Statistical Analysis Plan for Study M19-965

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-controlled Study to Evaluate Efficacy, Safety, Tolerability, and Pharmacokinetics of Budigalimab and/or ABBV-382 in People Living with HIV on Stable Antiretroviral Therapy Undergoing Analytical Treatment Interruption

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Version 2.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for the budigalimab and ABBV-382 Study M19-965, a phase 2, 2-part, multicenter study to evaluate efficacy, safety, tolerability, and pharmacokinetics (PK) of budigalimab and/or ABBV-382 in people living with HIV (PLWH) on stable antiretroviral therapy (ART) undergoing analytical treatment interruption (ATI). The first part of the study is a randomized, double-blind, placebo-controlled evaluation of budigalimab IV and ABBV-382 IV. The second part of the study is a single-arm, open-label evaluation of budigalimab SC.

The analyses of pharmacokinetic and exploratory biomarker research endpoints will not be covered in this SAP.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later.

2.0 Study Objectives and Design

2.1 Study Objectives

The main objectives of the trial are to evaluate efficacy, safety, tolerability, and PK of budigalimab and/or ABBV-382 in adult PLWH on stable ART and undergoing ATI.

The hypothesis corresponding to the primary efficacy objective, for the double-blind part of the study, is that the administration of budigalimab [redacted] mg IV every 2 weeks (total of 4 doses of budigalimab) in combination with ABBV-382 [redacted] mg or [redacted] mg IV every 4 weeks (total of 3 doses of ABBV-382) will demonstrate greater efficacy than placebo at Week 24 and will have favorable safety and tolerability in PLWH.

The estimands corresponding to the primary and secondary efficacy objectives are defined as follows in Table 1.

Table 1. Estimands for the Primary and Secondary Objectives

Primary and Secondary Endpoints	
Treatment	Budigalimab IV + ABBV-382 IV combination therapy, budigalimab monotherapy (IV or SC), ABBV-382 IV monotherapy, or placebo
Endpoint	Primary and secondary endpoints (see Section 3.1 and Section 3.2)
Population	Approximately 160 adults with chronic HIV-1 on stable ART undergoing ATI (approximately 140 eligible participants will be randomized in the double-blind part of the study and approximately 20 eligible participants will be enrolled in the open-label part of the study)
Handling of intercurrent events	For the primary endpoint, in the ITT population, for participants who restart ART prior to Week 24, all viral load data collected after ART restart will be excluded from the analysis; only viral load data collected during ATI will be considered for analysis. Premature discontinuations in participants who have not restarted ART will be handled by a treatment policy strategy. A supplementary analysis will be performed on the mITT population. For the secondary endpoints, only viral load measurements collected during the ATI (prior to ART restart) will be considered for analysis.
Population summary	• Primary: Difference in proportion of participants with viral control (viral load < 1,000 copies/mL) without ART restart at Week 24 between each active treatment arm and placebo for Arms A to E; Proportion of participants with viral control (viral load < 1000 copies/mL) without ART restart at Week 24 for Arm F • Secondary: Difference in median peak viral load (at rebound, before restarting ART) between each active treatment arm and placebo for Arms A to E; Median peak viral load (at rebound, before restarting ART) for Arm F • Secondary: Median time to rebound to ≥ 1,000 copies/mL during ART interruption in each treatment arm

Exploratory objectives of the trial are to evaluate:

- PK/PD relationships
- Longitudinal changes in immune cell profiles
- Longitudinal changes in HIV reservoir
- Impact on participant quality-of-life
- Duration of off-ART viral control

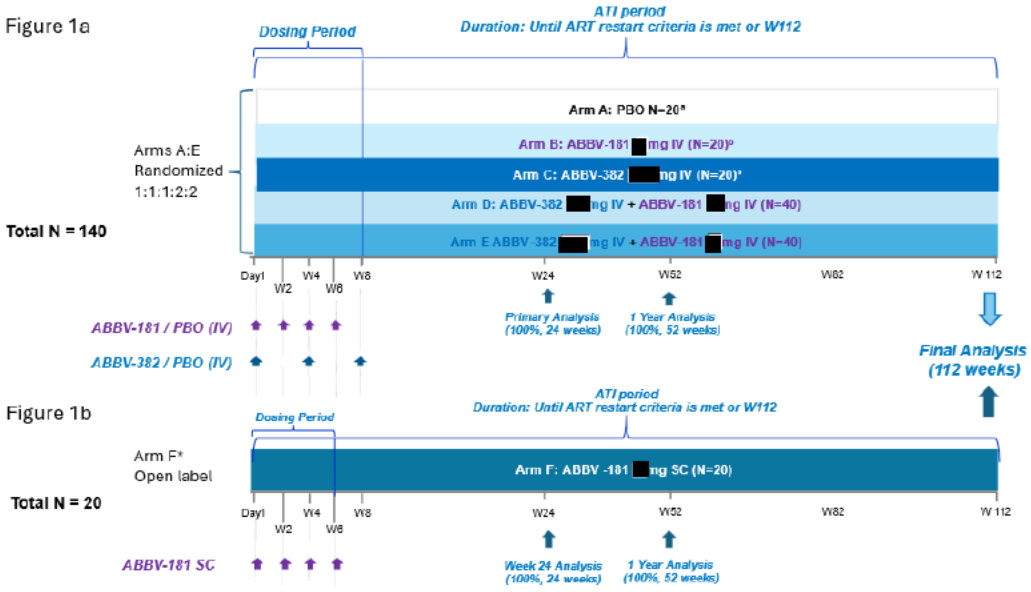
2.2 Study Design Overview

This is a multicenter, 2-part, Phase 2 proof-of-concept study to evaluate the efficacy, safety, tolerability, and PK of budigalimab and/or ABBV-382 in PLWH who are on stable ART undergoing ATI. The first part of the study is a randomized, double-blind, placebo-controlled evaluation of budigalimab IV and ABBV-382 IV. The second part of the study is a single-arm, open-label evaluation of budigalimab SC.

Approximately 160 participants with a confirmed HIV-1 diagnosis who are on stable ART and willing to undergo ATI will be enrolled in this trial.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



* Participants randomized to Arm F will receive only budigalimab [redacted] mg SC and no placebo. Enrollment of Arm F will start after the last participant is randomized into the first part of the study (Arms A to E).

a. Participants randomized to Arm A will receive placebo for budigalimab and matching placebo for ABBV 382.

b. Participant randomized to Arm B will receive budigalimab [redacted] mg IV and matching placebo for ABBV 382.

c. Participants randomized to Arm C will receive ABBV 382 [redacted] mg IV and placebo for budigalimab.

The screening period in this study is 35 days and may be extended to 42 days if needed for logistical reasons, upon TA MD/SD approval. Starting on Day 1, participants will undergo a closely monitored ART interruption throughout participation in the study or until ART restart criteria are met. Study duration is approximately 117 weeks (inclusive of the screening period).

2.3 Treatment Assignment and Blinding

At the start of the study, 140 participants will be randomized in a 1:1:1:2:2 randomization ratio to one of the following 5 study treatment arms in Part 1 of this trial:

- Arm A: Placebo
- Arm B: Budigalimab [redacted] mg IV
- Arm C: ABBV-382 [redacted] mg IV
- Arm D: Budigalimab [redacted] IV + ABBV-382 [redacted] mg IV
- Arm E: Budigalimab [redacted] mg IV + ABBV-382 [redacted] mg IV

After randomization of Arms A to E is completed and closed, the study will open enrollment to Arm F in Part 2 of this trial. Approximately 20 eligible participants will be assigned to the open-label Arm F, budigalimab [redacted] mg SC (note, no ABBV-382 or placebo will be administered to Arm F participants).

In Part 1 of this trial, the investigator, study site personnel (other than the unblinded pharmacist or designee), and the participant will remain blinded to each participant's study treatment assignment and to the PD-1 and α4β7 receptor saturation panel data throughout the study.

In Part 1 of this trial, AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of the AbbVie Drug Supply Management Team) will remain blinded to each participant's treatment assignment and to the PD-1 and α4β7 receptor saturation panel data until the database for the primary analysis (Week 24) is locked. The AbbVie study team will become unblinded to treatment assignments and to

all previously blinded data after the Week 24 primary analysis database lock for Arms A to E.

2.4 Sample Size Determination

The initial sample size planned for this study is 140 randomized participants across 5 arms (Part 1: Arms A to E): 20 participants each in the placebo, budigalimab IV monotherapy, and ABBV-382 IV monotherapy arms; and 40 participants in each of the 2 budigalimab + ABBV-382 IV combination arms. With a sample size of 40 participants in a combination treatment arm and 20 participants in the placebo arm, the study will have at least 90% power for the primary analysis pairwise comparisons between each of the budigalimab + ABBV-382 IV combination arms and the placebo arm, assuming a 50% viral control rate in the active arms and a 4% viral control rate in the placebo arm. Supplementary analyses of the primary endpoint will achieve at least 80% power assuming study discontinuations and ART restart due to non-disease related criteria occur in no more than 50% of participants.

The sample size calculation is based on a 2-sample Fisher's exact text with a 2-sided significance level of 0.1. The assumption of a 4% viral control rate in the placebo arm is based on the post-treatment control rate observed in PLWH treated during chronic infection identified by the Control of HIV After Antiretroviral Medication Pause (CHAMP) Study.[1]

A sample size of 20 participants in Part 2 (Arm F), the open-label, budigalimab SC monotherapy treatment arm in the second part of the study, was selected to align with the size of the budigalimab IV monotherapy arm in the first part of the study. Assuming a 25% viral control rate in the budigalimab SC monotherapy arm, a 90% confidence interval would be [13%, 43%].

3.0 Endpoints

3.1 Primary Endpoint

The primary endpoint is viral control (viral load < 1,000 copies/mL) at Week 24 without ART restart.

3.2 Secondary Endpoints

The secondary efficacy endpoints are:

- Peak viral load (at rebound) prior to re-starting ART
- Time to first rebound to ≥ 1,000 copies/mL during ART interruption

3.3 Additional Efficacy Endpoints

Additional efficacy endpoints are:

- Viral control (viral load < 1,000 copies/mL) at Weeks 12, 52, 68, 84, 98, and 112 without ART restart
- Viral control (viral load < 200 copies/mL) at Weeks 12, 24, 52, 68, 84, 98, and 112 without ART restart
- Viral control (viral load < 50 copies/mL) at Weeks 12, 24, 52, 68, 84, 98, and 112 without ART restart
- Viral control (viral load < 1,000 or < 200 or < 50 copies/mL) for at least two-thirds of the time between Weeks 10 and 24 without ART restart
- Viral control (viral load < 1,000 or < 200 or < 50 copies/mL) for at least two-thirds of the time between Weeks 24 and 52 without ART restart
- Viral control (viral load < 1,000 or < 200 or < 50 copies/mL) for at least two-thirds of the time between Weeks 52 and 112 without ART restart
- ART restart at Weeks 12, 24, 52, 68, 84, 98, and 112
- Time to ART restart
- Time to first rebound to ≥ 200 copies/mL during ART interruption
- Meeting ART restart criteria prior to Week 12 of ART interruption

- Viral re-suppression after ART restart

3.4 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, ECG measurements, and clinical laboratory testing (hematology and metabolic panels, thyroid function, plasma HIV-1 RNA, and CD4+ T cell counts) as measures of safety and tolerability throughout the study.

Safety endpoints include drug-related Grade 3 or higher AEs, frequency and severity of AEs, AESIs (irAEs, infusion-related reactions in Part 1 (Arms A to E only), injection site reactions in Part 2 (Arm F only), hepatic-related events, Retroviral Rebound Syndrome (RRS) during ATI, and virologic failure following ART restart.

3.5 Pharmacodynamic Endpoints

Exploratory pharmacodynamic endpoints will evaluate target engagement:

[redacted]

3.6 Patient Reported Outcome Endpoints

The following Patient Reported Outcomes (PROs) are collected in this study:

- EQ-5D-5L
- HIVTSQ
- HAT-QoL

4.0 Analysis Populations

The following population sets will be used for the analyses.

- The Intent-to-Treat (ITT) population will include all randomized participants who receive any amount of study drug. Participants will be analyzed according to the treatment arm as randomized. The ITT population will be used for all analyses of participant characteristics and efficacy.
- The modified Intent-to-Treat (mITT) population is a subpopulation of ITT, which will include only participants who restart ART due to meeting HIV disease-related ART restart criteria (i.e., increased viral load, decreased CD4 count, Grade 3 or higher RRS). It will be used to perform supplementary efficacy analyses.
- The Safety Analysis Set will include all participants who receive any amount of study drug. Participants will be analyzed according to the actual treatment they receive. The Safety Analysis Set will be used for all analyses of safety and pharmacodynamic endpoints.

5.0 Participant Disposition

Screened participants who do not randomize/enroll in the study (i.e., participants who consented to participate in the study but were not randomized/enrolled) and the associated reasons for not enrolling (e.g., screen failed [eligibility criteria not met], withdrawal by participant, etc.) will be tabulated for all screened participants.

A summary of participant accountability by investigator will be provided where the number of participants in each of the following categories will be tabulated for each treatment arm and overall:

- Participants enrolled (randomized) in the study;
- Participants who received any amount of study treatment;
- Participants who completed study treatment;
- Participants who prematurely discontinued study treatment;

- Participants who completed the study;
- Participants who prematurely discontinued from the study;
- Participants ongoing in the post-treatment period at the time of the primary analysis;
- Participants who re-started ART for any reason;
- Participants in each analysis population (as applicable).

The summary of participant accountability by investigator also will include the number of participants who screened and the number of participants who screen failed.

The number and percentage of participants in the ITT population who prematurely discontinued study treatment will be summarized by reason for not completing study treatment overall and by treatment arm.

The number and percentage of participants in the ITT population who did not complete the protocol defined follow-up period will be summarized by reason for not completing study overall and by treatment arm.

6.0 Study Treatment Duration and Dosing

For the Safety Analysis Set for each treatment group and overall, study treatment exposure will be summarized separately for each study drug using the following measures:

- Number of doses received,
- Volume of study drug received.

Duration of treatment (for the study treatment regimen) is defined for each participant as last dose date (of any study drug) minus first dose date (of any study drug) + 1 day. The number of doses and volume of study drug received is to be determined from the study treatment administration eCRF.

Duration of treatment, number of doses received, and volume of study drug received will be summarized using the number of participants treated, mean, standard deviation, median, minimum, and maximum.

7.0 Participant Characteristics

Categorical variables will be summarized with the number and percentage of participants. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum, and maximum).

7.1 Demographics and Baseline Characteristics

Demographics and baseline or disease characteristics will be summarized descriptively, overall and by treatment arm for the ITT population. Unless otherwise specified, baseline is defined as the last non-missing value prior to the first administration of any study treatment.

Continuous demographic variables include age, weight, height, and body mass index (BMI).

Categorical demographic and baseline variables include:

- Sex at birth (male, female, or undifferentiated)
- Gender identity (cisgender, transgender female, transgender male, gender fluid, or other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White)
- Age (< 40, 40 64, ≥ 65 years)
- Weight (< 60 or ≥ 60 kg)
- BMI (< 25 or ≥ 25 kg/m^2)
- Region (Europe, North America, or rest of world)

- Country
- Nicotine user (current, former, never, unknown)
- Alcohol user (current, former, never, unknown)
- Former injection drug user (yes, within the last 12 months; yes, more than 12 months ago; or no)
- Using stable opiate substitution (yes or no).

Other baseline and disease characteristics include:

- Duration of HIV-1 infection (continuous; < 5 or ≥ 5 years)
- Duration of HIV-1 diagnosis (continuous; < 5 or ≥ 5 years)
- Number of previous ART regimens (≤ 4 or 5) at Baseline
- Time to first ART initiation following infection (< 3; 3 6; > 6 months)
- Time to first ART initiation following diagnosis (< 3; 3 6; > 6 months)
- Baseline CD4 count (continuous; < 750 or ≥ 750 10^6/L)
- Baseline CD4:CD8 ratio (continuous; < 1 or ≥ 1)
- Historical CD4 nadir (< 500 or ≥ 500 10^6/L; < 350 or ≥ 350 10^6/L)
- Historical peak viral load (continuous)
- Historical viral load set point (continuous)
- Mode of HIV-1 acquisition
- Baseline HIV-1 tropism
- History of acute retroviral syndrome associated with primary HIV-1 infection (yes or no)
- History of retroviral rebound syndrome associated with ART interruption (yes or no)
- History of immune reconstitution inflammatory syndrome (yes or no)
- Time since first ART initiation (continuous; < 5 or ≥ 5 years)
- First ART initiation category (self-reported or documented)
- History of resistance to class of ARTs (yes or no; if yes, PI, NNRTI, NRTI, INSTI, and/or other class of ARTs)

7.2 Medical History and Prior and Concomitant Medications

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of participants in each medical history category (by MedDRA system organ class (SOC) and preferred term) will be summarized overall and by treatment arm for the ITT population. The SOC will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Participants reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

Prior and concomitant medications will be summarized separately. The number and percentage of participants taking prior and concomitant medications will be summarized by generic drug name, based on the World Health Organization (WHO) Drug Dictionary. The actual version of the WHO Drug Dictionary will be noted in the statistical tables and clinical study report.

Prior, concomitant, and post-study-treatment HIV-1 ART medications will be summarized separately. For prior, concomitant, and post-study-treatment ARTs, the number and percentage of participants taking ARTs will be summarized separately by ART regimen and generic drug name based on the WHO Drug Dictionary. For each participant, the class of ART regimen (PI-based, INSTI-based, or other) at study start and ART restart will be summarized separately. A listing of all prior, concomitant, post-study-treatment HIV-1 medications will be provided.

7.3 Protocol Deviations

Protocol deviations include:

- Eligibility criteria violations
- Receipt of wrong treatment or incorrect dose of study treatment
- Development of withdrawal criteria without being withdrawn
- Use of prohibited concomitant medications.

A listing of participants with protocol deviations will be provided.

8.0 Handling of Potential Intercurrent Events for the Primary and Secondary Endpoints

For the primary endpoint of viral control (defined in Section 3.1), in the ITT population, for participants who restart ART prior to Week 24, all viral load data collected after ART restart will be excluded from the analysis; only viral load data collected during ATI will be considered for analysis. If a participant restarts ART on or before Week 24, then, by definition, the participant has not achieved viral control at Week 24 without ART restart (a composite strategy). Premature study discontinuations or deaths among participants who have not restarted ART will be handled by a treatment policy strategy, where the ART restart status and viral load measurements collected during the analysis window will be used to determine the viral control status. A supplementary analysis will be performed on the mITT population.

For the secondary endpoints, only viral load measurements collected during the ATI (prior to ART restart) will be considered for analysis.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted on the ITT population, with a supplementary analysis of the primary endpoint conducted on the mITT population.

The primary analysis will be performed after all ongoing participants in Arms A to E have completed the Week 24 visit or restarted ART and the database has been locked. The primary analysis will be unblinded to the entire study team.

An interim look will occur when all randomized participants in Part 1 (Arms A to E) have reached Week 52 or prematurely discontinued from the study. In addition, depending on enrollment timelines for Arm F, interim looks of Arm F data in Part 2 (e.g., when all enrolled participants in Arm F have reached Week 24 or later, or prematurely

discontinued from the study at that timepoint) may be conducted to accelerate decisions on future development plans.

The final analysis will be conducted after all ongoing participants have completed (at Week 112) or prematurely discontinued from the study and the database has been locked.

Unless otherwise specified, categorical variables will be analyzed using the Mantel-Haenszel chi-square test. Continuous variables will be analyzed using the Wilcoxon rank sum test. Time to event variables will be analyzed using the Kaplan Meier (KM) method.

"Baseline" refers to the last non-missing observation before the first administration of study drug.

9.2 Handling of Missing Data

Missing data (not due to intercurrent events) will be handled using the following methods for the efficacy analyses:

- Backward Imputation: For participants with missing ART-free HIV-1 RNA viral load values at study visits, the next available ART-free HIV-1 RNA value will be imputed for the purposes of determining viral control. If the only subsequent HIV-1 RNA value is post-ART restart or there are no subsequent values, then the participant will be considered to not have viral control at that visit.
- As Observed (AO): The AO analysis will not impute values for missing evaluations, and thus a participant who does not have an evaluation on a scheduled visit will be excluded from the AO analysis for that visit. AO will include all values collected in the study.

9.3 Primary Efficacy Endpoint and Analyses

9.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is viral control (viral load < 1,000 copies/mL) at Week 24 without ART restart.

The estimands corresponding to the primary efficacy objective in Part 1 and the primary efficacy analysis in Part 2 are defined as follows in Table 2.

Table 2. Summary of the Estimand Attributes Corresponding to the Part 1 and Part 2 Primary Efficacy Analyses

Attributes of the Estimand				
Treatment	**Endpoint**	**Analysis Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Budigalimab + ABBV-382 IV combination therapy, budigalimab IV monotherapy, ABBV-382 IV monotherapy, or placebo	Viral control (viral load < 1,000 copies/mL) without ART restart at Week 24	All randomized participants in Arms A to E who receive any amount of study drug (ITT population)	For participants who restart ART prior to Week 24, all viral load data collected after ART restart will be excluded from the analysis; only viral load data collected during ATI will be considered for analysis. Premature study discontinuations or deaths in participants who have not restarted ART will be handled by a treatment policy strategy.	Main Analysis: Difference in the proportion of participants who achieve viral control (viral load < 1,000 copies/mL) without ART restart at Week 24 between each active treatment arm and placebo.

Attributes of the Estimand				
Treatment	**Endpoint**	**Analysis Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Budigalimab + ABBV-382 IV combination therapy, budigalimab IV monotherapy, ABBV-382 IV monotherapy, or placebo	Viral control (viral load < 1,000 copies/mL) without ART restart at Week 24	All randomized participants in Arms A to E who receive any amount of study drug, excluding participants who restart ART due to non-disease related criteria (mITT population)	For participants who restart ART prior to Week 24, all viral load data collected after ART restart will be excluded from the analysis; only viral load data collected during ATI will be considered for analysis. Premature study discontinuations or deaths in participants who have not restarted ART will be handled by a treatment policy strategy.	Supplementary Analysis: Difference in the proportion of participants who achieve viral control (viral load < 1,000 copies/mL) without ART restart at Week 24 between each active treatment arm and placebo.
Budigalimab SC	Viral control (viral load < 1,000 copies/mL) without ART restart at Week 24	All enrolled participants in Arm F who received any amount of study drug (ITT population)	For participants who restart ART prior to Week 24, all viral load data collected after ART restart will be excluded from the analysis; only viral load data collected during ATI will be considered for analysis. Premature study discontinuations or deaths in participants who have not restarted ART will be handled by a treatment policy strategy.	Main Analysis: Proportion of participants with viral control (viral load < 1,000 copies/mL) without ART restart at Week 24.

Attributes of the Estimand				
Treatment	**Endpoint**	**Analysis Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Budigalimab SC	Viral control (viral load < 1,000 copies/mL) without ART restart at Week 24	All enrolled participants in Arm F who received any amount of study drug, excluding participants who restart ART due to non-disease related criteria (mITT population)	For participants who restart ART prior to Week 24, all viral load data collected after ART restart will be excluded from the analysis; only viral load data collected during ATI will be considered for analysis. Premature study discontinuations or deaths in participants who have not restarted ART will be handled by a treatment policy strategy.	Supplementary Analysis: Proportion of participants who achieve viral control (viral load < 1,000 copies/mL) without ART restart at Week 24.

9.3.2 Main Analysis of Primary Efficacy Endpoint

The attributes of the estimand corresponding to the primary efficacy objective are summarized in Section 2.1 and Table 2.

Analysis of the primary endpoint will be conducted on the ITT population based on treatment as randomized in Part 1. Comparisons of the primary endpoint will be made between each active treatment arm and placebo in Part 1 using the Mantel-Haenszel chi-square test. The difference in rates between each active treatment arm and placebo in Part 1 will be provided, along with 90% and 95% CIs for the differences, and p-values. Proportions and confidence intervals also will be provided for each individual treatment arm (including Arm F in Part 2). Reasons for not achieving ART-free viral control (defined as HIV-1 RNA viral load < 1000 copies/mL without ART re-start) at Week 24 will also be summarized by treatment arm.

9.3.3 Supplementary Analyses of the Primary Efficacy Endpoint

A supplementary analysis will be conducted on the mITT population and will also use the Mantel-Haenszel chi-square test in order to estimate treatment effect among participants who did not restart ART for non-disease related criteria (such as pregnancy or participant's request). For Part 1, point estimates of the difference (vs. placebo) in proportions will be provided, along with 90% and 95% CIs for the differences, and p-values. Proportions and confidence intervals also will be provided for each individual treatment arm (including Arm F in Part 2).

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Peak viral load (at rebound) prior to re-starting ART
- Time to first rebound to ≥ 1,000 copies/mL during ART interruption.

9.4.2 Main Analyses of Secondary Efficacy Endpoints

The attributes of the estimands corresponding to the Part 1 secondary efficacy objectives and Part 2 secondary efficacy analyses are summarized in Table 3.

Table 3. Summary of the Estimand Attributes Corresponding to the Part 1 and Part 2 Secondary Efficacy Analyses

Attributes of the Estimand				
Treatment	**Endpoint**	**Analysis Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Budigalimab + ABBV-382 IV combination therapy, budigalimab IV monotherapy, ABBV-382 IV monotherapy, or placebo	Peak (maximum) viral load (at rebound) prior to re-starting ART	All randomized participants in Arms A to E who receive any amount of study drug (ITT population)	Only viral load measurements collected during the ATI (prior to ART restart) will be considered for analysis.	Difference in median peak viral load (at rebound, before restarting ART) between each active treatment arm and placebo
Budigalimab + ABBV-382 IV combination therapy, budigalimab IV monotherapy, ABBV-382 IV monotherapy, or placebo	Time to first rebound to ≥ 1,000 copies/mL during ART interruption	All randomized participants in Arms A to E who receive any amount of study drug (ITT population)	Only viral load measurements collected during the ATI (prior to ART restart) will be considered for analysis.	Median time to rebound to ≥ 1,000 copies/mL during ART interruption in each treatment arm
Budigalimab SC	Peak (maximum) viral load (at rebound) prior to re-starting ART	All enrolled participants in Arm F who received any amount of study drug (ITT population)	Only viral load measurements collected during the ATI (prior to ART restart) will be considered for analysis.	Median peak viral load (at rebound, before restarting ART)
Budigalimab SC	Time to first rebound to ≥ 1,000 copies/mL during ART interruption	All enrolled participants in Arm F who received any amount of study drug (ITT population)	Only viral load measurements collected during the ATI (prior to ART restart) will be considered for analysis.	Median time to rebound to ≥ 1,000 copies/mL during ART interruption

Analysis of the secondary endpoints will be conducted on the ITT population based on treatment as randomized in Part 1.

The difference in median peak viral load (at rebound, before restarting ART) between each active treatment arm and placebo in Part 1 will be analyzed using a Wilcoxon rank sum test. Additionally, 90% CIs and p-values will be provided for each difference, along with medians, means, and 90% CIs for each individual treatment arm. For Part 2, the median, mean, and 90% CI for Arm F will be provided.

The median time to rebound to ≥ 1,000 copies/mL during ART interruption in each treatment arm (including Arm F) will be analyzed using the Kaplan-Meier (KM) method. Kaplan-Meier summaries, including KM curves, with the median, quartiles, and range will be provided for each treatment arm. In Part 1, an estimate of the difference (vs. placebo) in median time to rebound along with 90% CIs and p-values will be provided for each active treatment arm.

9.5 Additional Efficacy Endpoints and Analyses

The following analyses of additional efficacy endpoints will be presented by treatment arm:

- Proportion of participants with viral control (viral load < 1,000 copies/mL) without ART restart by visit
- Proportion of participants with viral control (viral load < 200 copies/mL) without ART restart by visit
- Proportion of participants with viral control (viral load < 50 copies/mL) without ART restart by visit
- Proportion of participants with viral control (viral load < 1,000 copies/mL) for at least two-thirds of the time between Weeks 10 and 24 without ART restart
- Proportion of participants with viral control (viral load < 200 copies/mL) for at least two-thirds of the time between Weeks 10 and 24 without ART restart
- Proportion of participants with viral control (viral load < 50 copies/mL) for at least two-thirds of the time between Weeks 10 and 24 without ART restart
- Proportion of participants with viral control (viral load < 1,000 copies/mL) for at least two-thirds of the time between Weeks 24 and 52 without ART restart

- Proportion of participants with viral control (viral load < 200 copies/mL) for at least two-thirds of the time between Weeks 24 and 52 without ART restart
- Proportion of participants with viral control (viral load < 50 copies/mL) for at least two-thirds of the time between Weeks 24 and 52 without ART restart
- Proportion of participants with viral control (viral load < 1,000 copies/mL) for at least two-thirds of the time between Weeks 52 and 112 without ART restart
- Proportion of participants with viral control (viral load < 200 copies/mL) for at least two-thirds of the time between Weeks 52 and 112 without ART restart
- Proportion of participants with viral control (viral load < 50 copies/mL) for at least two-thirds of the time between Weeks 52 and 112 without ART restart
- Proportion of participants who re-started ART by visit
- Time to ART restart
- Time to first rebound to ≥ 200 copies/mL during ART interruption
- Proportion of participants meeting ART restart criteria prior to Week 12 of ART interruption
- Viral re-suppression after ART restart
- Number of days off ART
- ART-free $\log_{10}$ viral load over time

ART-free viral control can take on one of following, mutually exclusive, statuses at each timepoint:

- Complete response, defined as an ART-free viral load less than 1,000 copies/mL
- Partial response, defined as a post-peak decrease of > 1.2 $\log_{10}$ ART-free viral load from the peak ART-free viral load, excluding those who achieved complete response
- Non-response, defined as not achieving complete response nor partial response.

The Mantel-Haenszel chi-square test will be used to analyze other binary endpoints in Part 1 of this trial. For this additional analysis of viral control, testing will be done on complete/partial response (partial responders and complete responders) vs. non-response.

The same method (KM) described in the above Section 9.4.2 will be used to analyze other time to event endpoints.

Descriptive statistics will be presented by treatment arm for the proportion of participants who restart ART prior to Week 12 and the proportion of participants meeting ART restart criteria (overall and by reason) prior to Week 12.

Descriptive statistics will be presented by treatment arm for the proportion of participants with viral re-suppression after ART restart.

Descriptive statistics will be presented by treatment arm for the total number of days off ART among participants who achieve ART-free viral control (viral load < 1,000 copies/mL without ART re-start) at Week 24. A listing of participants with ART-free viral loads after Week 24 will also be presented.

Plots of ART-free $\log_{10}$ viral load over time by participant and treatment arm will be generated.

9.6 Efficacy Subgroup Analyses

Subgroup variables will include:

- Age (< 40; 40 64; ≥ 65 years)
- Race (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White)
- Region (Europe; North America; Rest of World)
- Country
- Gender identity (Cisgender; Transgender Female; Transgender Male; Gender Fluid; Other)

- Historical CD4 nadir (< 350 10^6/L; ≥ 350 10^6/L)
- Baseline CD4 count (< 750 10^6/L; ≥ 750 10^6/L)
- Baseline CD4:CD8 ratio (< 1; ≥ 1)
- Baseline ART regimen (PI-based; INSTI-based; Other)
- Time since HIV-1 diagnosis (< 5 years; ≥ 5 years)
- Time to ART start following diagnosis (< 3; 3 6; > 6 months)
- Baseline HIV-1 tropism
- History of cardiovascular disease (yes; no)
- History of low bone density (yes; no)
- History of diabetes (yes; no)
- History of renal disease (yes; no)
- History of psychiatric condition (yes; no)
- Did not have protocol deviation(s) which may impact the assessment of efficacy. For example:
    - Did not have prior exposure to long-acting antiretrovirals within 24 weeks or within a period defined by 5 half-lives, whichever is longer, prior to randomization and prior to the first dose of study drug
    - Have no known evidence of ART initiation < 3 months after estimated date of infection (or during acute HIV disease defined as HIV detection, p24Ag or HIV-RNA, in the absence of HIV antibody or HIV seroconversion in the first 3 months)

For each subgroup variable, descriptive statistics will be presented by treatment arm for the primary endpoint (viral control without ART restart at Week 24).

Viral control (viral load < 1,000 copies/mL) without ART restart at Weeks 12, 24, 52, 68, 84, 98, and 112 also will be summarized separately in those who have:

- Completed study treatment vs. those who prematurely discontinued study treatment
- Completed 6 weeks of treatment vs. those who prematurely discontinued before 6 weeks

- Completed 4 weeks of treatment vs. those who prematurely discontinued before 4 weeks.

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Safety Analysis Set. For the safety analyses, participants will be assigned to a treatment group based on the treatment actually received, regardless of the randomized treatment assignment in Part 1. For Part 2, participants will be assigned to Arm F in all safety analyses. Safety summaries will be presented by treatment group, including total group(s) for all participants on active study treatment.

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each participant for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a participant, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AE with an onset after the first dose of study treatment. Events where the onset date is the same as the study treatment start date are assumed to be treatment-emergent, unless the study treatment start time and the AE start time are collected and the AE start time is prior to the study treatment start time. If an incomplete onset date is collected for an AE, then the AE will be assumed to be treatment-emergent unless there is evidence that confirms that the AE

was not treatment-emergent (e.g., the known portion of the AE onset and/or the AE end date was prior to the date of the first dose of study treatment).

All treatment-emergent AEs will be summarized overall, as well as by primary MedDRA SOC and PT. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of participants experiencing treatment-emergent AEs will be summarized.

10.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of participants experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study treatment according to the investigator
- Any serious treatment-emergent AE
- Any serious treatment-emergent AE related to study treatment according to the investigator
- Any treatment-emergent AE leading to discontinuation of study treatment
- Any treatment-emergent AE leading to death
- Any Grade 3 or higher treatment-emergent AE
- Any Grade 3 or higher treatment-emergent AE related to study treatment according to the investigator
- Any immune-related treatment-emergent adverse event (irAE)
- Any infusion-related reaction (IRR) [Arms A to E only]
- Any injection site reaction (ISR) [Arm F only]
- Any hepatic-related serious treatment-emergent AE
- Any hepatic-related treatment-emergent AE leading to discontinuation of study treatment

- Any treatment-emergent AE corresponding to retroviral rebound syndrome (RRS) according to the investigator
- All deaths

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized by SOC and PT; by maximum relationship to study treatments as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum DAIDS grade (Grade 1, 2, 3, 4, or 5) and SOC and PT; and by participant number and SOC and PT. Specific adverse events will be counted once for each participant for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a participant, the highest grade and level of relationship to investigational product will be reported.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency for the total active group.

10.2.4 Deaths, Serious Adverse Events, and Adverse Events Leading to Study Treatment Discontinuation

Treatment-emergent serious adverse events (TESAEs), TEAEs leading to premature discontinuation of study treatment, and TEAEs leading to death will be summarized by SOC and PT.

Tabular listings will be provided for all deaths, all SAEs, TESAEs, TEAEs leading to death, TEAEs leading to premature discontinuation of study treatment, and TEAEs leading to interruption of study treatment.

10.2.5 Safety Topics of Interest

Detailed information about the search criteria for safety topics of interest, including adverse events of special interest, is provided in Appendix B.

Adverse events will be categorized on the AE eCRF by the investigator as immune-related adverse events, RRS, infusion-related reactions in Part 1 (Arms A to E only), injection site reactions in Part 2 (Arm F only), or hepatic-related events.

10.2.5.1 Adverse Events of Special Interest

The following adverse events of special interest will be summarized by SOC and PT:

- Immune-related adverse events (irAEs)
- Infusion-related reactions (IRRs) [Arms A to E only]
- Injection site reactions (ISRs) [Arm F only]
- Hepatic-related events

Detailed information about the search criteria is provided in Appendix B.

Tabular listings of all adverse events of special interest will be provided.

Assessment of hepatic-related events will be based on adverse events or laboratory parameters (as described in Section 10.3). The number and percentage of participants in each of the hepatic event categories defined below will be summarized by treatment group:

1. Hepatic-related, per investigator on AE eCRF, treatment-emergent adverse event leading to discontinuation of study treatment
2. Hepatic-related, per investigator on AE eCRF, serious treatment-emergent adverse event
3. Treatment-emergent adverse event based on the SMQ search (defined in Appendix B)
4. Hepatic-laboratory event (defined in Section 10.3)
5. Both hepatic-related adverse event [1, 2, or 3] and laboratory event [4]
6. Any hepatic event [1, 2, 3, or 4]

10.2.5.2 Additional Safety Topics of Interest

Retroviral Rebound Syndrome (RRS) during ATI is categorized as a safety topic of interest. Participants with RRS will be identified by the investigator on the AE eCRF.

Detailed information about the search criteria is provided in Appendix B.

Adverse events associated with RRS will be summarized by SOC and PT. Tabular listings of RRS will be provided and include symptoms associated with the events.

10.3 Analysis of Laboratory Data

The clinical laboratory tests defined in the protocol operations manual (e.g., hematology, clinical chemistry, urinalysis, and other tests) will be summarized.

Each laboratory variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for selected laboratory variables, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, median, minimum and maximum will be presented for the mean change from baseline within each treatment group.

Abnormal laboratory test values that are Grade 1, 2, 3, or 4, according to The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events V2.1,[1] will be identified. Changes in laboratory parameters will be tabulated using shift tables either by DAIDS criteria or categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample.

Laboratory abnormalities will be evaluated based on Potentially Clinically Significant (PCS) criteria, defined as increase from baseline grade to Grade 2 or higher (Appendix C). For each laboratory PCS criterion, the number and percentage of participants who have a laboratory value meeting the criteria (increase to Grade 2 or higher) will be summarized.

Listings will be provided to summarize participant-level laboratory data for participants meeting PCS criteria (increase to Grade 2 or higher).

For TSH and T4, the number and percentage of participants with laboratory values outside the normal range will be summarized by treatment group. A corresponding listing of relevant laboratory parameters will be provided for participants with values outside normal ranges for TSH and T4.

For CD4, for all time points (starting with Baseline) the number and percentage of participants with CD4 count < 350 10^6/L will be summarized by treatment group. A corresponding listing will be provided for participants with a baseline or post-baseline CD4 count < 350 10^6/L. Plots of CD4 over time will also be presented for any participants with CD4 count < 500 10^6/L at any point post-baseline.

Hepatic laboratory values will be categorized as:

- Confirmed ALT or AST > 3 × ULN (if baseline normal) or > 3 × baseline (if baseline abnormal)
- Confirmed total bilirubin > 1.5 × ULN (if baseline normal) or > 1.5 × baseline (if baseline abnormal)

A listing of participants meeting these criteria will be provided to evaluate potential hepatic-related events.

In addition, the Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot[7] will be generated to evaluate the liver safety profile of the study drugs. A corresponding listing of subjects with ALT or AST > 3 × ULN and total bilirubin > 2 × ULN, not necessarily concurrent, will be provided. The following will be summarized by treatment group:

- ALT > 5.0 × ULN
- AST > 5.0 × ULN

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, heart rate, body temperature, respiratory rate, and weight will be summarized.

Each vital sign variable will be summarized for all protocol specified time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, median, minimum and maximum will be presented for the mean change from baseline within each treatment group.

Vital sign variables will be evaluated based on potentially clinically significant (PCS) criteria in Table C-2 (Appendix C). For each vital sign PCS criterion, the number and percentage of participants who have a vital sign value meeting the criteria will be summarized. A participant who has at least one post-baseline measurement will be included in the summary. If a participant does not have a vital signs measurement at baseline but has a post-baseline measurement which met the above criteria for blood pressure and pulse rate, this participant is considered as meeting the potentially clinically significant vital signs values for the measurement. If a participant has both baseline and post-baseline measurements, the post-baseline value must also be more extreme than baseline value for blood pressures and pulse rates.

Listings will be provided to summarize participant-level vital sign data for participants meeting PCS criteria.

10.5 Virologic Failure and Viral Re-suppression

Virologic failures after ART Restart will be defined as:

- Confirmed plasma HIV-1 RNA rebound to ≥ 200 copies/mL (defined as 2 consecutive measurements of plasma HIV-1 RNA ≥ 200 copies/mL) following initial suppression after ART restart, OR

- Failure to reach confirmed re-suppression (defined as 2 consecutive measurements of plasma HIV-1 RNA < LLOQ) within 24 weeks after ART restart.

Participants who experience virologic failure following ART restart or whose baseline ART regimen needed to be changed after ART restart due to the presence of virus resistant to one or more components of the original ART regimen will be identified in a listing. The listing will include:

- ART classes with resistance to at least one drug in the class (if a resistance test associated with the virologic failure is present)
- Situations driving or significantly contributing to the virological failure (as assessed by investigator)
- Whether the participant was able to achieve viral re-suppression at a single timepoint post ART-restart

11.0 Other Analyses

11.1 ART Drug Resistance Analysis

The number and percentage of participants having ART drug resistance will be summarized by ART category.

11.2 ART Pharmacokinetic Analysis

A listing of ART concentrations (e.g., abacavir, bictegravir, cobicistat, dolutegravir, lamivudine, tenofovir, emtricitabine) during the ATI period will be provided by participant and time point.

11.3 Peak Viral Load During Study

Post-baseline, ART-free, peak viral load will be used to categorize participants as stated below. The number and percentage of participants in each treatment arm will be summarized in the following categories:

- ART-free peak viral load < 1,000 copies/mL
- ART-free peak viral load 1,000 copies/mL 9,999 copies/mL
- ART-free peak viral load 10,000 copies/mL 99,999 copies/mL
- ART-free peak viral load 100,000 copies/mL 999,999 copies/mL
- ART-free peak viral load > 1,000,000 copies/mL

11.4 HIV-1 Tropism

A listing of HIV-1 tropism results will be provided.

11.5 Pharmacodynamic Analysis

Pharmacodynamic results will be summarized by visit and treatment group.

PD-1 Expression and Receptor Saturation by Budigalimab

The parameters of interest are: %PD-1+ cells and PD-1-molecules of equivalent soluble fluorochrome (MESF) on CD4+ and CD8+ T cells and subsets, namely naïve (CD28+CD95), central/transient memory (CD28+/CD95+), effector memory/terminal effector (CD28 CD95+).

- Baseline %PD-1+ cells and PD-1-MESF on CD4+ and CD8+ T cells and subsets will be compared by treatment group using Mann-Whitney U and/or Kruskal-Wallis tests.
- Summary of fold-change (mean and standard deviation) in %PD-1+ CD4+, CD8+ and central/transient memory (CD28+/CD95+) cells at each post-baseline time point relative to baseline will be provided for each treatment group.

- Summary of > 95% %PD-1 RS on CD8+ cells will be provided for each treatment group.

Changes in α4β7 Receptor Coverage and Changes in β7+ Cells by ABBV-382

The parameters of interest are: %α4β7+ cells, α4β7+ molecules of equivalent soluble fluorochrome (MESF), %β7+ cells, and β7+ MESF on CD4+ and CD8+ T cells and their subsets, namely naïve (CD28+CD95-), central/transient memory (CD28+/CD95+), effector memory/terminal effector (CD28-CD95+), and memory (CD95+).

- Baseline %α4β7+, α4β7+ MESF, %β7+ cells, and β7+ MESF on CD4+ and CD8+ T cells and their subsets will be compared by treatment group using Mann-Whitney U and/or Kruskal-Wallis tests.
- Summary of fold-change (mean and standard deviation) in %α4β7+, α4β7+ MESF, %β7+ cells, and β7+ MESF on CD4+, CD8+ cells, naïve cells (CD28+/CD95-), memory CD4 cells (CD4+CD95+) and central/transient memory (CD28+/CD95+) cells at each post-baseline time point relative to baseline will be provided for each treatment group.
- Summary of >95% %a4b7 RS on CD4+ cells will be provided for each treatment group.

Changes in T Cells, B Cells, and NK Cells

- Baseline CD3, CD4, CD8, B (CD19), NK (CD16/56) cell counts and CD4:CD8 ratio will be provided for each treatment group.
- Summary of fold-change (mean and standard deviation) in CD3, CD4, CD8, B, NK cell counts and CD4/CD8 ratio at each post-baseline time point relative to baseline will be provided for each treatment group. This summary also will be reproduced separately for participants on and off ART at Week 24. A listing of CD4 and CD8 cell counts as well as CD4/CD8 ratios for participants not on ART at Week 24 will be provided.

11.6 EuroQol 5 Dimensions 5 Level Questionnaire (EQ-5D-5L)

The EQ-5D-5L has two parts: the EuroQol 5 Dimensions (EQ-5D) descriptive system and the EQ Visual Analogue Scale (EQ VAS). The EQ-5D-5L has five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These dimensions are measured on a five-level scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The responses for the 5 dimensions are used to compute a score which will be converted into a single preference-weighted health utility index score.[2,3] The VAS score will be analyzed separately and is not included in scoring the dimensions or the utility calculation. For the EQ VAS score, higher scores indicate better health-related quality of life. An increase from baseline in the EQ-5D-5L health index score represents an improvement.

For the EQ-5D-5L health index and EQ VAS scores, no imputation will be performed for missing items. A complete health state (non-missing responses to each of the 5 dimensions) is needed to derive the EQ-5D health index score.

Descriptive, summary statistics at each visit and change from baseline to each visit will be provided for the EQ-5D-5L health index and VAS scores by treatment arm. EQ-5D-5L will also be summarized separately for those on and off ART at each applicable visit.

11.7 HIV Treatment Satisfaction Questionnaire (HIVTSQ)

The HIVTSQ measures satisfaction with treatment among PLWH along with a change in satisfaction compared to baseline at various time points.[4,5] It is a 12-item patient-reported questionnaire covering satisfaction with current treatment, control, side effects, demands, convenience, flexibility, understanding, lifestyle, willingness to recommend to others, and willingness to continue. Two versions of the measurement are collected, a status version (HIVTSQs) and a change version (HIVTSQc). Scoring is described below:

- **HIVTSQs:** Response options for the HIVTSQ status version are provided on a 7-point Likert scale ranging from 0 (very dissatisfied, inconvenient, inflexible, etc.) to 6 (very satisfied, convenient, flexible, etc.). Items 1 to 11 are summed

to produce a Treatment Satisfaction (Status) score (range 0 to 66). Higher item-level and Treatment Satisfaction total scores represent a higher level of treatment satisfaction. Item 12 is not included in the Treatment Satisfaction (Status) score but is scored as a stand-alone item only.

- **HIVTSQc:** For the change version, response options are provided on a 7-point Likert scale ranging from +3 (much more satisfied now) to -3 (much less satisfied now), with 0 representing no change. Items 1-11 are summed to produce a Treatment Satisfaction (change) score (range -33 to +33). The higher the score, the greater the improvement in satisfaction with treatment; the lower the score, the greater the deterioration in satisfaction with treatment. A score of 0 represents no change. Item 12 is not included in the Treatment Satisfaction (Change) score but is scored as a stand-alone item only.

Descriptive, summary statistics at each collected visit for each HIVTSQ version and change from baseline to each visit for HIVTSQs will be provided by treatment arm. HIVTSQ will also be summarized separately for those on and off ART at each applicable visit.

11.8 HIV/AIDS-targeted QoL (HAT-QoL) Questionnaire

The HAT-QoL[6] measures quality of life concerns among PLWH. The questionnaire assesses 42 items in 9 domains: overall function, sexual function, disclosure worries, medication worries, health worries, financial worries, HIV mastery, life satisfaction, and provider trust.

Responses are provided on a 5-level verbal scale (all of the time, a lot of the time, some of the time, a little of the time, none of the time). To score the HAT-QOL, each item-level response is mapped to a value, summed to calculate a domain score, and transformed to a 0-100 scale, as instructed in the development paper.[6] Higher domain scores indicate better HIV-related quality of life.

Descriptive, summary statistics at each collected visit and change from baseline to each visit will be provided by treatment arm for each domain in the HAT-QoL. HAT-QoL will also be summarized separately for those on and off ART at each applicable visit.

11.9 Events Related to COVID-19 Infection

A listing of events related to COVID-19 infection will be provided.

12.0 Interim Analyses

After completion of the primary analysis (where the Sponsor will be unblinded), an interim look will occur when all randomized participants in Part 1 (Arms A to E) have reached Week 52 or prematurely discontinued from the study. In addition, depending on enrollment timelines for Part 2 (Arm F), interim looks of Arm F data (e.g., when all enrolled participants in Arm F have reached Week 24 or later, or prematurely discontinued from the study at that timepoint) may be conducted. The objective of these interim looks, which are to occur after the completion of the primary analysis for Arms A to E, is to accelerate decisions on future development plans.

Since there are no efficacy analyses for early stopping, no alpha adjustment is needed. All available data from Parts 1 and 2 will be included in the scope of analysis for each interim look.

12.1 Population PK and Exposure-Response Analyses

Interim (pre-database lock for the primary analysis and not associated with the above interim looks) population PK and exposure-response analyses may be initiated prior to full enrollment of study participants. These analyses will be conducted by a pre-specified internal unblinded group that is not involved or in charge of study conduct.

Study drug concentration information that may unblind the study will not be reported to study sites or blinded personnel.

12.2 Data Monitoring Committee

A DMC including at a minimum clinicians and statisticians independent of the study and project team and with relevant expertise in their field (and additional members qualified by relevant expertise, including community representative) will comprise a data and safety monitoring board to review unblinded safety data from the ongoing study. The DMC is responsible for safeguarding the interests of trial participants, assessing the safety of the treatment and interventions during the trial, as well as for monitoring the integrity and interpretability of the trial. The DMC will provide recommendations to the AbbVie study team regarding ongoing trial conduct or modifications to the trial as described in a separate DMC charter. In order to maintain study team blinding, a separate SDAC will be responsible for performing the analyses described in the DMC charter as well as additional analyses requested by the DMC and facilitating interpretation and answering questions that arise before, during, or after DMC review. The DMC will regularly review unblinded safety data from the ongoing study according to the schedule provided in the DMC charter, which could include AEs/SAEs, AESIs, RRS during ATI, study drug discontinuations, laboratory values, and vital sign values.

A separate DMC charter describes the roles and responsibilities of the DMC members, frequency of data reviews, relevant data to be assessed, and general operations.

Since there are no early stopping criteria for efficacy, no alpha adjustment is needed.

13.0 Overall Type-I Error Control

As this is a Phase 2 trial, there will be no adjustments for multiplicity. All statistical tests in Part 1 of this trial will be 2-sided hypothesis tests comparing active treatment arms versus placebo performed at a nominal significance level of 0.1. All CIs will be 2-sided 90% CIs, unless stated otherwise.

14.0 Version History

Table 4. SAP Version History Summary

Version	Date	Summary
1.0	13 December 2023	Initial version
2.0	22 April 2025	• Updated to align with protocol amendment, including the addition of Part 2 (Arm F); extension of follow-up from Week 52 to Week 112 for all arms • Removed the Part 1 (Arms A-E) interim analysis at Week 12 • Added additional exploratory analyses to better characterize ART-free viral control

15.0 References

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2. Szende A, Williams A. Measuring self-reported population health: an international perspective based on EQ-5D. EuroQol Group Monographs Volume 1. SpringMed Publishing; 2004.
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4. Woodcock A, Bradley C. Validation of the HIV Treatment Satisfaction Questionnaire (HIVTSQ). Qual Life Res. 2001;10(6):517-31.
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6. Holmes WC, Shea JA. Performance of a new, HIV/AIDS-targeted quality of life (HAT-QoL) instrument in asymptomatic seropositive individuals. Qual Life Res. 1997;6(6):561-71.

7. Merz M, Lee KR, Kullak-Ublick GA, et al. Methodology to assess clinical liver safety data. Drug Saf. 2014;37 (Suppl 1):S33-45.

Appendix A. List of SAP Signatories

Name	Title	Role/Functional Area
[redacted]		Author
		Clinical Statistics
		Statistical Programming
		Medical/Scientific Monitor
		Precision Medicine

Appendix B. Definition of Safety Topics of Interest

Safety Topics of Interest, including Adverse Events of Special Interest (AESI), will be identified using the following search criteria:

Safety Topic of Interest	Search Criteria
Immune-related Adverse Events (irAEs)	Adverse Event eCRF checkbox for "immune-related adverse events?" marked "yes" by investigator
Infusion Related Reactions (IRRs)	Adverse Event eCRF checkbox for "infusion related reaction?" marked "yes" by investigator
Injection Site Reactions (ISRs)	Adverse Event eCRF checkbox for "injection site reaction?" marked "yes" by investigator
Retroviral Rebound Syndrome (RRS)	Adverse Event eCRF checkbox for "retroviral rebound syndrome?" marked "yes" by investigator
Hepatic-Related Events	Adverse Event eCRF checkbox for "considered to be a Hepatic-Related Adverse Event?" marked "yes" by investigator **and** that led to discontinuation of study treatment
	Adverse Event eCRF checkbox for "considered to be a Hepatic-Related Adverse Event?" marked "yes" by investigator **and** considered "serious"
	Drug related hepatic disorders – comprehensive search (broad SMQ) [code: 20000006]
	Confirmed ALT or AST > 3 × ULN or > 3 × baseline (if baseline abnormal)
	Confirmed total bilirubin > 1.5 × ULN or > 1.5 × baseline (if baseline abnormal)

Appendix C. Potentially Clinically Significant Criteria for Safety Endpoints

The laboratory values in Table C-1 will be assigned a grade according to DAIDS.[1]

Table C-1. Definitions of Grades 1, 2, 3, and 4 and Criteria for Potentially Clinically Significant Laboratory Values

Test	Grade 1	Grade 2	Grade 3	Grade 4
ALT	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
AST	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Total Bilirubin	1.1 to < 1.6 × ULN	1.6 to < 2.6 × ULN	2.6 to < 5.0 × ULN	≥ 5.0 × ULN
INR, high	1.1 to < 1.5 × ULN	1.5 to < 2.0 × ULN	2.0 to < 3.0 × ULN	≥ 3.0 × ULN
Albumin (g/dL; g/L)	3.0 to < LLN 30 to < LLN	≥ 2.0 to < 3.0 ≥ 20 to < 30	< 2.0 < 20	NA NA
Alkaline Phosphatase	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Creatinine	1.1 to 1.3 × ULN	> 1.3 to 1.8 × ULN or 1.3 to < 1.5 × baseline	> 1.8 to < 3.5 × ULN or 1.5 to < 2.0 × baseline	≥ 3.5 × ULN or ≥ 2.0 × baseline
Creatinine Clearance (mL/min)	NA	< 90 to 60 or 10% to < 30% decrease from baseline	< 60 to 30 or 30% to < 50% decrease from baseline	< 30 or ≥ 50% decrease from baseline
Glucose (mg/dL; mmol/L; µmol) Fasting,* high	110 to 125 6.11 to < 6.95 6110 to < 6950	> 125 to 250 6.95 to < 13.89 6950 to < 13890	> 250 to 500 13.89 to < 27.75 13890 to < 27750	≥ 500 ≥ 27.75 ≥ 27750
Glucose (mg/dL; mmol/L; µmol) Non-Fasting,* high	116 to 160 6.44 to < 8.89 6440 to < 8890	> 160 to 250 8.89 to < 13.89 8890 to < 13890	> 250 to 500 13.89 to < 27.75 13890 to < 27750	≥ 500 ≥ 27.75 ≥ 27750
Glucose (mg/dL; mmol/L; µmol), low	55 to 64 3.05 to < 3.55 3050 to < 3550	40 to < 55 2.22 to < 3.05 2220 to < 3050	30 to < 40 1.67 to < 2.22 1670 to < 2220	< 30 < 1.67 < 1670
Hemoglobin (g/dL; g/L)	10.0 to 10.9 100 to 109	9.0 to < 10.0 90 to < 100	7.0 to < 9.0 70 to < 90	< 7.0 < 70

Test	Grade 1	Grade 2	Grade 3	Grade 4
Platelets (cells/mm^3; cells/L)	100,000 to < 125,000 100.000 × 10^9 to < 125.000 × 10^9	50,000 to < 100,000 50.000 × 10^9 to < 100.000 × 10^9	25,000 to < 50,000 25.000 × 10^9 to < 50.000 × 10^9	< 25,000 < 25.000 × 10^9
Neutrophil (cells/mm^3; cells/L) Absolute	800 to 1,000 .800 × 10^9 to 1.000 × 10^9	600 to 799 .600 × 10^9 to .799 × 10^9	400 to 599 .400 × 10^9 to .599 × 10^9	< 400 < .400 × 10^9
WBC (cells/mm^3; cells/L)	2,000 to 2,499 2.000 ×10^9 to 2.499 × 10^9	1,500 to 1,999 1.500 × 10^9 to 1.999 × 10^9	1,000 to 1,499 1.000 × 10^9 to 1.499 × 10^9	< 1,000 < 1.000 × 10^9
Absolute CD4+ Count (10^6/L)	300 to < 400	200 to < 300	100 to < 200	< 100
Absolute Lymphocyte Count (cell/mm^3; cells/L)	600 to < 650 0.600 × 10^9 to < 0.650 × 10^9	500 to < 600 0.500 × 10^9 to < 0.600 × 10^9	350 to < 500 0.350 × 10^9 to < 0.500 × 10^9	< 350 < 0.350 × 10^9
Bicarbonate, low (mEq/L; mmol/L)	16.0 to < LLN 16.0 to < LLN	11.0 to <16.0 11.0 to <16.0	8.0 to < 11.0 8.0 to < 11.0	< 8.0 < 8.0
Calcium, high (mg/dL; mmol/L)	10.6 to < 11.5 2.65 to < 2.88	11.5 to < 12.5 2.88 to < 3.13	12.5 to < 13.5 3.13 to < 3.38	≥ 13.5 ≥ 3.38
Calcium, low (mg/dL; mmol/L)	7.8 to < 8.4 1.95 to < 2.10	7.0 to < 7.8 1.75 to < 1.95	6.1 to < 7.0 1.53 to < 1.75	< 6.1 < 1.53
Sodium, high (mEq/L; mmol/L)	146 to < 150 146 to < 150	150 to < 154 150 to < 154	154 to < 160 154 to < 160	≥ 160 ≥ 160
Sodium, low (mEq/L; mmol/L)	130 to < 135 130 to < 135	125 to < 130 125 to < 130	121 to < 125 121 to < 125	≤ 120 ≤ 120
Uric Acid, high (mg/dL; mmol/L; µmol/L)	7.5 to < 10.0 0.45 to < 0.59 450 to < 590	10.0 to < 12.0 0.59 to < 0.71 590 to < 710	12.0 to < 15.0 0.71 to < 0.89 710 to < 890	≥ 15.0 ≥ 0.89 ≥ 890
Potassium, high (mEq/L; mmol/L)	5.6 to < 6.0 5.6 to < 6.0	6.0 to < 6.5 6.0 to < 6.5	6.5 to < 7.0 6.5 to < 7.0	≥ 7.0 ≥ 7.0
Potassium, low (mEq/L; mmol/L)	3.0 to < 3.4 3.0 to < 3.4	2.5 to < 3.0 2.5 to < 3.0	2.0 to < 2.5 2.0 to < 2.5	< 2.0 < 2.0
Magnesium, low (mEq/L; mmol/L)	1.2 to < 1.4 0.60 to < 0.70	0.9 to < 1.2 0.45 to < 0.60	0.6 to < 0.9 0.30 to < 0.45	< 0.6 < 0.30

* If fasting status is missing, non fasting criteria will be used for grading.

Note: A post baseline value must be in a more extreme grade than the grade for the baseline value to be considered for increases in grade. PCS will be defined as increase from baseline grade to Grade 2 or higher. If the corresponding baseline value is missing but the post baseline grade is 2 or higher, then the post baseline grade is considered a PCS finding.

Table C-2. Criteria for Potentially Clinically Significant Vital Sign Values

Vital Signs Variables	Criterion	Definition of Potentially Clinically Significant
Systolic Blood Pressure (mmHg)	High	> 160 mmHg and higher than baseline*
	Low	< 70 mmHg and a decrease of ≥ 30 mmHg from baseline*
Diastolic Blood Pressure (mmHg)	High	> 100 mmHg and higher than baseline*
	Low	< 50 mmHg and a decrease of ≥ 20 mmHg from baseline*
Pulse (bpm)	High	> 120 bpm and an increase of ≥ 30 bpm from baseline*
	Low	< 50 bpm and a decrease of ≥ 30 bpm from baseline*
Temperature	High	≥ 38.9°C
	Low	≤ 35.6°C

* If a participant does not have a vital signs measurement at baseline but has a post baseline measurement which met the other criteria listed, this participant is considered as meeting the potentially clinically significant vital signs values for the measurement.