participant completes all doses of study drug but is unable to complete all of the subsequent visits at the study site, as scheduled in Periods 3 and 4, for criteria other than those described in Section 3.5, the participant should be offered follow up for 250 days after mAb infusion. During this period, participants should be followed with telephone check-ups every 4 weeks to monitor for AEs and retrieve urine pregnancy results (kits to be provided at the last study site visit and a positive urine pregnancy result will require confirmation with a serum pregnancy test at the study site). At the end of the monitoring period, participants will undergo the end-of-follow-up visit at the study site.

If a participant experiences any AE or reports any unexpected symptoms during telephone check-ups, an unscheduled visit should be arranged to perform the following:

- Symptom-directed physical examination
- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature)
- Symptom-directed acquisition of blood and urine samples

Participants may be followed with weekly on-site visits until the AE has been treated successfully. Telephone check-ups every 4 weeks will resume thereafter, as applicable.

6.9.4. End-of-Follow-Up Visit

At the end of the monitoring period described in Sections 6.9.2 and 6.9.3, participants will complete a final visit at the study site. All participants will complete the following procedures:

- Symptom-directed physical examination
- Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature)
- Body weight
- Review of AEs and changes in concomitant medications
- 12-lead ECG
- Obtain urine collection for:
  - Urinalysis
  - Urine pregnancy testing; a positive result will be confirmed with a serum pregnancy test.
- Obtain blood samples for:
  - Plasma HIV-1 RNA
  - Plasma HIV-1 resistance testing (in case of viral rebound) to VRC07-523LS, CAP256V2LS, and baseline ART
  - Chemistry profile: ALP, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
  - Hematology profile: CBC with differential and platelet count
  - CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio
  - Creatinine clearance according to the Cockcroft-Gault formula:

    Female Estimated Creatinine Clearance = [(140 – age in years) × (weight in kg)] / [72 × (serum creatinine in mg/dL)] × 0.85

6.10. Management of Virologic Failure

Participants who experience virologic rebound (VR) or are viremic at their last visit, as defined below, will be considered to have virologic failure for the purposes of resistance analysis.

6.10.1. Virologic Rebound

Virologic rebound is defined as follows:

- At any visit a rebound in HIV-1 RNA to ≥ 50 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit

At any visit, if the HIV-1 RNA is ≥ 50 and < 200 copies/mL, a reflex HIV-1 RNA repeat test will be conducted on stored plasma samples, if available. If the repeat result is < 50 copies/mL, no further action is required. If the repeat result is ≥ 50 copies/mL, participants will be asked to return to the clinic for a scheduled or unscheduled blood draw (1 week after the date of the original test that resulted in HIV-1 RNA VR) for confirmation of VR.

A plasma sample from either the first instance or the VR confirmation visit will be tested for resistance to VRC07-523LS, CAP256V2LS, and baseline ART.

6.10.2. Viremia at Last Visit

Participants with HIV-1 RNA ≥ 50 copies/mL at their last study visit (ie, participants will not be returning to study site to confirm the result) will be tested for resistance to VRC07-523LS, CAP256V2LS, and baseline ART.

6.11. End of Study

The end of study will be the last participant's last observation (or visit).

6.12. Poststudy Care

After a participant has completed/terminated their participation in the study, long-term care for the participant will remain the responsibility of their primary treating physician.

6.13. Sample Storage

The stored biological samples may be used by Gilead or its research partner for future testing to provide additional data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period up to 15 years or per country requirements.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history

Preexisting events or conditions that increase in severity or change in nature after study drug initiation or as a consequence of participation in the clinical study will be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participants or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.2.1. Protocol-Specific Serious Adverse Event Definitions

Protocol-specific SAEs: In this study, thrombocytopenia < 50,000 platelets will be considered medically important and therefore "serious."

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration, or administration of a study drug while the medication is in the control of a health care professional, participant, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a participant.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively that is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the participant has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infectious agent through a Gilead study drug.

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).
- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Antiviral Toxicity Grading Scale, Version 01 April 2015 (Appendix 4). For each episode, the highest grade attained should be reported as defined in the Antiviral Toxicity Grading Scale (Appendix 4). The CTCAE v5 grading scale will be used to grade AEs determined to be cytokine release syndrome and infusion-related reactions.

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study drug, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until the end-of-study visit, after completion of Period 4, on the eCRFs as instructed. In case of early discontinuation or early transition from Periods 2 or 3 to Period 4, all AEs, regardless of cause or relationship, must be collected until 250 days after last dose of study drug.

All AEs should be followed until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the participant first consents to participate in the study (ie, signing the informed consent form) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and Gilead Global Patient Safety (GLPS) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the informed consent form is signed.

Any SAEs and deaths that occur throughout the duration of the study including the protocol-defined follow-up period, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead GLPS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead GLPS (Section 7.4.1.2). Adverse events and SAEs resulting from SSRs must be reported in accordance with the AE and SAE reporting guidance (Section 7.3.2).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation involving a Gilead concomitant therapy (not considered study drug), that occurs after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead GLPS utilizing the paper SSR form (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications does not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

- Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead GLPS within 24 hours of the investigator's knowledge of the event from informed consent form signature throughout the duration of the study, including the protocol-required posttreatment follow-up period

- If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit within 24 hours:

  Gilead GLPS
  Email: Safety_FC@gilead.com
  Or
  Fax: 1-650-522-5477

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to Gilead GLPS.

7.4.1.2. Reporting Process for Gilead Standard-of-Care Treatment

- If participants receive commercially available standard-of-care treatment for HIV during Periods 1 and 4, all AEs, SAEs, and SSRs associated with a Gilead product administered as part of standard-of-care treatment for HIV during participation in this study must be recorded on the paper noninterventional AE/SAE/SSR form and sent within 24 hours to:

  Gilead GLPS
  Email: Safety_FC@gilead.com
  Or
  Fax: 1-650-522-5477

- All AEs, SAEs, and SSRs associated with a non-Gilead product administered as part of standard-of-care treatment for HIV during participation in this study must be reported via available standard methods (eg, FDA MedWatch form) to the Marketing Authorization holder of the product.

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drug

- All special situations will be recorded on the SSR form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead GLPS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

  Gilead GLPS
  Email: Safety_FC@gilead.com
  Or
  Fax: 1-650-522-5477

7.4.2.2. Reporting Process for Gilead Concomitant Medications

- Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead GLPS utilizing the paper special situations report form to:

  Gilead GLPS
  Email: Safety_FC@gilead.com
  Or
  Fax: 1-650-522-5477

- Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

- Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a non-Gilead concomitant medication must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

- Participants will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 10 days after the last dose of VES or 250 days after the last dose of VRC07-523LS and CAP256V2LS, whichever date is later.

- The investigator should report pregnancies in female study participants that are identified after initiation of study drug and throughout the study, including the posttreatment follow-up period, to Gilead GLPS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

  Gilead GLPS
  Email: Safety_FC@gilead.com
  Or
  Fax: 1-650-522-5477

- The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

- All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

- A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after study must be reported to the Gilead GLPS.

- The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead GLPS using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead GLPS. Gilead GLPS contact information is as follows:

  Gilead GLPS
  Email: Safety_FC@gilead.com
  Or
  Fax: 1-650-522-5477

- Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the European Union Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, which may be in the form of line listings, serious adverse drug reactions, or SUSARs. In accordance with the European Union Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Antiviral Toxicity Grading Scale, Version 01, April 2015, and the CTCAE v5 grading scale. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not agree with the grading of the laboratory abnormality.

7.7. Toxicity Management

7.7.1. Safety Monitoring Plan for CRS

As described in Section 1.4 and the VES IB, clinical signs and symptoms consistent with CRS have been reported in a minority of participants administered VES. Clinical manifestations include influenza-like symptoms such as fever, fatigue, chills, myalgias, and headache, which are generally transient and mild to moderate in severity. Infrequent but serious clinical manifestations that may be associated with CRS include hypoxia and hypotension and may require hospitalization and treatment. It is possible that administration of CAP256V2LS and VRC07-523LS in a sequential regimen with VES may increase the risk of CRS. The grading scale of CRS is shown in Table 7.

Participants should be closely monitored for signs and symptoms of CRS during and after VES administration. For at least 24 hours following the first dose of VES and at least 4-8 hours following subsequent doses of VES, appropriately trained medical personnel and emergency equipment for the management of CRS should be on site and immediately available.

Following administration of VES, the participants will be monitored at the study site, and monitoring should include evaluation for signs and symptoms of CRS and assessment of vital signs (ie, blood pressure, pulse, respiration rate, oxygen saturation, and temperature) as follows:

First dose of VES (Day 0): Prior to administration of VES and then at 1, 2, 4, 8, 12, 18, and 24 hours after administration of VES, or if the participant experiences new or worsening symptoms, evaluate for signs and symptoms of CRS and vital signs.

Doses 2 of VES: Prior to administration and then at 1, 2, 4, and 8 hours after administration. If the participant experiences new or worsening symptoms, evaluate for signs and symptoms of CRS, including vital signs.

Dose 3 of VES: Prior to administration and then at 1, 2, and 4 hours after administration. If participants experience significant influenza-like AEs (eg, moderate or severe pyrexia, chills, headache, myalgia, fatigue, malaise, joint pain) after the first 2 VES doses, or if dose is escalated to 8 mg, monitoring may be extended to > 4 hours for subsequent doses. If the participant experiences new or worsening symptoms, evaluate for signs and symptoms of CRS, including vital signs.

Doses of VRC07-523LS and CAP256V2LS: Prior to administration and at 1, 2, 4, and 8 hours after administration. If the participant experiences new or worsening symptoms, evaluate for signs and symptoms of CRS, including vital signs.

Doses 4 to 10 of VES: Prior to administration and at 1, 2, and 4, hours after administration. If the participant experiences abnormal vital signs, new or worsening symptoms, evaluate for signs and symptoms of CRS, including vital signs.

Following VES administration, treatment-related Grade 1 CRS with influenza-like symptoms such as fever, fatigue, chills, myalgia, or headache without more severe manifestations such as changes in blood pressure or oxygen saturation may be managed with supportive care at the clinical site (eg, acetaminophen [paracetamol] for myalgia or fever). Vesatolimod may be continued at the discretion of the investigator.

For ≥ Grade 2 treatment-related CRS, including hypotension and/or hypoxia, immediate transfer to a hospital or emergency department for management in a monitored setting is advised. Administration of steroids, IV fluid for hypotension, and supplemental oxygen for hypoxia should also be considered. Vesatolimod may be continued at the discretion of the investigator and in consultation with the Gilead medical monitor.

Vesatolimod may be discontinued for treatment-related ≥ Grade 3 CRS.

Table 7. The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Grading Scale for Infusion-related Reaction and Cytokine Release Syndrome

General Disorders and Administration Site Conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to < 40% O_2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.					
Navigational Note: Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusion; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache.					

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous, NSAID = non-steroidal anti-inflammatory drugs
Source: National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0

7.7.2. Management of Other Toxicities

Unless otherwise specified in Section 7.7.1, toxicities will be managed according to the guidelines below.

- All clinically significant Grade 3 and 4 laboratory abnormalities should be repeated within 3 calendar days to confirm toxicity grade. Confirmation of toxicity grade is required prior to the next dose of study drug for any Grade 3 and 4 laboratory abnormality that in the opinion of the investigator is clinically significant and may pose a risk to the participant's safety.
- Clinical events and clinically significant laboratory abnormalities will be graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (refer to Appendix 4).
- Infusion-related reactions and cytokine release syndrome should be graded according to the CTCAE Version 5.0 grading scale (see Table 7).

Any questions regarding toxicity management should be directed to the Gilead medical monitor.

7.7.2.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.7.2.2. Grades 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, study drug may be continued if the event is considered to be unrelated to study drug.
- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to study drug, study drug should be withheld until the toxicity returns to ≤ Grade 2.
- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with study drug and is considered related to study drug, then study drug should be permanently discontinued, and the participant managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation.

7.7.2.3. Grade 4 Laboratory Abnormality or Clinical Event

For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to study drug, study drug should be permanently discontinued, and the participant managed according to local practice. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Study drug may be continued without dose interruption for a clinically nonsignificant Grade 3 to 4 laboratory abnormality (eg, CK elevation after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed) or a Grade 3 to 4 clinical event considered unrelated to study drug.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of dual anti-HIV envelope mAbs, VRC07-523LS and CAP256V2LS, in a sequential regimen with a TLR7 agonist, VES, when administered in virologically suppressed HIV-1 Clade C-infected women on ART and during ATI

The secondary objectives of this study are as follows:

- To evaluate the PK of VRC07-523LS, CAP256V2LS, and VES
- To evaluate whether VRC07-523LS and CAP256V2LS induce anti-VRC07-523LS and/or anti-CAP256V2LS antibodies
- To evaluate the effect of VRC07-523LS and CAP256V2LS in a sequential regimen with VES on viral control or the need for resumption of ART following an ATI.

CCI

8.1.2. Primary Endpoints

The primary endpoints of this study are as follows:

- The proportion of participants with treatment-emergent AEs
- The proportion of participants with treatment-emergent graded laboratory abnormalities

8.1.3. Secondary Endpoints

The secondary endpoints of this study are as follows:

Virology/Efficacy

- Time to viral rebound (confirmed ≥ 50 copies/mL and ≥ 200 copies/mL) following ATI
- The change in plasma viral load set-point following ATI
- Viral load at the end of ATI
- Time to ART resumption following ATI

Pharmacokinetics

- PK parameters for VES in plasma will include C_{max}, T_{max}, C_{last}, T_{last}, AUC_{inf}, AUC_{last}, AUC_{exp}, $t_{1/2}$, CL/F, and V_z/F. PK parameters for VRC07-523LS and CAP256V2LS in serum will include C_{max}, T_{max}, C_{last}, T_{last}, AUC_{inf}, AUC_{last}, AUC_{exp}, $t_{1/2}$, CL, V_{ss}, and V_z

Immunogenicity

- The proportion of participants with positive anti-VRC07-523LS or anti-CAP256V2LS antibodies

CCI [redacted]

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

8.2. Planned Analyses

8.2.1. Interim Analysis

Prior to the final analysis, interim analyses will be conducted. These analyses may be submitted to regulatory agencies to seek guidance regarding the overall clinical development program.

8.2.1.1. Data Monitoring Committee Analysis

There will be 1 planned DMC analysis of safety. The committee will convene after the 5 participants from the sentinel cohort have completed their Day 21 visit or have prematurely discontinued the study.

No formal stopping rules will be used by the DMC for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and severity of AEs associated with a study regimen warrant the early termination of the study in the best interest of the participants.

8.2.1.2. Planned Internal Analysis

Two interim internal analyses will be conducted:

- After all participants have completed their Day 133 visit (last scheduled study visit of Period 2), started Period 4A (if the ART restart criteria are met), or prematurely discontinued from the study
- After all participants have completed the end-of-Period 3 visit, or prematurely discontinued from the study

8.2.2. Final Analysis

The final analysis will be performed after all participants have completed the study or prematurely terminated from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. All Enrolled

The Enrolled Analysis Set includes all participants who are enrolled into the study. This is the primary analysis set for by-participant listings.

8.3.1.2. Efficacy

8.3.1.2.1. Full Analysis Set

The FAS will include all participants who (1) are enrolled into the study and (2) have received at least 1 dose of study drug.

8.3.1.3. Safety

The Safety Analysis Set will include all enrolled participants who received at least 1 dose of study drug. All safety data, including data collected after the last dose of study drug through the end of the protocol-defined follow-up period, will be included in the safety summaries.

8.3.1.4. Pharmacokinetics

The VES PK Analysis Set will include all participants who are enrolled and have received at least 1 dose of VES and for whom PK concentrations of analyte VES are available.

The VRC07-523LS PK Analysis Set will include all participants who are enrolled and have received at least 1 dose of VRC07-523LS and for whom PK concentrations of analyte VRC07-523LS are available.

The CAP256V2LS PK Analysis Set will include all participants who are enrolled and have received at least 1 dose of CAP256V2LS and for whom PK concentrations of analyte CAP256V2LS are available.

8.3.1.5. Immunogenicity

The VRC07-523LS Immunogenicity Analysis Set will include all enrolled participants who received at least 1 dose of VRC07-523LS and have had at least 1 nonmissing value for the immunogenicity evaluation of interest (ie, anti-VRC07-523LS antibody).

The CAP256V2LS Immunogenicity Analysis Set will include all enrolled participants who received at least 1 dose of CAP256V2LS and have had at least 1 nonmissing value for the immunogenicity evaluation of interest (ie, anti-CAP256V2LS antibody).

8.3.2. Data Handling Conventions

Natural logarithm transformation for key PK parameters, such as C_{max} and AUC_{inf}, will be applied for PK analysis, as appropriate.

For summary statistics, PK concentration values below the limit of quantitation (BLQ) will be imputed as zero at predose and one-half the LLOQ at postdose, where LLOQ is corrected for the dilution factor (ie, reported dilution/dilution factor). Individual values that are BLQ will be presented as "BLQ" in the concentration data listing and will be imputed as specified above for summary purpose.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods.

Demographic summaries will include sex, race/ethnicity, and age.

Baseline data including body weight, height, body mass index, and HIV-1 infection will be summarized.

8.5. Efficacy Analysis

The efficacy analysis will be based on the FAS.

8.5.1. Virology Analysis

Time to viral rebound (confirmed ≥ 50 copies/mL and ≥ 200 copies/mL) following ATI will be summarized.

The change in plasma viral load set-point between pre-ART value and prior to ART reinitiation following ATI will be summarized.

Viral load at the end of ATI will also be summarized.

8.5.2. Other Efficacy Analysis

Time to ART resumption following ATI will be summarized.

8.6. Safety Analysis

All safety analyses will be performed using the Safety Analysis Set.

All safety data collected on or after the date that study drug was first taken up to the date of last dose of study drug through the end of the protocol-defined follow-up period will be summarized according to the study drug received. Data for the pretreatment period and after the first dose of the study drug will be included in data listings.

8.6.1. Extent of Exposure

A participant's extent of exposure to study drug will be generated from the study drug administration data. Exposure data will be summarized.

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration and summarized.

Dosing information for individual participants will be listed.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class, high-level group term, high-level term, preferred term, and lower-level term will be attached to the clinical database.

Summaries (number and percentage of participants) of treatment-emergent AEs (by system organ class, high-level term [if applicable], and preferred term) will be provided. Additional summaries will include summaries for AEs by grade, investigator's assessment of relationship to study drug, and effect on study drug dosing.

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized using only observed data. Absolute values and changes from baseline at all scheduled visits will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme defined in Appendix 4.

Incidence of treatment-emergent laboratory abnormalities will be summarized. If baseline data are missing, any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent. The maximum toxicity grade will be summarized by laboratory parameter.

Laboratory abnormalities that occur before the first dose of study drug or after the participant has been discontinued from treatment through the end of the protocol-defined follow-up period will be included in a data listing.

8.7. Pharmacokinetic Analysis

The concentration data of each analyte (VES, VRC07-523LS, CAP256V2LS) will be summarized by nominal sampling time using descriptive statistics. For each analyte, PK parameters will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean (CV%), coefficient of variation [%], SD, median, minimum, and maximum). PK parameters for VES in plasma will include C_{max}, T_{max}, C_{last}, T_{last}, AUC_{inf}, AUC_{last}, AUC_{exp}, $t_{1/2}$, CL/F, and V_z/F. PK parameters for VRC07-523LS and CAP256V2LS in serum will include C_{max}, T_{max}, C_{last}, T_{last}, AUC_{inf}, AUC_{last}, AUC_{exp}, $t_{1/2}$, CL, V_{ss}, and V_z. Plasma concentrations over time will be plotted in semilogarithmic and linear scales as mean ± SD and median (Q1, Q3). The PK of dolutegravir may be explored.

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8.9. Pharmacodynamic/Immunology Analysis

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CCI [redacted]

8.10. Immunogenicity Analysis

The proportion of participants with positive anti-VRC07-523LS or anti-CAP256V2LS antibodies will be summarized.

8.11. Sample Size

The sample size in this study is determined based on practical considerations and empirical experience with similar types of studies. No sample size and power calculation was performed. Up to 25 participants will provide a preliminary assessment of descriptive safety, efficacy, and PK.

8.12. Data Monitoring Committee

An external multidisciplinary DMC includes independent experts who do not have direct involvement in the conduct of the study. The DMC will review the progress of the study, perform an interim review of safety data of a sentinel cohort before opening enrollment of up to a further 20 participants, and provide recommendation to Gilead whether the nature, frequency, and severity of AEs associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or whether the study should continue with modifications. The DMC's specific activities will be defined by a mutually agreed charter that will define the DMC's membership, conduct, and meeting schedule. While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead, or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last participant completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study participant activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the participant after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study participant.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved informed consent form for documenting written informed consent. Each informed consent form (or assent as applicable) will be appropriately signed and dated by the participant or the participant's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB or IEC or local requirements).

The informed consent form will inform participant about planned sample retention. In addition to the study-specific informed consent form to be signed by each participant participating in the study, participants will be required to document agreement to provide additional samples or to allow the use of the remainder of their already-collected specimens for optional future research, in accordance with applicable regulations. In addition to the study-specific informed consent form to be signed by each participant participating in the study, participants will be required to document agreement to provide additional samples for optional pharmacogenomic research. The results of the tests done on the samples will not be given to the participant or the investigator.

9.1.5. Confidentiality

The investigator must ensure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all participants screened and enrolled in the study, in accordance with the site procedures and regulations. Participant data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, case report form (CRFs)/eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, participants' eCRFs, and governmental approval with correspondence, the informed consent form(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each participant:

- Participant identification
- Documentation that participant meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria])
- Documentation of the reason(s) a consented participant is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the participant, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the EDC system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the case report form Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Gilead. The investigator must submit all protocol modifications to Gilead in accordance with local requirements and receive documented approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any participant records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Gilead reserves the right to terminate the study at any time, and the investigator has the right to terminate the study at his or her site. Should this be necessary, both parties will arrange discontinuation procedures and notify the participants, appropriate regulatory authority, IRBs, and IECs. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

A Phase 2a Study to Evaluate the Safety and Tolerability of a Regimen of Dual Anti-HIV Envelope Antibodies, VRC07-523LS and CAP256V2LS, in a Sequential Regimen with a TLR7 Agonist, Vesatolimod, in Early Antiretroviral-Treated HIV-1 Clade C-Infected Women

GS-US-382-5445, Original Version 1.0, dated 18 December 2020
Amendment 1, dated 17 June 2021, Amendment 2, dated 26 August 2022

Amendment 3, dated 07 October 2022

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD
Medical Monitor

Signature

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2a. Study Procedures Table

			P1									P2[a]																P3[a,b]		P4[a,b]		
Visit[c]	Screening[d]	Day –13/Prebaseline	VES Dose1-Day 0/Baseline	Day 1	Day 2	VRC & CAP Dose–Day 7	Day 8	Day 9	VES Dose 2-Day 14	Day 21	VES Dose 3-Day 28[e]	Day 35	VES Dose 4-Day 42	Day 49	VES Dose 5-Day 56	Day 57	Day 63	VES Dose 6-Day 70	Day 77	VES Dose 7-Day 84	Day 91	VES Dose 8-Day 98	Day 105	VES Dose 9-Day 112	Day 119	VES Dose 10-Day 126	Day 127	Day 128	Day 133	Day 134-336	End-of-Period 3 Visit[f]	Day 337-413	End-of-Study Visit[g]	ESDD[h]
Informed consent	X																																	
Medical history	X[i]	X																																
AE and Con Med	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical exam	X																																	
Symptom-directed physical exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X	X[k]	X	X
12-Lead ECG	X																														X		X	
Vital signs[l]	X		X	X		X			X		X		X		X			X		X		X		X		X				X[j]	X	X[k]	X	X
Body weight	X	X	X	X	X	X	X	X	X	X	X		X		X			X		X		X		X		X				X[j]	X	X[k]	X	X
Height	X																																	
Review of I/E criteria		X																																
Urinalysis	X	X	X	X	X	X			X	X	X		X		X			X		X		X		X		X			X	X[j]		X[k]	X	X
Urine pregnancy test[m]		X	X								X		X					X				X				X				X[j]		X[k]	X	X
Chemistry[n]	X	X	X[o]	X	X	X			X	X	X		X		X			X		X		X		X		X				X[j]		X[k]	X	X
Hematology[p]	X	X	X[o]	X	X	X			X	X	X		X		X			X		X		X		X		X				X[j]		X[k]	X	X
Metabolic assessment[q]	X																																	
Creatinine clearance[r]	X	X	X	X	X	X			X	X	X		X		X			X		X		X		X		X				X[j]		X[k]	X	X
Follicle-stimulating hormone[s]	X																																	

			P1										P2[a]																	P3[a,b]		P4[a,b]		
Visit[c]	**Screening[d]**	**Day −13/Prebaseline**	**VES Dose1-Day 0/Baseline**	**Day 1**	**Day 2**	**VRC & CAP Dose–Day 7**	**Day 8**	**Day 9**	**VES Dose 2-Day 14**	**Day 21**	**VES Dose 3-Day 28[e]**	**Day 35**	**VES Dose 4-Day 42**	**Day 49**	**VES Dose 5-Day 56**	**Day 57**	**Day 63**	**VES Dose 6-Day 70**	**Day 77**	**VES Dose 7-Day 84**	**Day 91**	**VES Dose 8-Day 98**	**Day 105**	**VES Dose 9-Day 112**	**Day 119**	**VES Dose 10-Day 126**	**Day 127**	**Day 128**	**Day 133**	**Day 134-336**	**End-of-Period 3 Visit[f]**	**Day 337-413**	**End-of-Study Visit[g]**	**ESDD[h]**
Whole blood ISG mRNA panel		X	X[o]	X											X	X									X	X				X		X	X
HIV-specific antibody profiling using plasma		X	X[o]				X																		X			X		X		X	
HIV staging[ff]	X																																	
Serum pregnancy test[m]	X																																	
CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio	X		X[o]						X		X		X		X			X		X		X		X		X		X		X[j]	X	X[k]	X	X
HBV/HCV serology[t]	X																																	
VES PK[u]			X	X	X																													
Serum VRC07-523LS & CAP256V2LS PK[v]						X	X	X	X	X	X				X					X				X					X	X		X		
Plasma dolutegravir PK[w]															X					X				X					X	X		X		
Plasma HIV-1 RNA[x]	X	X	X[o]			X			X	X	X		X		X			X		X		X		X		X				X	X	X	X	X
Plasma HIV-1 resistance testing to VRC07-523LS, CAP256V2LS, and baseline ART			X[o]			X			X	X	X		X		X			X		X		X		X		X				X	X	X	X	X
Plasma for active HIV-1 reservoir		X	X[o]	X	X										X	X									X	X	X			X		X	
Soluble proteins in the TruCulture® Whole Blood Culture System		X																																

			P1										P2[a]																	P3 [a,b]		P4 [a,b]		
Visit[c]	**Screening[d]**	**Day −13/Prebaseline**	**VES Dose1-Day 0/Baseline**	**Day 1**	**Day 2**	**VRC & CAP Dose–Day 7**	**Day 8**	**Day 9**	**VES Dose 2-Day 14**	**Day 21**	**VES Dose 3-Day 28[e]**	**Day 35**	**VES Dose 4-Day 42**	**Day 49**	**VES Dose 5-Day 56**	**Day 57**	**Day 63**	**VES Dose 6-Day 70**	**Day 77**	**VES Dose 7-Day 84**	**Day 91**	**VES Dose 8-Day 98**	**Day 105**	**VES Dose 9-Day 112**	**Day 119**	**VES Dose 10-Day 126**	**Day 127**	**Day 128**	**Day 133**	**Day 134-336**	**End-of-Period 3 Visit[f]**	**Day 337-413**	**End-of-Study Visit[g]**	**FSDD[h]**
Soluble proteins (cytokines, chemokines, and inflammatory markers)		X	X[o]	X			X								X	X	X									X	X		X		X		X	X
PBMC sample for testing of viral sensitivity to the VRC07-523LS and CAP256V2LS mAbs	X[y]																												X[z]	X		X	
PBMC HIV-specific T cell responses		X					X										X											X		X		X	
PBMC immune cell frequency, activation and phenotyping		X	X[o]	X			X								X	X	X									X	X		X		X		X	
PBMC latent HIV-1 reservoir		X																											X[z]	X		X	
PBMC active HIV-1 reservoir		X	X[o]	X	X										X	X										X	X	X		X		X	

			P1									P2[a]																P3 [a,b]		P4 [a,b]		
Visit[c]	**Screening[d]**	**Day −13/Prebaseline**	**VES Dose1-Day 0/Baseline**	**Day 1**	**Day 2**	**VRC & CAP Dose–Day 7**	**Day 8**	**Day 9**	**VES Dose 2-Day 14**	**Day 21**	**VES Dose 3-Day 28[e]**	**Day 35**	**VES Dose 4-Day 42**	**Day 49**	**VES Dose 5-Day 56**	**Day 57**	**Day 63**	**VES Dose 6-Day 70**	**Day 77**	**VES Dose 7-Day 84**	**Day 91**	**VES Dose 8-Day 98**	**Day 105**	**VES Dose 9-Day 112**	**Day 119**	**VES Dose 10-Day 126**	**Day 127**	**Day 128**	**Day 133**	**Day 134-336**	**End-of-Period 3 Visit[f]**	**Day 337-413**	**End-of-Study Visit[g]**	**ESDD[h]**
Anti-VRC07-523LS and anti-CAP256V2LS antibody profiling from serum[aa]		X									X				X					X				X					X	X[bb]		X[cc]		
Review of ongoing eligibility check prior to study dosing			X			X			X		X		X		X			X		X		X		X		X								
Birth control check		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Participant agreement to follow study contraceptive requirements	X																																	
In-clinic dosing			X			X			X		X[gg]		X[hh]		X[hh]			X[hh]		X[hh]		X[hh]		X[hh]		X[hh]								
VES dose			X						X		X		X		X			X		X		X		X		X								
VRC07-523LS and CAP256V2LS dose						X																												
CCI																																		
HLA genotype, TLR7, FcgR SNP		X																																

			P1									P2[a]																P3 [a,b]		P4 [a,b]		
Visit[c]	Screening[d]	Day −13/Prebaseline	VES Dose1-Day 0/Baseline	Day 1	Day 2	VRC & CAP Dose–Day 7	Day 8	Day 9	VES Dose 2-Day 14	Day 21	VES Dose 3-Day 28[e]	Day 35	VES Dose 4-Day 42	Day 49	VES Dose 5-Day 56	Day 57	Day 63	VES Dose 6-Day 70	Day 77	VES Dose 7-Day 84	Day 91	VES Dose 8-Day 98	Day 105	VES Dose 9-Day 112	Day 119	VES Dose 10-Day 126	Day 127	Day 128	Day 133	Day 134-336	End-of-Period 3 Visit[f]	Day 337-413	End-of-Study Visit[g]	ESDD[h]
CCI																																		
HIV-1 reservoir measurement		X																											X[ee]	X		X	
Gene expression		X																											X[ee]	X		X	
HIV-specific T cell responses		X																											X[ee]	X		X	
Immune cell frequency, activation and phenotyping		X																											X[ee]	X		X	

ESDD = early study drug discontinuation; GALT = gut-associated lymphoid tissue; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leucocyte antigen; I/E = inclusion/exclusion; ISG = interferon-stimulated gene; mAb = monoclonal antibody; mRNA = messenger RNA; P1/2/3/4 = Period ½/3/4; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic(s); PrEP = preexposure prophylaxis; SNP = single nucleotide polymorphism; TLR = toll-like receptor; VES = vesatolimod; VRC = VRC07-523LS

a Known HIV-1 seronegative sexual partners of enrolled study participants may be referred for HIV PrEP to decrease risk of HIV transmission during ATI in Periods 2, 3, and 4B.

b Periods 3 and 4 have study visit every 2 weeks.

c All study visits are to be completed within ± 3 days of the protocol-specified visit date (except end-of-Period 3 visit, which is ± 1 day). This tolerance window does not apply to screening, pre-baseline, Day 0, and Day 7.

d Evaluations to be completed within 35 days prior to prebaseline/Day −13.

e At the Day 28 visit and prior to the Period 2 Day 35 visit, participants will be assessed to determine whether the criteria necessary to begin ATI are met. All of the following criteria must be met for a participant to begin ATI: Viral load < 50 copies/mL; CD4+ T cell count > 400 cells/µL; negative urine pregnancy test; participant has received VRC07-523LS, CAP256V2LS, and at least 3 of the 10 scheduled doses of VES. Participant confirms agreement to request their partners to use condoms throughout the ATI period. The initiation of ATI (Period 2) may be postponed for up to 4 weeks after the last VES dose for participants to meet these requirements.

f Participants who complete Period 3 or meet the ART restart criteria will be required to complete an end-of-Period 3 visit 1 week after their last visit.

g End-of-study visit will occur 7 days (± 3 days) after completion of the final Period 4 visit.

h ESDD visit is required for participants who prematurely discontinue study drug prior to completing the infusions of the VRC07-523LS and CAP256V2LS, or all 10 doses of VES, as described in Section 6.9.1, will complete an ESDD visit within 3 days of informing the investigator/site.

i Medical history including route and estimated duration of HIV-1 infection, history of HIV-1 disease-related events, ART history for at least 12 consecutive months prior to screening, and prior concomitant medications within 35 days of the screening visit.

j Day 147 and at each visit every 4 weeks thereafter

k Day 343 and at each visit every 4 weeks thereafter
l Vital signs (blood pressure, pulse, respiration rate, oxygen saturation, and temperature) will be monitored on dosing days at the following time points: (1) VES Dose 1 on baseline/Day 0, at predose, then at 1, 2, 4, 8, 12, 18, and 24 hours (Day 1) postdose (2) VRC07-523LS and CAP256V2LS infusion, and remaining VES Doses 2 to 10 at predose, then at 1, 2, 4, and 8 hours postdose.
m Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
n Alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct and indirect bilirubin, total protein, albumin, creatine kinase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid.
o Sample to be taken before VES dosing.
p Complete blood count with differential and platelet count.
q Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, high-density lipoprotein, direct low-density lipoprotein, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
r Creatinine clearance according to the Cockcroft-Gault formula: Female Estimated Creatinine Clearance = [(140–− age in years) × (weight in kg)]/[72 × (serum creatinine in mg/dL)] × 0.85.
s Serum follicle-stimulating hormone test is required for female participants < 54 years old who have stopped menstruating for ≥ 12 months, but are not permanently sterile or do not have documentation of ovarian hormonal failure.
t Hepatitis B virus blood panel will be performed at screening (hepatitis B virus surface antigen, hepatitis B virus surface antibody, and hepatitis B virus core antibody). Hepatitis C antibody will also be performed.
u PK samples for VES will be collected at predose (≤ 5 minutes prior to dosing), 1, 2, 4, 8, 12, 24 (Day 1), and 48 hours (Day 2) after the first dose.
v Serum VRC07-523LS and CAP256V2LS PK collection on Day 7, at 0 hours (predose), end of infusion, 1, 2, 4, and 8 hours after end of infusion, and then at Days 8, 9, 14, 21, 28, 56, 84, 112, 133, 161, 189, 217, 245, 273, 301, 329, 343, 371, and 413.
w Plasma dolutegravir PK collections will be obtained at: Days 56, 84, 112, 133, 161, 189, 217, 245, 273, 301, 329, and for participants in Period 4B PK collections at Days 343, 371, and 413.
x From Period 2, if a confirmed rebound of HIV-1 RNA viral load ≥ 50 copies/mL occurs, the test should be completed weekly.
y Only if not previously conducted.
z Only at Day 147 visit.
aa Blood samples anti-VRC07-523LS and anti-CAP256V2LS antibody profiling from serum will be collected at the following timepoints: prebaseline/Day −13, Days 28, 56, 84, 112, 133, 161, 189, 217, 245, 273, 301, 329, 343, 371, and 413.
bb Days 161, 189, 217, 245, 273, 301, and 329 only.
cc Days 343, 371 and 413 only.
dd Lymph node and GALT biopsy will be collected from participants who provide additional consent at prebaseline/Day −13, Week 21 (beginning of Period 3), end-of-Period 3 visit, and the end-of-study visit. The samples can be collected within a window of ± 5 days.
ee Only at Day 134 visit.
ff Obtain HIV staging at detection using standard markers (eg, HIV-1 RNA, p24 antigen, fourth generation combination antigen/antibody enzyme-linked immunosorbent assay, HIV-1 Western blot), duration of viremia during acute HIV infection and peak HIV RNA
gg For Dose 3 only, 6 mg [3x2 mg tablets] or 8 mg [4x2 mg tablets]) will be administered per discussion with and approval from the Gilead medical monitor based on safety and tolerability of prior doses.
hh For Doses 4 to 10, 6 mg [3x2 mg tablets] or 8 mg [4x2 mg tablets]) will be administered per discussion with and approval from the Gilead medical monitor based on safety and tolerability of prior doses.

Appendix 2b. Follow-up Period: Study Procedures Table

	Follow-up period for participants who discontinued study drug after having received VES alone[a,b]	Follow-up period for participants who discontinued study drug after having received CAP256V2LS and VRC07-523LS, and before ATI is initiated[b,c]	Follow-up period for participants who discontinued study drug after having received CAP256V2LS and VRC07-523LS, and after ATI is initiated[c,d,e]	Follow-up period for participants who completed all doses of study drug but is unable to complete all of the subsequent visits at the study site[b,f]	End-of-Follow-up visit[b]
Telephone check-up	X	X	X	X	
Symptom-directed physical exam	X[g]	X[g]	X[g]	X[g]	X
Vital signs	X[g]	X[g]	X[g]	X[g]	X
Symptom-directed acquisition of blood and urine samples	X[g]	X[g]	X[g]	X[g]	
Body weight					X
Review of AEs and changes in concomitant medications	X	X	X	X	X
12-Lead ECG					X
Urinalysis					X
Urine pregnancy test		X[h]	X[h]	X[h]	X
Plasma HIV-1 RNA					X
Plasma resistance testing to VRC07-523LS, CAP256V2LS, and baseline ART					X

	Follow-up period for participants who discontinued study drug after having received VES alone[a,b]	Follow-up period for participants who discontinued study drug after having received CAP256V2LS and VRC07-523LS, and before ATI is initiated[b,c]	Follow-up period for participants who discontinued study drug after having received CAP256V2LS and VRC07-523LS, and after ATI is initiated[c,d,e]	Follow-up period for participants who completed all doses of study drug but is unable to complete all of the subsequent visits at the study site[b,f]	End-of-Follow-up visit[b]
Chemistry					X
Hematology					X
CD4+ and CD8+ T cell absolute count, percentage, and CD4/CD8 ratio					X
Creatinine clearance					X

AE = adverse event; ART = antiretroviral therapy; ATI = analytical treatment interruption; ECG = electrocardiogram; ESDD = early study drug discontinuation; mAb = monoclonal antibody; VES = vesatolimod

a Participants should be followed with a telephone check-up at 14 days after the last VES dose to monitor for AEs. The end of the monitoring period will be 30 days after the last VES dose and participants will undergo the end-of-follow-up visit at the study site.

b All follow-up visits/calls are to be completed within ± 3 days of the protocol-specified visit date.

c Participants should continue the study visit schedule and undergo all other planned study-related procedures. If participants are not able to attend the visit, participants may then be followed with telephone check-ups every 4 weeks thereafter to monitor for AEs and retrieve urine pregnancy results. At the end of the monitoring period, participants will undergo the end-of-follow-up visit at the study site.

d If ART is reinitiated, the participant should be followed for 250 days after mAb infusion. An ESDD visit will be completed within 3 days for the last study drug dose. Participants should continue the study visit schedule and undergo all other planned study-related procedures. If participants are not able to attend the visit, participants may then be followed with telephone check-ups every 4 weeks thereafter to monitor for AEs and retrieve urine pregnancy results. At the end of the monitoring period, participants will undergo the end-of-follow-up visit at the study site.

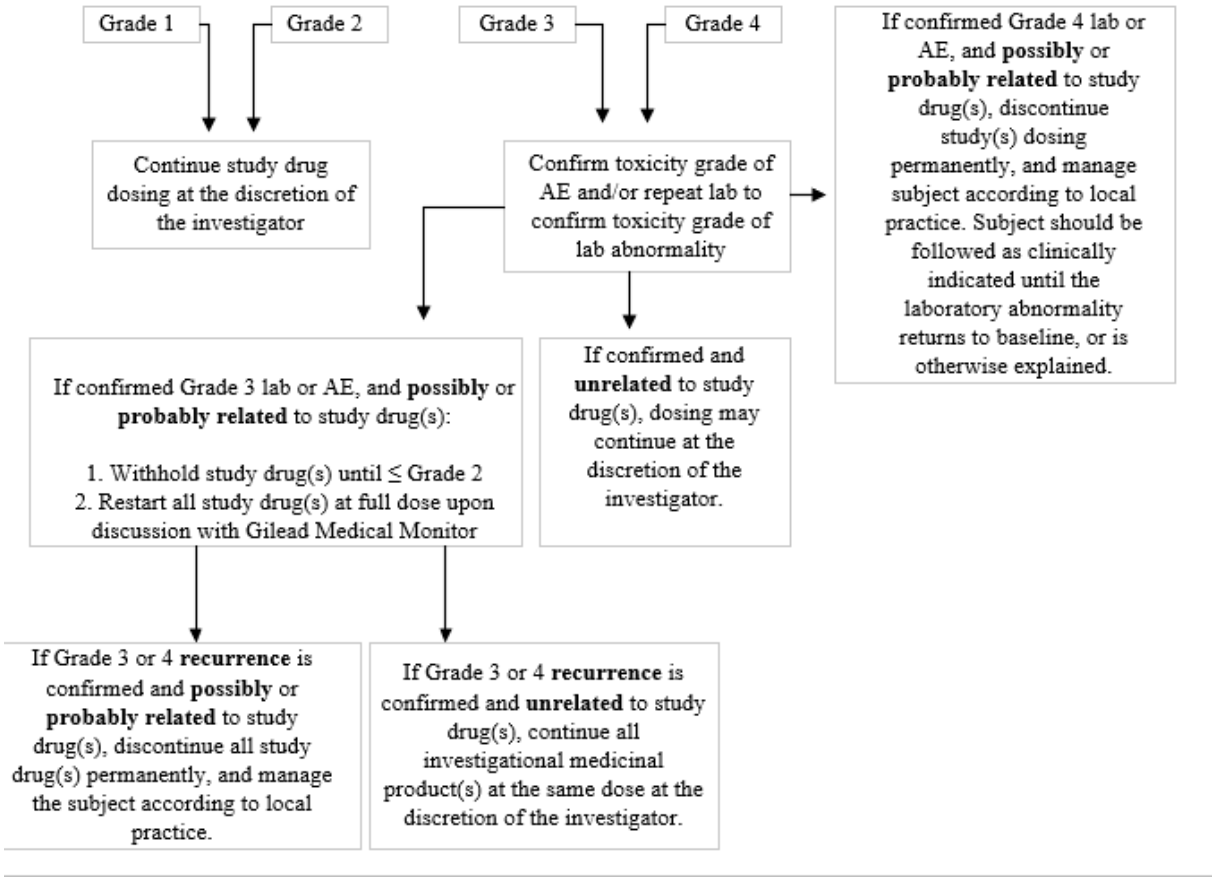
e If ART is not reinitiated (ATI is continued), an ESDD visit will be completed within 3 days of last study drug dose informing the investigator/site and the participant should continue the study visit schedule and undergo all other planned study-related procedures.

f The participant should be offered follow up for 250 days after mAb infusion. During this period, participants should be followed with a telephone check-ups every 4 weeks to monitor for AEs and retrieve urine pregnancy results.

g If participant experiences any AE or reports any unexpected symptoms during telephone check-ups, an unscheduled visit should be arranged to perform these assessments. Participants may be followed with weekly on-site visits until the AE has been treated successfully. Telephone check-up every 4 weeks will resume thereafter, as applicable.

h A positive urine pregnancy result will require confirmation with a serum pregnancy test at the study site.

Appendix 3. Management of Adverse Events and Laboratory Abnormalities



Grade 3 or 4 laboratory abnormalities include drop in platelets to < 50,000/mm^3.

Appendix 4. Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Antiviral Toxicity Grading Scale, Version 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count **Adult and Pediatric, ≥ 7 Months[a]**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
White Blood Cells	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of Prothrombin Time	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

a An overlap between the Grade 1 scale and the laboratory's normal range for absolute neutrophils may result for pediatric participants. Please follow the Gilead convention of grading any result within the lower limit of normal and upper limit of normal (ULN) a 0.

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to < LLN mEq/L 130 to < LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year**	3.0 to < LLN mEq/L 3.0 to < LLN mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Infant < 1 Year	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia **Adult and Pediatric ≥ 1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Infant < 1 Year	>ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Infant < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L
Hyperglycemia (nonfasting)	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia (fasting)	110 to 125 mg/dL 6.08 to 6.96 mmol/L	> 125 to 250 mg/dL > 6.96 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate[a]) **Adult and Pediatric ≥ 2 Years**	7.8 to < LLN mg/dL 1.94 to < LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥ 7 Days to 2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Infant < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (corrected for albumin if appropriate[a]) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to <LLN 0.74 mmol/L to <LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	>ULN to 6.0 mg/dL >ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to < LLN mg/dL 1.2 to < LLN mEq/L 0.58 to < LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to <LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1–14 Years	3.0 to < LLN mg/dL 0.96 to < LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to < LLN mg/dL 1.12 to < LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant ≤ 14 Days (nonhemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 Year** **Infant < 1 Year**	1.5 mg/dL to <LLN 87 µmol/L to <LLN N/A	to < 1.5 mg/dL 57 to < 87 µmol/L mg/dL to < LLN 57 µmol/L to < LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L 0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L < 0.5 mg/dL < 27 µmol/L
Creatinine[b]	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **Adult and Pediatric ≥ 4 Years** **Pediatric < 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN NA	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L 11.0 mEq/L to < LLN 11.0 mmol/L to < LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L 8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L < 8.0 mEq/L < 8.0 mmol/L
Triglycerides (fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47 to 13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
Low-Density Lipoprotein (fasting) **Adult** Low-Density Lipoprotein (fasting) **Pediatric > 2 to < 18 Years**	130 to 160 mg/dL 3.35 to 4.15 mmol/L 110 to 130 mg/dL 2.84 to 3.37 mmol/L	> 160 to 190 mg/dL > 4.15 to 4.92 mmol/L > 130 to 190 mg/dL > 3.37 to 4.92 mmol/L	> 190 mg/dL > 4.92 mmol/L > 190 mg/dL > 4.92 mmol/L	NA NA
Hypercholesterolemia (fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

a Calcium should be corrected for albumin if albumin is < 4.0 g/dL

b An overlap between the Grade 1 scale and the laboratory's normal range for creatinine may result for male participants > 70 years. Please follow the Gilead convention of grading any result within the lower limit of normal (LLN) and upper limit of normal (ULN) a 0.

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin **Pediatric < 16 Years**	-	2.0 g/dL to <LLN 20 g/L to <LLN	< 2.0 g/dL < 20 g/L	NA
Adult and Pediatric ≥ 16 Years	3.0 g/dL to <LLN 30 g/L to <LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; LLN = lower limit of normal; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (dipstick)	1+	2+	3-4+	NA
Hematuria (quantitative) See Note below				
Females	>ULN to 10 RBC/HPF	> 10 to 75 RBC/HPF	> 75 RBC/HPF	NA
Males	6 to 10 RBC/HPF	> 10 to 75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (dipstick)	1+	2–3+	4+	NA
Proteinuria, 24-Hour Collection				
Adult and Pediatric ≥ 10 Years	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Months to < 10 Years	201 to 499 mg/m^2/24 h	>499 to 799 mg/m^2/24 h	>799 to 1000 mg/m^2/24 h	> 1000 mg/m^2/24 h
Glycosuria (dipstick)	1+	2-3+	4+	NA

RBC/HPF = red blood cells per high power field
Notes:

- Toxicity grades for quantitative and dipstick hematuria will be assigned by Covance Laboratory; however, for other laboratories, toxicity grades will only be assigned to dipstick hematuria.
- With the exception of lipid tests, any graded laboratory test with a result that is between the lower limit of normal (LLN) and upper limit of normal (ULN) should be assigned Grade 0.
- If the severity of a clinical adverse event (AE) could fall under either 1 of 2 grades (eg, the severity of an AE could be either Grade 2 or Grade 3), select the higher of the 2 grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (by ECG or physical examination)	Asymptomatic AND No intervention indicated	Asymptomatic AND Nonurgent medical intervention indicated	Symptomatic, non-life-threatening AND Nonurgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140 to 159 mmHg systolic OR 90 to 99 mmHg diastolic	> 159 to 179 mmHg systolic OR > 99 to 109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st to 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure [CHF])	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

AV = atrioventricular; ECG = electrocardiogram; ER = emergency room; IV = intravenous; RBC = red blood cell

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV_1 or peak flow reduced to 70% to 80%	FEV_1 or peak flow 50% to 69%	FEV_1 or peak flow 25% to 49%	Cyanosis OR FEV_1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

FEV_1 = forced expiratory volume in the first second of expiration

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction–Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR Toxic epidermal necrolysis
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching–no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hours	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24 hours.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis/Stomatitis (clinical examination) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24-48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional- symptomatic) Also see Mucositis/Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

ER = emergency room; IV = intravenous

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Central Nervous System Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (stroke) with neurological deficit
Developmental delay **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (nonrepetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure –**Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 to 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

ER = emergency room

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (noninjection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

BMD = bone mineral density

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (eg, tube feeding or total parenteral nutrition)

ER = emergency room

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (localized) **Adult and Pediatric > 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ER = emergency room

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar nonketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a) Definition of Childbearing Potential

For the purposes of this study, a female-born participant is considered of childbearing potential following the initiation of puberty (Tanner Stage 2) until becoming postmenopausal, unless the participant is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women < 54 years of any age with amenorrhea of ≥ 12 months are not permanently sterile may also be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female participant of any age.

2) Contraception Requirements for Female Participants

a) Study Drug Effects on Pregnancy and Hormonal Contraception

The overall potential for genetic toxicity of VES is considered to be low. In developmental toxicity studies in mice and rabbits, dose-developmental findings were observed in the rabbit only at doses that caused maternal toxicity (see VES IB edition 09, Sections 3.3.5. and 6.1.1.1.2). Such findings included increased incidence of early and late fetal resorptions, reduced fetal weights, and increased incidence of soft tissue/skeletal alterations (malformations and variations) at 15 and 30 mg/kg doses. Given these findings in nonclinical studies, VES has shown the potential for embryofetal developmental effects.

There are no clinical data regarding the use of VES in pregnant women. The effects of VES on an unborn child are unknown. A clinical PK study evaluating the drug interaction potential of VES has not been conducted; however, based on the nonoverlapping metabolic pathways for VES and oral contraceptives, no clinically relevant drug interactions are expected upon co-administration of these agents. Please refer to the latest version of the VES investigator's brochure (IB) for additional information.

VRC07-523LS and CAP256V2LS are contraindicated in pregnancy as their teratogenicity/fetotoxicity profile is unknown. A reduction in the clinical efficacy of hormonal contraception is not expected as VRC07-523LS and CAP256V2LS are not cytokine modulators. As protein biologics, VRC07-523LS and CAP256V2LS are not expected to be genotoxic but genotoxicity has not been evaluated in these compounds. Please refer to the latest version of the IB for additional information.

B) Contraception Requirements for Female Participants of Childbearing Potential

The inclusion of female participants of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline/Day 0 visit prior to enrollment. Pregnancy tests will be performed at regular intervals thereafter until the end of contraception requirement.

Duration of required contraception for female participants in this clinical trial should start from screening visit until 10 days after the last dose of VES or until 250 days after the last dose of VRC07-523LS and CAP256V2LS, whichever date is later.

Female participants must agree to one of the following contraceptive methods:

- Nonhormonal intrauterine device (IUD)
- Hormonal IUD (must be used in conjunction with a barrier method)
- Bilateral tubal occlusion (upon medical assessment of surgical success)

OR

Female participants who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:

Hormonal methods (each method must be used with a barrier method, preferably male condom)

- Oral contraceptives (either combined or progesterone only)
- Injectable progesterone
- Subdermal contraceptive implant
- Transdermal contraceptive patch
- Contraceptive vaginal ring

Barrier methods (each method must be used with a hormonal method)

- Male condom (with or without spermicide)
- Female condom (with or without spermicide)
- Diaphragm with spermicide
- Cervical cap with spermicide
- Sponge with spermicide

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female participants must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

3) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

4) Procedures to be Followed in the Event of Pregnancy

Participants will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 10 days after the last dose of VES or 250 days after the last dose of VRC07-523LS and CAP256V2LS, whichever date is later. Participants who become pregnant or who suspect that they are pregnant must report the information to the investigator and discontinue study drug immediately. Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 6. Definitions of Stage 3 Opportunistic Illnesses in HIV (Centers for Disease Control and Prevention [CDC] Guidelines)

1) Candidiasis of bronchi, trachea, or lungs
2) Candidiasis of esophagus
3) Cervical cancer, invasive
4) Coccidioidomycosis, disseminated or extrapulmonary
5) Cryptococcosis, extrapulmonary
6) Cryptosporidiosis, chronic intestinal (> 1-month duration)
7) Cytomegalovirus disease (other than liver, spleen, or nodes)
8) Cytomegalovirus retinitis (with loss of vision)
9) Encephalopathy, HIV-related
10) Herpes simplex: chronic ulcer(s) (> 1-month duration); or bronchitis, pneumonitis, or esophagitis
11) Histoplasmosis, disseminated or extrapulmonary
12) Isosporiasis, chronic intestinal (> 1-month duration)
13) Kaposi's sarcoma
14) Lymphoma, Burkitt's (or equivalent term)
15) Lymphoma, immunoblastic (or equivalent term)
16) Lymphoma, primary, of brain
17) Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
18) Mycobacterium tuberculosis, of any site, pulmonary, disseminated or extrapulmonary
19) Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
20) *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii)* pneumonia
21) Pneumonia, recurrent
22) Progressive multifocal leukoencephalopathy
23) Salmonella septicemia, recurrent
24) Toxoplasmosis of brain
25) Wasting syndrome attributed to HIV infection

CDC Stage-3-Defining Opportunistic Illnesses in HIV Infection - 2014 (57221)

Appendix 7. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with participants being unable to attend study visits have been identified for this study. For infectious disease pandemics, sites will utilize regional or local guidelines to manage the clinic and participants. Based on the nature of the local epidemic at the time of study initiation, participants may be screened prior to enrollment and administration of VES and may be subsequently tested for following any "flu-like AEs" after VES that may overlap with potential signs/symptoms of pandemic disease.

These risks can be summarized as follows:

1) Study drug supplies to participants and sites:

   Due to the on-site study drug dosing requirements, there will be a pause in dosing during the pandemic. There will be no mitigation options available.

   Shipments of study drug could be delayed because of transportation issues. Without study drug, the participant would not be able to continue receiving the study drug as planned per protocol.

   Mitigation plan: The site's study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and investigational sites. Manual shipments will be triggered as necessary.

2) Participant safety monitoring and follow up:

   A. Participants may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

      Mitigation plan: For participants who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the participant within the target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

      i. Confirm if participant has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow up on any unresolved AE/SAEs.

      ii. Review current list of concomitant medications and document any new concomitant medications.

      iii. If applicable, confirm electronic diary questionnaires and participant-reported outcomes have been completed and transmitted.

iv. If applicable, confirm participant's study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed it will be provided as described above in (1).

v. If applicable, remind participant to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

B. Participants may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

Mitigation plan: Local laboratories may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular follow up per protocol. Any laboratory assessments conducted at a local laboratory due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

C. Participants may be unable or unwilling to attend the study visit to sign an updated informed consent form version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local ethics committee (EC)/institutional review board (IRB) and national laws and regulations. Remote consent will be allowed if has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

A. Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed participant visits or deviation to the protocol due to the pandemic must be reported in the electronic case report form and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

B. Monitors may be unable to carry out source data review or source data verification (SDV), or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote SDV may be arranged if allowed. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or participants on site must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

   A. There may be an increased amount of missing data due to participants missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical trial data.

      Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with Regulatory Authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of the study drug(s) in study participants remain unchanged.

Prot GS-US-382-5445 Amd 3

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	07-Oct-2022 21:37:17