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# Protocol for Study M19-965

## HIV: Budigalimab and/or ABBV-382 in People Living with HIV on Stable Antiretroviral Therapy

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FULL TITLE: 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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# 1 SYNOPSIS

| Title: 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 | |
|---|---|
| **Background and Rationale:** | HIV disease is a chronic condition that remains a major global health problem, with an estimated 39 million people world-wide living with HIV in 2022. Although ART can suppress HIV replication, significantly decreasing AIDS-related mortality and improving the lives of PLWH, these regimens cannot eliminate the HIV DNA integrated in the genome of CD4+ lymphoid and myeloid cells. A high adherence rate to lifelong chronic ART (which is very stigmatizing) is required to maintain viral suppression in plasma and prevent resistance. However, even for ART-treated PLWH with good adherence and suppressed viremia, a state of chronic low-level inflammation persists, which is associated with increased risk of cardiovascular disease, HIV-associated neurocognitive disorder, and other comorbidities. Chronic use of ART is also associated with long-term toxicities.<br>Therefore, there is a significant unmet need for a regimen with a finite duration of therapy that could lead to sustained immune-mediated viral suppression (sustained ART-free remission for HIV). Removing the need for chronic ART treatment would revolutionize the standard of care for PLWH. |
| **Objectives and Endpoints:** | The main objectives of this trial are to evaluate efficacy, safety, tolerability, and PK of budigalimab and/or ABBV-382 in PLWH on stable ART undergoing ATI.<br>The primary endpoint is:<br>• Viral control (viral load < 1000 copies/mL) at Week 24 without ART restart.<br>The secondary endpoints are:<br>• Peak viral load (at rebound) prior to re-starting ART<br>• Time to first rebound to ≥ 1000 copies/mL during ART interruption. |
| **Investigators:** | Multicenter |
| **Study Sites:** | Approximately 90 sites in Belgium, Brazil, Canada, France, Germany, Italy, Japan, Poland, Puerto Rico, South Africa, Spain, United Kingdom, and United States. |
| **Study Population and Number of Participants to be Enrolled:** | 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. |


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| **Investigational Plan:** | This is a multicenter, Phase 2 proof of concept, 2-part 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[redacted]<br>This study will consist of a 35-day screening period. At the start of the study, eligible participants will be randomized in a 1:1:1:2:2 ratio to placebo, budigalimab [redacted]mg IV, ABBV-382 [redacted]mg IV, budigalimab [redacted]mg IV + ABBV-382 [redacted]mg IV, or budigalimab [redacted]mg IV + ABBV-382 [redacted]mg IV (Arms A, B, C, D, or E, respectively). After randomization of Arms A to E is completed and closed, the study will open enrollment to Arm F. Eligible participants will be assigned to the open-label arm of budigalimab [redacted]mg [redacted] For all arms, starting on Day 1, participants will undergo a closely monitored ART interruption planned for 112 weeks or until ART restart criteria are met.<br>Additional arms may be proposed at the discretion of the sponsor and implemented where and when approved by local regulatory authorities. Any additional arms will be submitted to regulatory authorities as substantial modifications/amendments prior to initiation. |
| **Key Inclusion/Exclusion Criteria:** | Inclusion criteria: PLWH between 18-70 years old, in general good health and on ART for at least 12 months prior to screening and on current ART regimen for at least 8 weeks prior to screening. Participants must have negative HIV-2 Ab at screening, plasma HIV-1 RNA below LLOQ at screening and for at least 12 months prior to screening, and CD4+ T cell count ≥ 500 cells/µL at screening and no known evidence of CD4+ T cell count < 500 cells/µL in the last 12 months prior to screening.<br>Exclusion criteria: Participants that have had 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. Participants with known history of CD4+ T cell nadir of ≤ 200 cells/µL during chronic HIV disease.<br>Participants with clinically significant medical disorders per investigator's assessment that might expose the participants to undue risk of harm, confound study outcomes, or prevent the participant from completing the study will also be excluded. |
| **Study Drug and Duration of Treatment:** | Budigalimab (ABBV-181) in vials for IV infusion and[redacted]; placebo for budigalimab IV (0.9% sodium chloride).<br>ABBV-382 in vials for infusion administration; matching placebo for ABBV-382.<br>Starting on Day 1, participants randomized in the first part of the study will be treated with budigalimab IV or placebo Q2W 4 doses and ABBV-382 or placebo Q4W 3 doses, for a total duration of study treatment of 8 weeks. The participants enrolled in the second part of |


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| **Date of Protocol Synopsis:** | 19 July 2024 |


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# 2 INTRODUCTION

## 2.1 Background and Rationale

### Why Is This Study Being Conducted?

HIV disease is a chronic condition that remains a major global health problem, with an estimated 39 million people world-wide living with HIV and 1.3 million new cases in 2022.[1] Although ART can suppress HIV replication, significantly decreasing AIDS-related mortality and improving PLWH lives, these regimens cannot eliminate the HIV DNA integrated in the genome of CD4+ T and myeloid cells. A high adherence rate to lifelong ART (which is very challenging and stigmatizing) is required to maintain viral suppression in plasma, prevent resistance to ART and prevent HIV transmission.[2] Over time, the risk of treatment failure increases, with 20% to 30% of patients discontinuing their initial ART regimen during the first 2 years of therapy. Real-world virologic response rates with first line integrase inhibitor-containing ART regimens in developed countries are still at or below 75%.[3] However, even for ART-treated PLWH with good adherence and suppressed viremia, a state of chronic low-level inflammation persists, which is associated with significant increases in cardiovascular risk, HIV-associated neurological disorder, cerebrovascular risk, cancer, and decreases in life expectancy, particularly in those starting ART at late stages with history of AIDS.[4-9] These co-morbidities are becoming increasingly prevalent as PLWH are living longer lives.[10,11] In addition, frailty (a geriatric clinical syndrome associated with decreased reserve, high vulnerability to stressors and associated with risk of negative health-related outcomes including mortality), is more prevalent than expected in PLWH compared to HIV-negative matched controls and may occur at an earlier age.[12] In addition, while the safety profile of ART has improved, these treatments are still associated with long-term toxicities, including mitochondrial toxicity, renal failure, osteoporosis, neuropsychiatric effects, weight gain, and dyslipidemia.[13-17]

Therefore, there is a significant unmet medical need for regimens of finite duration (as opposed to chronic treatment requiring high adherence for life) that could lead to sustained immune-mediated viral suppression (sustained ART-free remission for HIV). Removing the need for chronic ART treatment would revolutionize the standard of care for PLWH.

Meeting these needs should considerably alleviate patients' stigma burden, mitigate long-term health sequelae including the effects of chronic immune activation/inflammation, and eliminate ART associated toxicity and resistance. Importantly, sustained ART-free HIV control may represent a more reliable approach to reducing HIV transmission and have a large impact on public health.

The achievement of sustained, immune-mediated, viral suppression without ART (ART-free control) may not necessarily require the complete eradication of the HIV reservoir. Rather, immunotherapies may strengthen the immune response against HIV, building effective anti-HIV immune surveillance that would allow PLWH to suppress viral replication (preventing new infection cycles), without the need for chronic ART (similar to elite controllers). Sustained ART-free immune mediated virologic control, if continued over time, may ultimately lead to attenuation of the reservoir, thus contributing to the achievement of complete cure.


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There is growing consensus among clinical and basic science HIV researchers that a combination of (1) agents generating new HIV-specific immune responses against non-escape viral epitopes with (2) agents with potential for enhancement of HIV-specific T cell functionality is a promising approach for achieving immune-mediated long lasting suppression of the virus.[18]

Emerging data suggest some antibodies binding to the envelope of HIV-infected cells or HIV virion, enhance antigen presentation to T cells through immune-complex formation, which is critical for generating IgG1 opsonization.[19] Antigen presentation is enhanced when antigen and IgG are present within the same phagosome (a cytoplasmic vacuole containing a phagocytosed particle enclosed within a part of the cell membrane), whereas cells containing phagosomes with either antigen or IgG alone do not present antigen efficiently. Immune checkpoint inhibitors such as anti-PD-1 antibodies have been studied for their potential to boost $CD8^+$ T cell-mediated responses in various HIV and SIV studies.[18,20-22]

Budigalimab is a humanized, recombinant IgG1 mAb, which is a genetically recombinant product manufactured using a Chinese hamster cell line, that binds to cell surface expressed PD-1 receptor and blocks the interaction of the receptor with its ligands, PD-L1 and PD-L2. T cell control of HIV has been recognized in HIV elite controllers. Therefore, it is hypothesized that anti-PD-1 will contribute to reversing T cell exhaustion and boosting HIV-specific T cell response in PLWH, inducing immune-mediated viral control.[23]

ABBV-382 is a humanized, recombinant IgG1 mAb with FcγR binding ability, which is a genetically recombinant product manufactured using a Chinese hamster cell line, that binds to cell surface expressed α4β7 and blocks interaction of the integrin with its ligand, MAdCAM-1, but not to VCAM-1. ABBV-382 has been demonstrated to bind the HIV envelope and form immune complexes, enhancing FcγR mediated phagocytosis of the immune complex and leading to antigen presentation to T cells. Direct antagonism of the α4β7 interaction with its ligand MAdCAM-1 or HIV gp120, could contribute to inhibition of HIV replication/spread and localization to immune sanctuary sites in lymphatic tissues that is dependent on these interactions.[24,25]

## Clinical Hypothesis

This trial will evaluate the activity of budigalimab [redacted]mg IV Q2W (total of 4 doses) in combination with ABBV-382 [redacted]mg or [redacted]mg) IV Q4W (total of 3 doses) to demonstrate higher efficacy than placebo at 24 weeks of ATI in PLWH who were previously on stable ART. The combination of budigalimab and ABBV-382 is hypothesized to act synergistically to boost HIV specific T cell response, leading to immuno-surveillance for ART-free viral control. The rationale for the participant population selection is presented in Section 4.2.

In addition, this study will evaluate budigalimab [redacted]mg [redacted] Q2W (total of 4 doses) monotherapy. In a Phase 1b study (Study M19-972),[redacted]of budigalimab administered [redacted]to PLWH suppressed on ART demonstrated exposure and receptor saturation similar to those seen with [redacted]mg IV. There were no deaths, no study drug-related Grade 3 or higher AEs, and no injection site reactions associated with [redacted] administration in that study. A single irAE was reported in 1 participant, which was a nonserious, Grade 2, reversible event of lichenoid keratosis assessed as having a reasonable possibility of relationship to study drug by the PI, which resolved after 19 days. It is hypothesized that [redacted]mg budigalimab [redacted] Q2W will have a comparable PK, PD, and safety profile to [redacted] mg budigalimab IV Q2W.


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## 2.2 Benefits and Risks to Participants

### Budigalimab and ABBV-382

Budigalimab was evaluated in Phase 1b in aviremic PLWH on stable ART as single dose IV or [redacted] (Study M19-972), as well as in multiple IV doses compared to placebo in PLWH undergoing ATI (Study M19-939). Both studies evaluated [redacted] the lowest dose(s) of budigalimab that will maintain favorable PD effects (e.g., boosting of HIV-specific immune responses) while minimizing safety risks. Overall, in Studies M19-972 and M19-939, there were no SAEs, no deaths, and no DAIDS Grade ≥ 3 AEs related to the study drug. There were no infusion-related reactions and no injection site reactions. Retroviral rebound syndrome (RRS) is a potential risk in ATI studies; no Grade ≥ 2 RRS events occurred in Study M19-939. In addition, although efficacy endpoints were only exploratory in Study M19-939, delayed viral rebound and sustained ART-free viral control were observed in a subset of PLWH who received budigalimab [redacted] mg IV (total 4 doses).

Immune-related AEs, which are a known risk for immune checkpoint inhibitors such as budigalimab, were observed in 3 participants in the Phase 1 PLWH program: a Grade 2 lichenoid keratosis; a Grade 1 thyroiditis, and a Grade 1 hyperthyroidism; all cases were nonserious and reversible without intervention besides cessation of dosing. This observation is of a lower frequency and severity than what has been observed in monotherapy trials of budigalimab in oncology participants.[26]

Overall, favorable efficacy signs (delay in viral rebound and viral load control) and safety profiles were observed for budigalimab in the Phase 1b program.

[redacted]

Progressive multifocal leukoencephalopathy, or PML, a rare infection of the brain that is caused by JC virus, has been described in some patients who were treated with natalizumab, a monoclonal antibody indicated for multiple sclerosis and Crohn's disease. A recently published meta-analysis also found that that PML risk is highest during long-term natalizumab therapy for multiple sclerosis.[27] The risk of PML for natalizumab has been attributed to inhibition of an α4β1/vascular cell adhesion molecule 1 (VCAM-1) interaction.[28] Of note, vedolizumab does not cause this inhibition, and therefore, the α4β7 inhibitor vedolizumab has been described as having no theoretical risk of PML in a recent published safety


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review.[28] Similarly, in contrast to natalizumab, ABBV-382 does not bind to α4β1 nor inhibit α4β1/VCAM-1 interaction, and it is being explored in this study in PLWH with a limited treatment duration of 3 doses. No cases of PML have been reported to date in participants receiving ABBV-382. For these reasons, although the risk of PML in PLWH receiving ABBV-382 has not yet been established, it is anticipated to be low. The eligibility criteria for Study M19-965, requiring participants to be stable on ART at study entry, with baseline CD4 of 500 cells/$mm^3$ or higher and baseline CD4 nadir above 200 cells/$mm^3$, in addition to limited exposure to treatment (up to 3 doses) during the study, together are expected to further mitigate the risk of PML related to HIV disease. Although PML is unlikely to occur in this study, investigators should be aware of the symptoms and contact the TA MD/SD if there is any suspicion of PML.

For both budigalimab and ABBV-382, there is a potential risk of infusion-related reaction which could occur during or after infusion. There were no Grade 2 or higher infusion-related reactions or injection site reactions in the Phase 1 studies. Based on nonclinical data and Phase 1 clinical data, budigalimab and ABBV-382 are not expected to have overlapping toxicities. Based on the MOA, there is no plausible basis for a PK and/or pharmacodynamic interaction leading to a new DLT.

Overall, the benefit-risk assessment for budigalimab and ABBV-382 is favorable for PLWH.

For further details, please see findings from completed studies, including safety data, in the current budigalimab and ABBV-382 Investigator's Brochures.

Mitigations for the known and potential risks from budigalimab and ABBV-382 incorporated in this study are addressed in the appropriate selection of participants (eligibility criteria), frequency of visits and tests being monitored (activity table), infusion and post-infusion period monitoring, study drug discontinuation criteria, and an unblinded DMC. Infusion-related reactions, injection site reactions, irAEs, RRS during ATI, and hepatic-related AEs and liver function tests will be monitored in the current study. Guidance for their management can be found in Section 6.2.

### Analytic Treatment Interruption

ATI remains an essential component of clinical trials to evaluate interventions aiming to achieve ART-free viral suppression as a biomarker to predict post-treatment viral control is not available.[17,28-30] In addition, some immunotherapies might need a transient viremia and HIV antigen stimulation to trigger an effective immune response, which can only be done in stable patients during ATI. Consensus recommendations on how to operationalize ATI studies to maximize scientific return while mitigating potential risk to study participants have been considered when designing this trial along with expert advice on study design. Furthermore, there is evidence suggesting that short term ATI does not increase viral diversity and/or reservoir size and that closely monitoring ATI period mitigates potential ATI risks on healthy HIV-infected patients.[31]

Nevertheless, viral rebound during ATI and the associated inflammatory response may expose participants and their partner(s) to potential risks, including worsening of immune function, antiretroviral resistance, RRS, and HIV transmission to seronegative partners. Mitigations for the potential risks posed from ATI were addressed through careful consideration of the selection of the population (eligibility criteria, Section 5.1), frequency of safety monitoring/study visits (including allowance for additional/unscheduled visits, laboratory and diagnostic testing as determined by the


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investigator) (Appendix D), clear and detailed ART restart criteria (including at a participant's request) (Section 5.7), and guidance for preventing HIV transmission (Section 5.2).

# 3 OBJECTIVES AND ENDPOINTS

## 3.1 Objectives, Hypotheses, and Estimands

### Primary

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.


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### Table 1. Estimands for the Primary and Secondary Objectives

| **Primary and Secondary Endpoints** | |
|---|---|
| Treatment | Budigalimab IV + ABBV-382 combination therapy, budigalimab monotherapy (IV or [redacted], ABBV-382 monotherapy, or placebo |
| Endpoint | Primary and secondary endpoints (see Section 3.2 and Section 3.3) |
| Population | Adults with chronic HIV-1 on stable ART undergoing ATI |
| 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.<br>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 < 1000 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<br>• 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<br>• Secondary: Median time to rebound to ≥ 1000 copies/mL during ART interruption in each treatment arm |

Note: Arms A to F are defined in Section 4.1.

### Exploratory

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

## 3.2 Primary Endpoint

The primary endpoint is viral control (viral load < 1000 copies/mL) at Week 24 without ART restart.


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## 3.3 Secondary Endpoints

The secondary efficacy endpoints are:

- Peak viral load (at rebound) prior to re-starting ART
- Time to first rebound to ≥ 1000 copies/mL during ART interruption

## 3.4 Additional Efficacy Endpoints

Additional efficacy endpoints are:

- Viral control (viral load < 1000 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 < 1000 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 < 1000 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 < 1000 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

## 3.5 Pharmacodynamic Endpoints

Exploratory pharmacodynamic endpoints will evaluate target engagement:

[redacted]


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## 3.6 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, injection site reactions, and hepatic-related events), RRS during ATI, and virologic failure following ART restart.

## 3.7 Pharmacokinetic Endpoints

PK endpoints for both ABBV-382 and budigalimab include the following assessments for each medication:

- $C_{max}$ after the first and the last dose
- $T_{max}$ after the first and the last dose
- $AUC_{tau}$ after the first and the last dose
- $t_{1/2}$ after the last dose

Additional PK parameters may be calculated if deemed appropriate and useful for the interpretation of results. Exposures of ABBV-382 and budigalimab will be summarized and may be used to develop population PK models.

Immunogenicity of both ABBV-382 and budigalimab will be assessed by using a tiered approach for detecting ADAs. Neutralizing ADAs may be evaluated if useful for the interpretation of results.

## 3.8 Biomarker Research

Biospecimens (whole blood, plasma, serum, PBMCs, and stool) will be collected, as described in Protocol Activity Schedule (Appendix D), throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers. Some of these samples may be optional. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites either free or in association with particular markers. The objective of this research is to analyze samples for biomarkers that will help to understand HIV infection, related conditions, response to treatment with budigalimab, ABBV-382, or similar therapeutic agents. This research is exploratory in nature and the results may not be included with the clinical study report.

Immune cell profiling: whole blood including serum/plasma proteomics and cellular immunophenotyping to evaluate longitudinal changes in proximal target engagement, cytokine, chemokine, and T cell phenotype to inform on-target biological effects and enable exploratory PK/PD modeling.


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Virologic profiling: serum, plasma, and PBMC samples to evaluate size of HIV-1 reservoir, HIV-1 genotypic resistance, HIV-1 subtype, HIV-1 tropism, and other possible predictors of response.

Genomics profiling: whole blood samples for genetic analysis and to measure changes in epigenetics, gene expression, and proteomics that may associate with HIV infection, related conditions, or the participant's response to treatment.

Microbiome profiling: optional stool samples to evaluate gut microbiota composition in PLWH, the impact of immunotherapy on gut microbiota composition, and potential impact of microbiota composition on treatment response.

Provision of biospecimens for biomarker research is mandatory, but they will not be collected from sites where local regulations do not allow for the collection, use, and storage of samples as described in the protocol.

# 4 INVESTIGATIONAL PLAN

## 4.1 Overall Study Design and Plan

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. [redacted]

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. Further details regarding study procedures are located in the Operations Manual.

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.

[redacted]

The number of participants and dosing per arm is as follows:

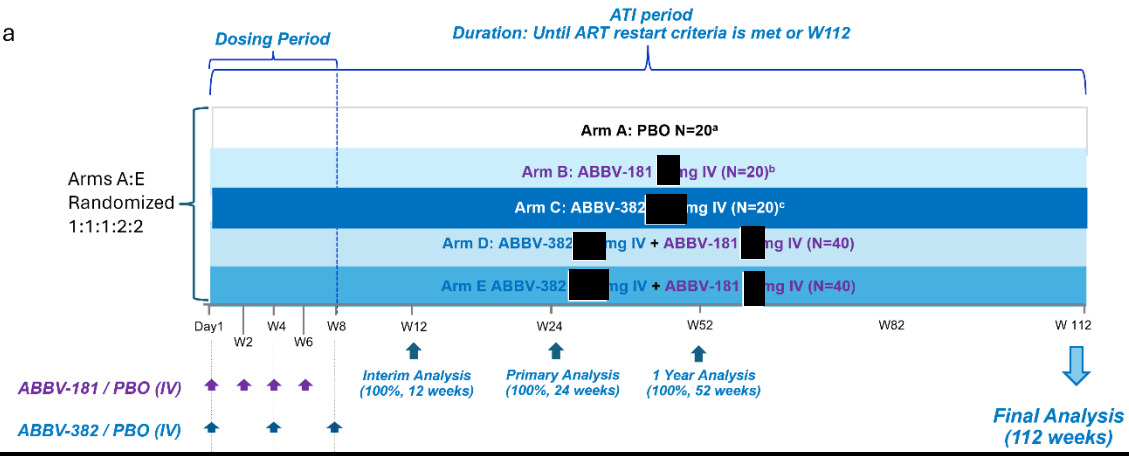
- **Arm A:** budigalimab placebo IV Q2W for 4 doses on Study Day 1, and Weeks 2, 4, and 6 + ABBV-382 matching placebo IV Q4W for 3 doses on Day 1 and Weeks 4 and 8 (n = 20)
- **Arm B:** budigalimab [redacted] mg IV Q2W for 4 doses on Study Day 1 and Weeks 2, 4, and 6 + ABBV-382 matching placebo IV Q4W for 3 doses on Day 1 and Weeks 4 and 8 (n = 20)


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- **Arm C:** budigalimab placebo IV Q2W for 4 doses on Study Day 1 and Weeks 2, 4, and 6 + ABBV-382 [redacted] mg IV Q4W for 3 doses on Day 1 and Weeks 4 and 8 (n = 20)
- **Arm D:** budigalimab IV [redacted] mg Q2W for 4 doses on Study Day 1 and Weeks 2, 4, and 6 combined with ABBV-382 [redacted] mg IV Q4W for 3 doses on Day 1 and Weeks 4 and 8 (n = 40)
- **Arm E:** budigalimab IV [redacted] mg Q2W for 4 doses on Study Day 1 and Weeks 2, 4, and 6 combined with ABBV-382 [redacted] mg IV Q4W for 3 doses on Day 1 and Weeks 4 and 8 (n = 40)
- [redacted]

## Figure 1. Study Schema/EPOCHS

Figure 1a




[redacted]

* [redacted]

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.

Starting on Day 1, participants will undergo a closely monitored ART interruption throughout participation in the study. As ART is currently standard of care for treatment of PLWH, as part of this study, standard of care is withdrawn. ART is to be restarted when a participant meets any of the protocol ART restart criteria (see Section 5.7).

See Section 5 for information regarding eligibility criteria.


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A planned unblinded interim analysis will be conducted once all randomized participants (Arms A to E) have reached Week 12 or prematurely discontinued (refer to Section 7.6).

Study duration is approximately 117 weeks (inclusive of the screening period).

## 4.2 Discussion of Study Design

### Choice of Control Group

The first part of this study is a randomized, double-blind, placebo-controlled study with budigalimab and/or ABBV-382.

There are currently no treatments (monotherapy or combination) that have been approved for ART-free, immune-mediated control of HIV.

The rationale of a placebo-controlled study is built upon the need to demonstrate viral control as an efficacy measurement as well as to further evaluate the safety of active treatment against placebo.[29,31] Previous studies [redacted] of participants from ATI trials reach ART-free viral control (in the absence of any other treatment), some of them even after presenting a post-ATI rebound of viremia known as HIV PTC. However, data on PTC is limited and the occurrence of PTC may have changed over the years impacted by the latest recommendations of early ART start and availability of more potent antiretrovirals. Therefore, the use of historical controls would not be adequate to demonstrate the treatment effect on ART-free viral control of the budigalimab and ABBV-382 combinations in the presence of low levels of nonstudy drug-related post-treatment control.

[redacted]

### Appropriateness of Measurements

Standard statistical, clinical, PK, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are considered acceptable and/or standard for assessing disease activity and treatment response in PLWH. All clinical and laboratory procedures in this study are standard and/or generally accepted.

### Suitability of Participant Population

This study is evaluating budigalimab and/or ABBV-382 in PLWH who are on stable ART, who are willing to undergo ATI and not restart ART unless ART restart criteria are met. This population was selected to ensure participants can safely receive the drugs under study or placebo and undergo ATI for 112 weeks (unless ART restart criteria are met), while retaining an ART treatment option should they need to


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restart ART. Participants will need to demonstrate prior stability on ART with viral control and sufficient CD4 counts to minimize risks associated with ATI and viral rebound. Participants will need to be in a condition of general good health, and willing to undergo ATI on Day 1, and maintain ATI unless restart criteria are met, to allow for sufficient evaluation of viral load control and durability of viral load control. See Section 5 for further information regarding eligibility criteria.

Based on the efficacy, safety, tolerability, and pharmacodynamic data from this study, Phase 3 and other future studies of budigalimab and/or ABBV-382 may evaluate a broader population in PLWH (e.g., with significant comorbidities, low CD4+ counts, adolescents, etc.).

### Selection of Doses in the Study

The dosing regimens of budigalimab and ABBV-382 were selected based on the totality of clinical safety, tolerability, PK/PD, and exploratory efficacy data from the Phase 1 Studies M19-939, M19-972, M19-968, and M19-966. Provided below is a summary of the rationale for dose selection of each of these agents for the Phase 2 Study M19-965.

#### Selection of Budigalimab Dosing Regimen

[redacted]

- Efficacy: In the Phase 1b Study M19-939, although efficacy endpoints were only exploratory, delayed viral rebound and sustained ART-free viral control in a subset of PLWH who received budigalimab [redacted] mg IV Q2W (total 4 doses) were observed. In the Phase 1b Study M19-972 for budigalimab SC, efficacy was not evaluated. Thus, there are currently no efficacy data in PLWH for any SC dose of budigalimab.
- Safety and tolerability: There were no ≥ Grade 3 irAEs observed in the budigalimab Phase 1 studies. Overall, the IV doses evaluated in Phase 1 were generally well-tolerated in PLWH. Moreover, the [redacted] mg IV Q2W (4 doses) regimen was the highest evaluated total dose in Phase 1 in PLWH and was demonstrated to be safe and tolerable. A single dose of [redacted] mg [redacted] was evaluated in Phase 1 in PLWH and was considered safe and tolerable.
- Clinical PK and PD: The [redacted] mg IV dose of budigalimab demonstrated favorable clinical PK and PD profiles in PLWH based on preliminary data from Phase 1 studies. Briefly, the PK of budigalimab at this dose level was approximately linear and dose-proportional with the higher oncology doses of budigalimab that have been previously evaluated (250 mg IV Q2W in oncology). Complete (≥ 95%) and sustained PD-1 receptor saturation was achieved in the peripheral blood with the [redacted] mg IV Q2W (4 doses) regimen for a duration of approximately 10 weeks in Study M19-939. In Study M19-972, the [redacted] mg SC single dose of budigalimab demonstrated approximately 62% bioavailability as well as favorable PK/PD and safety profiles. Based on preliminary PK simulations (model version 2024), the [redacted] mg [redacted] Q2W (total 4 doses) regimen is expected to provide similar $AUC_{2weeks}$ following the last dose, compared to [redacted] mg IV Q2W (total 4 doses) regimen. The preliminary budigalimab population PK model predicts similar receptor saturation between budigalimab [redacted] mg IV Q2W (4 doses) and budigalimab [redacted] mg SC Q2W


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(4 doses). This is particularly important because with these regimens, relatively high budigalimab serum exposures and PD-1 receptor saturation are maintained during the period of viral antigenemia (i.e., viral rebound), based on observations regarding the timing of viral rebound in placebo-treated participants in Study M19-939.

- Furthermore, preliminary population PK/PD modeling and simulation suggests that relatively high PD-1 receptor saturation is achieved with this regimen in the blood (approximately ≥ 95%) as well as in the lymphoid tissue (approximately ≥ 80%), which is the main site of the viral reservoir/replication and where a majority of the body's T lymphocytes reside. Compared to [redacted]mg IV Q2W (4 doses), other dose regimens demonstrate transient and lower levels of PD-1 receptor saturation in the lymph based on PK/PD simulations.
- In addition to achieving high levels of sustained PD-1 receptor saturation, a relatively low dose finite regimen such as [redacted]mg IV budigalimab Q2W (4 doses) and [redacted]mg SC budigalimab Q2W (4 doses) ensures that PD-1 receptor saturation returns to baseline prior to entering a window of time when ≥ Grade 3 irAEs are typically observed with chronic dosing of PD-1 or PD-L1 inhibitors in oncology.[36] Therefore, the dosing regimen of [redacted]mg IV Q2W (4 doses) of budigalimab or [redacted]mg SC Q2W (4 doses) may enable mitigation of any potential risks of developing Grade 3 or higher irAEs in PLWH. Additionally, Q2W dosing may enable potential early discontinuation of dosing in case of any safety events during the study drug dosing period based on safety monitoring.

Budigalimab [redacted]mg IV Q2W (4 doses) regimen is selected for the current study based on its favorable safety, efficacy, PK, and PD profile. Budigalimab [redacted]mg SC Q2W (4 doses) regimen is chosen for this study based on clinical data [redacted]mg SC single dose) as well as PK/PD modeling and simulations.

### Selection of ABBV-382 Dosing Regimens

[redacted]


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[redacted]

# 5 STUDY ACTIVITIES

## 5.1 Eligibility Criteria

Participants are eligible to be included in the study if they meet all of the inclusion criteria and none of the exclusion criteria specified in this protocol.

A participant who has failed screening may be re-screened once at investigator's discretion with TA MD/SD approval (see Operations Manual for exceptions to rescreen). If the participant fails screening a second time, the participant will be excluded from the study.

### Inclusion Criteria

#### Consent

- 1. Participant or their legally authorized representative must voluntarily sign and date an informed consent, approved by an IEC/IRB, prior to the initiation of any screening or study-specific procedures.

#### Demographic and Laboratory Assessments

- 2. Adult individuals of any sex and gender, 18 to 70 years of age, inclusive, at the time of screening.
- 3. Body mass index ≥ 18.0 to < 35.0 kg/$m^2$ (see Operations Manual for calculation and adjustments allowed).
- 4. Must weigh at least 35 kg.
- 5. A condition of general good health in the opinion of the investigator, based upon the results of a medical history, physical examination, vital signs, laboratory profile, and a 12-lead ECG.
- 6. **Laboratory values** meeting the following criteria within the screening period prior to randomization and the first dose of study drug:
  - Negative HIV-2 Ab


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- Absence of current HBV infection on screening tests. Current infection is defined as: a positive HBsAg, or HBV DNA > LLOQ in participants with isolated positive anti-HBc (i.e., negative HBsAg and anti-HBsAb)
- Negative test result for HCV antibody OR absence of detectable HCV RNA result if HCV antibody is positive. Participants with a history of hepatitis C who achieved SVR12 after antiviral therapy may be enrolled if all other inclusion and exclusion criteria are met.
- CD4+ T cell count ≥ 500 cells/µL at screening and no known evidence of CD4+ T cell count < 500 cells/µL in the last 12 months prior to screening
- ALT and AST ≤ 1.25 × ULN
- Total bilirubin ≤ 1.1 × ULN (unless taking atazanavir or known history of Gilbert's Syndrome)
- INR ≤ 1.1 × ULN
- Hemoglobin A1C level ≤ 6.5%
- TSH and T4 results within normal reference range
- Negative anti-thyroglobulin antibody and anti-thyroid peroxidase antibody
- ACTH results within normal reference range
- Platelet count > 125,000 cells/$mm^3$
- Hemoglobin level ≥ 10 g/dL (males) and ≥ 9.5 g/dL (females) (NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [v2.1] [July 2017])
- Calculated creatinine clearance (using Cockcroft-Gault method) of ≥ 60 mL/minute
- Negative IGRA (unless participant already has a documented negative IGRA result within 90 days prior to screening and nothing has changed in participant's medical history to warrant repeat testing at screening).

7. No clinically significant abnormality on screening chest x-ray, including calcified granuloma, and/or pleural scarring.
8. Absence of clinically significant abnormality detected on screening ECG regarding rate, rhythm, or conduction (e.g., QTcF should be < 450 msec for males and < 460 msec for females).
9. Are willing and able to comply with procedures required in this protocol.

### Disease (HIV)/Condition Activity

10. Participant must have diagnosis of HIV-1 with a positive test result for anti-HIV antibody at screening.
11. Participant must have plasma HIV-1 RNA below the LLOQ at screening and for at least 12 months prior to screening; a single unconfirmed "blip" (i.e., plasma HIV-1 RNA value greater than or equal to the lower limit of quantification but < 200 copies/mL) is allowed if preceded and followed by values below the LLOQ (by a validated and approved plasma HIV-1 RNA quantitative assay).


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- 12. Must be on ART for at least 12 months prior to screening and on a stable ART regimen for at least 8 weeks prior to screening (current ART regimen cannot include an NNRTI or long-acting ART).
- 13. Site investigator anticipates that further fully active alternative ART regimens could be constructed and would be available in the event of virologic failure on the participant's current ART regimen.
- 14. After receiving counseling on HIV transmission risk during the study (and especially during treatment interruption), and discussed HIV transmission prevention measurements with the investigator, participant is committed to taking precautions to prevent HIV transmission during the study.

### ART Interruption

- 15. Must be willing to undergo ART interruption and maintain ART interruption for the duration of the study unless ART restart criteria are met.

### Contraception

- 16. Participants must not be pregnant, breastfeeding, or considering having a child or donating eggs or sperm during the study (including at least 6 months after the last dose of study drug for participants who discontinue the study early).
- 17. Negative serum pregnancy test at screening and negative urine pregnancy test on the Study Day 1 visit prior to randomization and prior to the first dose of study drug for all persons of childbearing potential and all persons who are having sexual relationship in which they may become pregnant.
- 18. All persons with assigned female sex at birth who do not meet nonchildbearing potential definition must agree to practice at least 1 additional protocol-specified highly effective **method of birth control** from at least 30 days prior to Study Day 1 through last study visit for the purposes of birth control (including at least 6 months after the last dose of study drug for participants who discontinue the study early).
- 19. If the chosen HIV prevention method (as per inclusion Criterion #14) is not also a highly effective contraception method (in the case of PrEP use, for example) and participant has a partner whose sex was assigned female at birth who does not meet nonchildbearing potential definition, participant and their partner must agree to use an additional highly effective contraceptive method from at least 30 days prior to Study Day 1 through the last study visit for the purposes of birth control (including at least 6 months after the last dose of study drug for participants who discontinue the study early).
    - Nonchildbearing potential is defined in Section 5.2.


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## Exclusion Criteria

### Disease (HIV) Condition/Activity

- 1. 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.
- 2. 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).
- 3. History of CD4+ T cell nadir of ≤ 200 cells/µL during chronic HIV disease. Participant's recall of medical history information is acceptable.
- 4. History of or ongoing diagnosis of AIDS-defining illness.
- 5. History of being diagnosed in the past as an HIV elite controller, defined as control of HIV viral load below the limit of detection for at least 12 consecutive months, in the absence of antiretroviral therapy and any other HIV treatment (including experimental therapies).

### Participant History

- 6. History of or active immunodeficiency (other than HIV).
- 7. Current suspicion of STI or history of recent untreated STI. Screening for STIs is at the discretion of the investigator considering epidemiologic situation in their country/region, participant's medical history, and clinical examination.
- 8. HTLV-1 and/or HTLV-2 co-infection. Screening for HTLV-1/HTLV-2 infection is at the discretion of the investigator considering epidemiologic situation in their country/region.
- 9. History of any tuberculosis (including latent tuberculosis or any non-pulmonary tuberculosis) even if previously treated and no evidence or suspicion of TB disease at screening.
- 10. Active autoimmune disease or history of autoimmune disease that has required systemic treatment (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs) including but not limited to inflammatory bowel diseases, scleroderma, severe psoriasis, myocarditis, uveitis, pneumonitis, systemic lupus erythematosus, rheumatoid arthritis, optic neuritis, myasthenia gravis, adrenal insufficiency, hypothyroidism and/or hyperthyroidism, autoimmune thyroiditis, hypophysitis, or sarcoidosis.
- 11. Prior receipt of immunomodulatory or immunosuppressive (including IV/PO steroids at any dose, but excluding steroids that are inhaled, topical, or via local injection) therapy within 6 months prior to the first dose of study drug.
- 12. Prior therapy/exposure to budigalimab or any other immune checkpoint inhibitor (e.g., anti-PD-L1, anti-PD-L2, anti-CTLA4) or ABBV-382 or any mAb targeting α4β7 or β7 integrins (e.g., vedolizumab).
- 13. Prior exposure to antibody-based immunotherapy or previous enrollment in antibody-based immunotherapy clinical trials within 24 weeks or within a period defined as 5 half-lives, whichever is longer, prior to the first dose of study drug.


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- 14. Participation in ATI study or any HIV-cure based (also including HIV broadly neutralizing Abs) investigation study in the 48 weeks prior to randomization.
- 15. History of medical disorders (other than HIV-1 infection) that, in the opinion of the investigator, might expose the participant to undue risk of harm, confound study outcomes or prevent the participant from completing the study, including but not limited to:
  - significant or unstable cardiac disease (e.g., congestive heart failure, angina, myocardial infarction)
  - significant pulmonary disease (e.g., COPD, asthma requiring systemic therapy)
  - significant neurologic disease (e.g., stroke, dementia)
  - chronic active infectious disease (except for HIV) (e.g., sinusitis, chronic chest infection)
  - chronic liver disease
  - poorly controlled diabetes mellitus
  - history of Stevens-Johnson Syndrome, TENS, or DRESS
- 16. Active or suspected malignancy, or history of malignancy except for basal cell skin cancer and superficially invasive vulvar squamous cell carcinoma of the lower anogenital tract.
- 17. History of any clinically significant illness/infection/major febrile illness, hospitalization, or any surgical procedure within 4 weeks prior to the first dose of study drug.
- 18. Known psychiatric disorders or substance use disorders (including alcohol) that, in the opinion of the principal investigator, could pose additional risk to the participant or their HIV negative partner or that could interfere with adherence to study requirements.
- 19. History of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class, including reaction to any IgG-containing agent.
- 20. Has donated blood (including plasmapheresis), lost ≥ 550 mL blood volume, or received a transfusion of any blood product within 8 weeks prior to study drug administration.
- 21. Is currently enrolled in another interventional clinical study.
- 22. Has been previously enrolled in this study.
- 23. In the opinion of the investigator, this participant is not a suitable candidate for enrollment in this study.

### Laboratory and Other Assessments

- 24. Clinically significant laboratory values at screening that would pose undue risk for the participant or interfere with safety assessments (per the investigator).

### Concomitant Medications

- 25. Current treatment with immunoglobulin therapy and IgG-containing agents.


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- 26. History of treatment with **any investigational drug** within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug.
- 27. Participant has received **any live vaccine (including live, non-replicant, vaccines)** within 4 weeks prior to the first dose of study drug or there is expected need of live vaccination during study participation including at least 4 months after the last dose of study drug.

## 5.2 Contraception Recommendations and Prevention of HIV Transmission Guidance

### Prevention of HIV Transmission

All enrolled participants of any sex and gender are at risk for HIV transmission to their HIV negative sexual partners throughout the study, particularly during the scheduled ATI.

The following actions will also be taken to mitigate this risk:

- Participants will be clearly informed of the potential increased risk of onward transmission, particularly during period off ART therapy during ATI, when there is a possibility of detectable viremia.
- All enrolled participants should receive counseling and discuss methods of HIV transmission prevention with the investigator such as use of an effective barrier method of protection during sexual activity.
- All enrolled participants must receive clear and frequent (i.e., at each study visit) counseling regarding the risk of transmitting HIV to their HIV negative sexual partner(s).
- In accordance with local regulations, policies, and standards, participants must receive referrals to PrEP or PEP and prevention services for their HIV negative sexual partner(s). In the situation where a sexual partner chooses and is deemed eligible to take PrEP but is unable to access PrEP through the usual means (e.g., insurance does not cover PrEP, ineligible for medication assistance program), AbbVie will assist in providing PrEP to the participant's partner (duration of assistance will be from the time the participant starts the study until the last study visit, or participant discontinues the study). PrEP use should be restricted to participant's HIV negative sexual partners only. Investigators should emphasize that participants participating in the trial should not be using PrEP.

### Contraception Requirements

All persons with female sex assigned at birth are defined as nonchildbearing potential if meeting either:

1. Premenopausal persons with assigned female sex at birth with permanent sterility or permanent infertility due to one of the following:
    - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy.


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- Nonsurgical permanent infertility due to Mullerian agenesis, androgen insensitivity syndrome, or gonadal dysgenesis; investigator discretion should be applied to determining contraception needs for these individuals.

2. Postmenopausal persons with assigned female sex at birth that:
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 with no menses for 12 or more months without an alternative medical cause AND a FSH level ≥ 30 IU/L.

**All other persons with female sex assigned at birth that do not meet the above nonchildbearing criteria are considered persons with childbearing potential.** For those participants, the site should:

- Inform the participant that they must avoid pregnancy starting 30 days prior to Study Day 1 through last study visit. For participants who discontinue the study earlier, pregnancy must be avoided until at least 6 months after the last dose of study drug. Inform the participant that they must also commit to 1 of the additional acceptable methods of contraception starting from at least 30 days prior to Study Day 1 through last study visit for the purposes of birth control (including for at least 6 months after the last dose of study drug for participants who discontinue the study early).
- Acceptable methods, as listed below, are contraceptive methods that are highly effective (with a failure rate of < 1% per year, when used consistently and correctly).
- Review and document pregnancy avoidance recommendations (in addition to the method to prevent HIV transmission).

The acceptable methods of additional contraception for persons with childbearing potential, in addition to the HIV transmission prevention method, are:

- Combined (estrogen- and progestogen-containing) hormonal birth control (oral, intravaginal*, transdermal*, or injectable*) associated with inhibition of ovulation initiated at least 30 days prior to Study Day 1.
- Progestogen-only hormonal birth control (oral*, injectable*, implantable*) associated with inhibition of ovulation initiated at least 30 days prior to Study Day 1.
- Bilateral tubal occlusion*/ligation (if done via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
- Intrauterine device initiated at least 30 days prior to Study Day 1.
- Intrauterine hormone-releasing system initiated at least 30 days prior to Study Day 1.
- Vasectomized* partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the study participant). In addition, the vasectomy must have been completed at least 3 months prior to Study Day 1 or the vasectomized partner must have a documented sperm count of zero.

Note: methods marked with an asterisk (*) are not approved in Japan as methods of contraception.


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Contraception recommendations related to use of concomitant therapies prescribed per standard of care should be based on the local label.

## 5.3 Prohibited Medications and Therapy

Prohibited prior medications and therapies are described in the eligibility criteria (Section 5.1).

During the study, all therapies with any immune checkpoint inhibitor (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4) or any anti-α4β7 integrin inhibitor and other investigational drugs are prohibited.

Live vaccine **(including live, non-replicant vaccine**) administration is prohibited during the dosing period and for 4 months following the last dose of study drug administration.

Any ART, including PrEP, is prohibited during the ATI, unless ART restart criteria have been met. Any ART use must be appropriately documented in EDC.

## 5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded from 4 weeks prior to study drug administration through Week 112.

Any questions regarding concomitant or prior therapy should be raised to the TA MD/SD. Drug interactions with budigalimab and/or ABBV-382 and other medications are unlikely. Further information can be located in the respective budigalimab and ABBV-382 Investigator's Brochures.

### Other Concomitant Therapy

For each participant, premedications for the purpose of preventing infusion-related reactions during IV administration of study drug should be avoided prior to the first infusion of the study drug, unless discussed with the AbbVie TA MD/SD. Premedications may be given prior to subsequent doses if a participant exhibits signs or symptoms of infusion-related reaction during the first infusion of the study drug. Additional guidance is provided in Section 6.2.

### Prior and Concomitant HIV-1 Therapy

Participants must be on a qualifying HIV-1 ART regimen (see Section 5.1). Participants will stop taking their ART regimen on Day 1. While ART can be restarted at the participants request as per ART restart criteria (see Section 5.7), participants should not restart ART on their own, without discussing first with the study investigator.


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## 5.5 Withdrawal of Participants and Discontinuation of Study

A participant may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the sponsor.
- The investigator believes it is in the best interest of the participant.
- The participant requests withdrawal from the study.
- Eligibility criteria violation was noted after the participant started study drug and continuation of the study drug would place the participant at risk.
- Introduction of prohibited medications (per Section 5.3) for which continuation of the study drug would place the participant at risk.
- The participant becomes pregnant while on study drug.
- The investigator determines the participant is significantly noncompliant with study procedures.

For participants who prematurely discontinue from the study before completing a minimum of 90 days of follow-up after the last study drug dose: the investigator should make reasonable attempts to follow the participant for safety including collecting any potential emerging AEs (including irAEs) through at least 90 days after the last study drug dose. Those follow-ups will also document viral load resuppression after ART restart. The investigator should make every effort to obtain information on the emergence of any potential AEs and irAEs during the 30 days and 90 days after the last dose of study drug, either at a clinic visit or by telephone contact.

For participants to be considered lost to follow-up, reasonable attempts must be made to obtain information on the participant's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the participant's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at their site if they have safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

### Discontinuation of Study Drug for Study Drug-Related Adverse Events or Laboratory Abnormalities

Study drug must be permanently discontinued for participants experiencing the events listed below if assessed by the investigator as having a "reasonable possibility" of relationship to study drug (note: investigators should consult with the AbbVie TA MD regarding risk/benefit of permanently discontinuing study drug).

- Any Grade ≥ 2 drug-related infusion reaction, including bronchospasm, hypoxia, hypotension, hypertension, tachycardia, or bradycardia, regardless of duration.
- Any Grade ≥ 2 drug-related anaphylactic, cytokine release syndrome, or allergic reaction to study drug [redacted]


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- The participant becomes pregnant while on study drug.
- Any confirmed drug-related, immune-related adverse event of any grade per investigator evaluation (TA MD should be contacted immediately to discuss any suspected or confirmed immune-related adverse event).
- Drug-related liver function test abnormalities meeting the following criteria:
  - ALT or AST > 8 × ULN; OR
  - Confirmed ALT or AST > 5 x ULN for more than 2 weeks; OR
  - ALT or AST > 3 x ULN and total bilirubin > 2 × ULN (with mixed or direct predominance or INR > 1.5); OR
  - ALT or AST > 3 × ULN with presentation of related symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%).
- Participant met ART restart criteria and has restarted ART during the study drug dosing period.
- Any AE, laboratory abnormality, intercurrent illness, or behavior which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued study drug treatment.
- The investigator determines the participant is significantly noncompliant with study procedures.

Participants who are discontinued from study drug will be monitored during the Follow-Up Period for safety reasons (see Section 5.6).

## 5.6 Follow-Up After Participant Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, participants who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless participants have decided to discontinue the study participation entirely (withdrawal of informed consent). Participants should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a participant prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit should be completed as soon as possible, preferably within 2 weeks. In addition, if participant is willing, a 30-day and a 90-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs/irAEs have been collected and resolved.

In the event a participant withdraws consent from the clinical study, biomarker research will continue unless the participant explicitly requests analysis to be stopped. When AbbVie is informed the participant has withdrawn and no longer wishes biomarker samples research to continue, samples will not be analyzed, and no new biomarker analysis data will be collected for the withdrawn participant or added to the existing data or database(s). A participant may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from clinical study and/or optional biomarker research, before participant withdrawal of consent, will remain part of the study results.


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## 5.7 ART Restart

Participants meeting at least one of the following ART restart criteria should re-initiate ART use:

1. Confirmed HIV-1 viral load ≥ 100,000 copies/mL (defined as 2 consecutive measurements). Confirmatory testing for the viral load criteria should be completed as soon as possible, but not earlier than 5 days from the previous test.
2. HIV-1 viral load ≥ 10,000 copies/mL (confirmed over a 4-week (28-day) period).
3. HIV-1 viral load ≥ 1,000 copies/mL (confirmed over a 6-week (42-day) period).
4. Confirmed absolute CD4 count < 350 cells/µL (defined as 2 consecutive measurements). Confirmatory testing for the CD4 criteria should be completed as soon as possible but not earlier than 5 days from the previous test.
5. Grade ≥ 3 RRS during ATI.
6. Pregnancy.
7. Any AE which, in the judgment of the investigator, presents a substantial clinical risk to the participant to continue ATI.
8. Any social or behavioral condition which, in the judgement of the investigator, presents a substantial clinical risk to the participant to continue ATI, including participant's request.

All participants will remain off ART until the end of the study, unless at any time they meet ART restart criteria. For instances where a participant's HIV-1 viral load and/or CD4 measurements meet the threshold for ART restart only intermittently during the relevant time period, the investigator should consult with the AbbVie TA MD/SD regarding potential restart of ART.

Participants who have not met ART restart criteria by the end of the study should discuss with the investigator about potential risks (to the participant and any HIV negative partner(s)) of remaining off ART beyond the last study visit.

### Monitoring Following ART Restart

For ART restart, participants should be re-initiated on the same ART regimen they were taking prior to ART interruption and continue to attend the scheduled study visits as per Activity Table. Plasma HIV-1 levels will be checked closely to monitor for viral re-suppression (defined as confirmed plasma HIV-1 RNA levels < LLOQ); plasma HIV-1 RNA assays to confirm re-suppression may be conducted as an unscheduled visit. Additional plasma HIV-1 RNA levels may be checked per discussion between the AbbVie TA MD/SD and the investigator. The site should notify the AbbVie TA MD/SD if the investigator uses an ART regimen that is different than the ART regimen the participant was taking prior to ART interruption or changes the ART regimen for a participant at any time after ART restart. Any ART use must be appropriately documented in EDC.

The investigator/site should discuss with the AbbVie TA MD/SD a plan for continued monitoring as needed for participants who have not achieved confirmed viral re-suppression following ART restart by Week 112.


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### Virologic Failure Criteria Following ART Restart

Virologic failure following re-initiation of ART 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. Confirmatory testing should be completed as soon as possible, OR
- Failure to reach re-suppression (as defined in preceding section above) within 24 weeks after ART restart.

Clinical management of confirmed virologic failure during the study will be handled by the investigator according to current HIV treatment guidelines and local standard of care. The site should notify the AbbVie TA MD/SD if the investigator changes the HIV-1 ART regimen for a participant. Further guidance is found in the Operations Manual, Section 3.18.

A participant should remain on his/her current ART regimen while the virologic failure is being confirmed.

ART adherence should also be assessed. A confirmatory HIV-1 RNA and HIV-1 genotypic resistance blood draw can be done as an unscheduled visit. However, if this blood draw falls on the date of a scheduled study visit, only a single HIV-1 RNA and HIV-1 genotypic resistance blood draw needs to be performed at this visit. If the participant's repeat HIV-1 RNA is < 200 copies/mL, then the participant will resume routine plasma HIV-1 RNA assessments as indicated in the Activity Schedule (Appendix D).

## 5.8 Study Drug

[redacted] will be administered via IV or SC Q2W beginning on Day 1 (baseline). The study drug can be administered with or without food.

Placebo for budigalimab IV will be a solution of 0.9% sodium chloride for infusion.

ABBV-382 or matching placebo manufactured by AbbVie will be administered via IV Q4W beginning on Day 1 (baseline). The study drug can be administered with or without food.

On Day 1 and Week 4 when budigalimab and ABBV-382 are administered on the same day, budigalimab or its placebo should be administered prior to ABBV-382. A monitoring interval of 1 hour is planned between completion of budigalimab administration and start of ABBV-382 administration, as well as after ABBV-382 administration. Details on dose preparation and administration instructions, infusion management, and time of infusion including blinding of the study drugs are in the operational manual and will be provided in a separate dose preparation and administration manual.

AbbVie will provide study drug for budigalimab (for IV or SC use) and ABBV-382 or matching placebo (Table 2). AbbVie provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.


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## Table 2. Identity of Study Drugs

| | Investigational Products | | | |
|---|---|---|---|---|
| | **Budigalimab (ABBV-181)** | **Placebo for Budigalimab IV (ABBV-181) 0.9% Sodium Chloride or DILUENT** | **ABBV-382** | **Matching Placebo for ABBV-382** |
| **Dosage form** | Powder for solution for infusion/injection | Solution for infusion | Solution for infusion | Solution for infusion |
| **Manufacturer** | AbbVie | Various, locally sourced by clinical site | AbbVie | AbbVie |
| **Strength (mg)** | [redacted] mg/vial | N/A | [redacted] mg [redacted] mL vial | N/A |
| **Route of administration** | IV or SC | IV | IV | IV |

IV = intravenous; N/A = not applicable; SC = subcutaneous

Note: 0.9% sodium chloride (USP or comparable locally approved alternative) will be administered to those participants not receiving budigalimab and as a vehicle for administration. Placebo for budigalimab (0.9% sodium chloride) will be supplied as commercially available material in either bags or bottles. However, if mandated by local regulation or in case of exceptional circumstance when sites are unable to procure on their own, AbbVie may supply 0.9% sodium chloride, if necessary.

Budigalimab (ABBV-181) IV and SC, ABBV-382, and matching placebo for ABBV-382 will be packaged in vials with quantities sufficient to accommodate study design. Placebo for budigalimab IV (0.9% sodium chloride) will be supplied as commercially available material in either bags or bottles.

Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number.

The IRT will assign the appropriate kits to a designated unblinded pharmacist or other appropriately trained unblinded site personnel at each study drug dispensing visit. Site staff will complete all blank spaces on the label before dispensing to participants. Study drug will only be used for the conduct of this study.

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs) will be returned to the sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug accountability procedures.

AbbVie will provide instructions for drug preparation.


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## 5.9 Randomization/Drug Assignment

All participants will be assigned a unique identification number by the IRT at the screening visit. For participants who rescreen, the screening number assigned by the IRT at the initial screening visit should be used.

For participants who are eligible for randomization, the IRT will assign a randomization number that will encode the participant's treatment arm assignment according to the randomization schedule.

At the start of the study, eligible participants will be randomized in a 1:1:1:2:2 randomization ratio to Arms A, B, C, D, or E:

- Arm A: Placebo
- Arm B: Budigalimab [redacted] mg IV
- Arm C: ABBV-382 [redacted] mg IV
- Arm D: Budigalimab [redacted] mg 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 [redacted] Eligible participants will be assigned to the open-label [redacted]

- [redacted] Budigalimab [redacted] mg [redacted]

For Arms A to E, the investigator, study site personnel (other than the unblinded pharmacist or designee), and the participant will remain blinded to each participant's treatment assignment and the PD-1 and a4b7 receptor saturation panel data throughout the study. The IRT will provide direct access to the investigator(s) to unblind participant treatment information in the case of a medical emergency. The IRT system can be used by the investigator(s) 24 hours a day, 7 days per week, without any prior contact with AbbVie.

Selected AbbVie personnel, described in Section 7.6, will remain blinded to each participant's treatment assignment and to the PD-1 and a4b7 receptor saturation panel data until the Week 12 interim analysis for Arms A to E. All other AbbVie personnel with direct oversight of the conduct and management of the trial will remain blinded to each participant's treatment assignment and to the PD-1 and a4b7 receptor saturation panel data until the database for the primary analysis (Week 24) for Arms A to E is locked.

## 5.10 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study participants. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified), including those that may be due to the COVID-19 pandemic or outbreaks that disproportionately affect PLWH, the investigator is responsible for IEC/IRB, regulatory authorities (as applicable), and AbbVie.


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## 5.11 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 potentially 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 (irAEs, infusion-related reactions, injection site reactions, hepatic-related events), RRS during ATI, study drug discontinuations, laboratory values, vital sign values, and ECG results (if conducted postbaseline).

A separate DMC charter will be prepared outside of the protocol and will further describe the roles and responsibilities of the DMC members, frequency and scope of the data reviews, and expectations for blinded communications.

## 5.12 Independent External Hepatic Event Committee

An independent external Hepatic Event Committee, comprised of DILI experts, will review blinded cases meeting hepatoxicity criteria suspicious for DILI, if applicable, consistent with the FDA DILI Guidance for Industry (see Section 6.2). A Hepatic Event Committee charter, separate from the DMC charter, describes the roles and responsibilities of the members, expectations for review and determination of causality assessment for each case, and meeting summarization.

## 5.13 Publication Policy

AbbVie as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and sponsor personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final clinical study report of the multicenter study except as agreed with the sponsor.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.


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Investigators are NOT employed by the organization sponsoring the study. There is an agreement between investigators and the sponsor (or its agents) that restricts the investigator's rights to discuss or publish study results after the study is completed.

AbbVie requests that any investigator or institution that plans on presenting/publishing results, provide written notification of their request 60 days prior to their presentation/publication. AbbVie requests that no presentation/publication will be instituted until 12 months after a study is completed or after the first presentation/publication, whichever occurs first. A delay may be proposed for a presentation/publication if AbbVie needs to secure patent or proprietary protection.

# 6 SAFETY CONSIDERATIONS

## 6.1 Complaints and Adverse Events

### Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

### Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie. All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

### Medical Complaints/Adverse Events and Serious Adverse Events: Budigalimab and ABBV-382

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with


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this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

The investigators will monitor each participant for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If any of the following events are reported, then a supplemental report (eCRF) must be completed: irAEs, infusion-related reactions, injection site reactions, hepatic-related AEs, and RRS during ATI.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as an SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

| | |
|---|---|
| **Death of Participant** | An event that results in the death of a participant. |
| **Life-Threatening** | An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form. |
| **Hospitalization or Prolongation of Hospitalization** | An event that results in an admission to the hospital for any length of time or prolongs the participant's hospital stay. This does not include an emergency room visit or admission to an outpatient facility. |
| **Congenital Anomaly** | An anomaly detected at or after birth, or any anomaly that results in fetal loss. |


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| | |
|---|---|
| **Persistent or Significant Disability/Incapacity** | An event that results in a condition that substantially interferes with the activities of daily living of a study participant. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle). |
| **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** | An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the participant and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of participant, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event along with any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug use disorder. |

All AEs reported from the time of study drug administration until Week 24 will be collected, whether solicited or spontaneously reported by the participant. After Week 24, only spontaneously reported SAEs, AESIs, RRS during ATI, and any AE that led to ART restart will be collected (nonserious AEs that are not AESIs and have not led to ART restart will not be collected). In addition, study procedure-related serious and nonserious AEs will be collected from the time the participant signs the study-specific informed consent.

The following definitions will be used for SAR and SUSAR:

| | |
|---|---|
| **SAR** | Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above. |
| **SUSAR** | Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information) and meets one of the above serious criteria. |

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements, including reporting to the EudraVigilance database in accordance with EU Clinical Trial Regulation. AEs will be monitored throughout the study to identify any that may indicate a trend or risk to participants.


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## Safety Topics of Interest

The following AESIs will be monitored during the study: irAEs, infusion-related reactions (Arms A to E only), injection site reactions (Arm F only), and hepatic AEs/laboratory abnormalities.

RRS also will be monitored during the ATI period. A special supplemental eCRF is to be completed for each of these events.

| Safety Topics of Interest[a] | Supplemental Report |
|---|---|
| Retroviral Rebound Syndrome during ATI (RRS)[b] | RRS eCRF |
| **Adverse events of special interest (AESIs)** | |
| Immune-related AE (irAE) | irAE eCRF |
| Infusion-related reaction (IRR) – Arms A to E only | IRR eCRF |
| Injection site reaction (ISR) - Arm F only | ISR eCRF |
| Hepatic-related AESI defined as:<br>• Any hepatic-related AE that led to discontinuation of study drug<br>• Any hepatic-related SAE<br>• Confirmed ALT or AST > 3 × ULN or > 3 x baseline (if baseline abnormal) OR confirmed total bilirubin > 1.5 × ULN or > 1.5 × baseline (if baseline abnormal) | Hepatic AE eCRF |

a. See Section 6.2 for further description and management of these events.

b. AEs consistent with RRS.

## Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE based on the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.1).

The investigator will use the following definitions to rate the severity of each AE when there are no specific DAIDS criteria available, including for grading RRS events:

| | |
|---|---|
| **Grade 1 (Mild)** | Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated. |
| **Grade 2 (Moderate)** | Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated. |
| **Grade 3 (Severe)** | Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated. |
| **Grade 4 (Potentially Life-Threatening)** | Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death. |

In addition, all AEs leading to death are to be classified as Grade 5.


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The investigator will use the following definitions to assess the relationship of the AE to the use of each study drug:

| | |
|---|---|
| **Reasonable Possibility** | After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship. |
| **No Reasonable Possibility** | After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship. |

### Pregnancy

While not an AE, pregnancy in a study participant must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Participants who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study participant or in the partner of a study participant, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a participant's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a participant's partners will be collected from the date of the first dose through 6 months following the last dose of study drug.

A pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

## 6.2 Toxicity Management

### Management of Suspected irAEs

Immune-related AEs are known AEs from checkpoint inhibitors (including anti-PD1 agents such as budigalimab). Data in oncology populations show that irAE may involve any organ or system of the body, however, GI, dermatologic, hepatic, endocrine, and pulmonary irAEs predominate. In cancer patients, the incidence and time to onset of irAEs vary based on the class (anti-PD-1 or PD-L1 antibodies having a lower incidence of any-grade irAEs when compared to anti-CTLA-4 agents). Also, time to onset varies from early occurrence (within days) to delayed onset up to 26 weeks, with a median onset of approximately 40 days.[37]

Table 3 includes some of the most common presentations of the irAEs described in the Oncology indication, by affected organ systems.[38]


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## Table 3. Immune-Related Adverse Events and Affected Organ Systems

| Organ System | Types of irAEs | |
|---|---|---|
| | Frequent | Rare or Infrequent |
| Cutaneous | Rash, pruritus, vitiligo | Acneiform rash, alopecia, bullous pemphigoid, papulopustular rosacea, psoriasis, Stevens-Johnson syndrome, toxic epidermal necrolysis, sweet syndrome |
| Gastrointestinal | Diarrhea, colitis, lichenoid mucositis | Enteritis, gastritis, pancreatitis |
| Endocrine | Hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis | Autoimmune type 1 diabetes, diabetic ketoacidosis (DKA), primary adrenal insufficiency |
| Hepatic | Transaminitis, hepatitis | |
| Respiratory | Pneumonitis | Pleuritis, sarcoidosis |
| Rheumatologic | Arthralgia, inflammatory arthritis, myalgia | Dermatomyositis, myositis, polymyalgia-like syndrome, Sjögren's syndrome, vasculitis |
| Renal | Increase in serum creatinine, nephritis | |
| Ocular | | Uveitis, conjunctivitis, scleritis, episcleritis, blepharitis, retinitis |
| Neurological | Sensorimotor neuropathy | Aseptic meningitis, autonomic neuropathy, encephalitis, facial nerve palsy, Guillain–Barré syndrome, myasthenia gravis, posterior reversible leukoencephalopathy, transverse myelitis |
| Hematological | | Aplastic anemia, hemolytic anemia, idiopathic thrombocytopenic, purpura, lymphopenia, hemophilia |
| Cardiac | | Cardiomyopathy, myocarditis, pericarditis |

The frequency and severity of irAEs in PLWH receiving immune checkpoint inhibitors at lower doses and shorter treatment durations than are used for oncology indications is still unknown. In this study, participants will be monitored frequently, as irAEs occurring at any time during the study will be collected. Investigators should be aware that irAEs can occur at any time during or after discontinuation of study drug therapy.

**General principles for management of suspected or confirmed immune-related adverse event during the study are:**

- Investigators should immediately contact the TA MD/SD to discuss all cases of suspected and/or confirmed irAEs.


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- Diagnosing an AE as an irAE (immune-related AE) can be challenging, and requires a comprehensive overall assessment including symptoms, clinical examination, laboratory abnormalities, changes in co-medications and medical history. Differential diagnosis should be promptly and diligently evaluated according to standard medical practice. Other etiologies should be considered and appropriately treated. Confirmation of the diagnosis of an irAE should be based on the investigator's judgment, taking into account clinical findings, complementary tests and specialist evaluation as appropriate. In certain circumstances, response of the AE to treatment and/or tissue biopsy may be helpful. However, depending on the grade/severity and affected organ system, treatment and/or restart of ART may be initiated before irAE confirmation, if clinically appropriate.
- An early consultation with a specialist may be helpful. Local practices and guidelines on diagnosing irAEs should be consulted.
- If immune-related adverse events occur during the **study drug dosing period** (Day 1 through Week 8), investigators should review the guidance in Section 5.5 regarding study drug discontinuation. If any irAE is confirmed, study drugs should be discontinued. For suspected, not yet confirmed, immune-related events, investigators should review appropriate local and/or international guidelines and contact the TA MD to discuss study drug discontinuation.
- Immune-related adverse events should be graded using the DAIDS grade system as per protocol (NIH DAIDS v2.1).
- Consultation with a medical or surgical specialist is required for any Grade ≥ 2 irAE and recommended for Grade 1 irAEs.
- A supplemental eCRF for an AE confirmed to be immune-related must be completed (Section 6.1).

Clinical management including treatment of irAEs should follow local guidelines and local clinical practice. Table 4 gives general guidance on management according to irAE grade. Corticosteroids are the primary therapy for most immune-related adverse events (with the exception of DKA where corticosteroids should not be used) and may need to be initiated promptly even for some suspected irAEs. Appropriate guidelines should be consulted for specific management guidance of the affected organ system.[37,38]


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### Table 4. General Recommendations for the Management of irAEs

| irAE Grade (DAIDS) | Recommendation |
|---|---|
| Grade 1 | Investigate and exclude other causes.<br>If laboratory abnormalities only, repeat testing for confirmation.<br>Closely monitor evolution for 1-2 weeks. Advise participant to report worsening symptoms immediately.<br>Symptom management, usually without systemic glucocorticoids.<br>Exception: Cardiovascular toxicity with symptoms compatible with myocarditis – Immediate treatment with systemic glucocorticoid may be needed. Consult appropriate specialist and local practices/ guidelines.<br>Exception: Neurologic or Ocular Toxicity – Immediately consult appropriate specialist and local practices/ guidelines. |
| Grade 2 | Investigate and exclude other causes. Consult with the appropriate specialist depending on the affected organ system.<br>Consider systemic glucocorticoid in addition to symptom management (except in suspicion of diabetic ketoacidosis). Refer to appropriate guidelines for the choice of glucocorticoid and dosing according to the affected organ system.<br>Monitor closely. If no improvement in 2–3 days, consider increasing glucocorticoid dose.<br>Once improved to at least grade 1, taper glucocorticoid slowly (4–6 weeks). |
| Grade 3–4 | Investigate and exclude other causes. Urgent consultancy with the appropriate specialist (depending on the affected organ system) if not yet done.<br>Evaluate clinical conditions and consider hospitalization if needed.<br>Require systemic glucocorticoid (usually high dose). Refer to appropriate guidelines for the choice of glucocorticoid and dosing according to the affected organ system.<br>If no improvement in 2–3 days, consider adding another immune suppressant, according to specific local guidelines/recommendations.<br>Once improved to at least G1, taper glucocorticoid slowly (4–6 weeks). |

irAE = immune-related adverse event

To ensure early recognition of symptoms of potential irAEs and appropriate and timely initiation of management of irAEs, investigators will receive training and training updates as needed and after significant guidelines changes.

## Management of Increases in ALT, AST, or Total Bilirubin

If a participant experiences a postbaseline increase in ALT or AST to > 3 × ULN (or > 3 × baseline if baseline abnormal) and/or a postbaseline increase in total bilirubin to > 1.5 × ULN (or > 1.5 × baseline if baseline abnormal), repeat testing should occur within 24 to 48 hours of all of the usual measures (ALT, AST, INR, alkaline phosphatase, total bilirubin [including direct and indirect bilirubin]) to confirm the abnormalities and to determine if they are increasing or decreasing. Inquiry regarding symptoms should also be made (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash). Participants may be retested locally, but normal laboratory ranges should be recorded and results provided to the investigator immediately. All data must be recorded in the eCRF.


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**All confirmed increases in ALT or AST to > 3 × ULN (or > 3 × baseline if baseline abnormal) or confirmed increase in total bilirubin to > 1.5 × ULN (or > 1.5 × baseline if baseline abnormal) must be reported as AEs, with relatedness to study drug recorded in the eCRF; a supplemental eCRF for this AESI must also be completed.**

If repeat testing shows ALT or AST > 3 × ULN (or > 3 × baseline if baseline abnormal) and/or total bilirubin > 1.5 × ULN (or > 1.5 × baseline if baseline abnormal), the recommendations below should be followed:

- Repeat liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the participant is asymptomatic.
- Obtain a more detailed history of symptoms and prior or concurrent diseases.
- Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune hepatitis (e.g., checking ANA, anti-smooth muscle antibodies, anti-neutrophil cytoplasmic antibodies); alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtain a history of exposure to environmental chemical agents.
- Obtain additional tests to evaluate liver function, as appropriate.
- Consider imaging (e.g., liver ultrasound) to evaluate for obstruction.
- Consider gastroenterology or hepatology consultations.

Investigators should also refer to Section 6.2 for guidance on management of suspected hepatic irAEs and immediately contact the AbbVie TA MD to discuss participants with these confirmed liver abnormalities.

Discontinuation of study drug may also apply (see Section 5.5).

All participants with these ALT, AST, and/or total bilirubin abnormalities should be followed until all abnormalities return to normal or to the baseline state.

### Management of Infusion-Related Reactions (Arms A to E only)

For each participant, premedications for the purpose of preventing infusion reactions during IV administration of study drug should be avoided prior to the first infusion of the study drug, unless discussed with the AbbVie TA MD.

Premedications such as acetaminophen/paracetamol, diphenhydramine, H2-blockers, or steroids (e.g., 50 mg diphenhydramine, 50 mg ranitidine, and 500 to 1000 mg acetaminophen) may be given prior to the subsequent dose(s) if a participant exhibits signs or symptoms of infusion reaction during the first infusion of study drug. The subsequent dose should be started at an infusion rate no higher than the maximum tolerated infusion rate of the prior infusion(s).


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In the event of a suspected allergic reaction, anaphylaxis or cytokine release syndrome related to the infusion, the infusion should be interrupted or stopped, close observation should be initiated, management should be initiated per Table 5, and institutional standard supportive care should also be administered. Refer to the pharmacy manual for further information on suggested changes to the infusion rate, maximum infusion time/duration, and approach to subsequent infusions (when applicable), for any participant for whom permanent discontinuation of study drugs is not required.

For any participants from whom permanent discontinuation of the first study drug infusion was needed due to AE ≥ Grade 2, infusion of the second study drug and any subsequent infusions of study drugs should also be discontinued (see Table 5).

### Management of Injection Site Reactions (ISR) - Arm F only

For each participant, premedications for the purpose of preventing injection site reactions during SC administration of study drug should be avoided prior to the first injection of the study drug, unless discussed with the AbbVie TA MD.

Premedications, such as acetaminophen/paracetamol, diphenhydramine, H2-blockers, or steroids (e.g., 50 mg diphenhydramine, 50 mg ranitidine, and 500 to 1000 mg acetaminophen) may be given prior to the subsequent dose(s) if a participant exhibits signs or symptoms of reaction during the first injection of study drug.

If an anaphylactic, allergic, or cytokine release syndrome reaction Grade 2 or higher related to the injection occurs, it should be managed with appropriate medical therapy, such as diphenhydramine, H2-blockers, albuterol, or steroids as per local guidelines or per institutional standard of care (see Table 5). Subsequent doses should NOT be administered, and study drug should be discontinued permanently (see Section 5.5).

Other signs/symptoms of injection site reactions (e.g., pain, erythema, swelling, pruritus, bleeding) should be managed with appropriate medical therapy as per local standard of care, as applicable. For all ISR Grade 2 or higher, a supplement eCRF must be completed (Section 6.1). Study drug need not be discontinued for these types of reactions.


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## Table 5. General Recommendations for the Management of Allergic Reaction, Cytokine Release Syndrome or Anaphylaxis Related to Investigational Drug(s) Infusion or Injection

| Grade of allergic, anaphylactic, or CRS IRR[a] or ISR | Intervention for reactions to the study drug |
|---|---|
| **If reaction is observed during an infusion/injection:** | |
| Grade 1<br>Transient symptoms;[b] resolves with interruption of study drug; does not require any additional intervention | • Stop infusion/injection of study drug if not yet completed.<br>• If intervention (including medical therapy) is needed, it should be administered, and the event should be considered Grade 2 at a minimum. In this case, subsequent infusions or additional injections should not be completed.<br>• Only if symptoms have resolved without intervention, within a period that still allows the drug to be infused within the maximum infusion time, continuation of treatment is allowed. Please verify pharmacy manual for information on study drug maximum infusion time. |
| Grade 2<br>Requires intervention in addition to study drug interruption; responds quickly to intervention (e.g., antihistamines, corticosteroids, etc.) | • Permanently discontinue all study drugs<br>• Appropriate medical therapy should be administered (such as diphenhydramine, H2-blockers, albuterol, or steroids as per local guidelines or per institutional standard of care). |
| Grade ≥ 3<br>Not rapidly responsive to additional intervention; recurrent after initial improvement; requiring emergent intervention due to life-threatening consequences (e.g., anaphylaxis, anaphylactic shock) | • Permanently discontinue all study drugs<br>• If clinical concern for anaphylaxis,[c] immediate management should include:<br>  • Calling for additional medical assistance as soon as possible (e.g., for potential transfer to emergency room).<br>  • Secure intravenous access and fluid resuscitation.<br>  • Intramuscular injection of epinephrine 0.01 mg/kg (1 mg/mL dilution, to a maximum total dose of 0.5 mL) into lateral thigh muscle. Can be repeated every 5 – 15 minutes.<br>  • Combination of H1 and H2 antagonist[d]<br>  • Administration of albuterol inhaler if patient develops wheezing and or shortness of breath. |
| **If reaction is observed after completion of an infusion/injection:** | |
| **Any Grade** | • Participants with any new signs or symptoms suggestive of allergic reaction, anaphylactic reaction, or cytokine release syndrome due to an infusion or injection during the post-infusion/post-injection monitoring period(s) should undergo clinical monitoring as dictated by the participant's clinical status and/or the opinion of the investigator.[e]<br>• Supportive treatment should be initiated as described in the sections above. |


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| Grade of allergic, anaphylactic, or CRS IRR[a] or ISR | Intervention for reactions to the study drug |
|---|---|
| | • If the reaction is grade 2 or higher, as per guidance above, all study drugs should be permanently discontinued. |

a. The AE of infusion-related reaction is not specifically described in NIH DAIDS v2.1. Consequently, grading of infusion-related reactions in this study are based on the criteria in NIH DAIDS2 v2.1 for the AE of cytokine release syndrome or allergic reactions and the criteria in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 5.0) for the AE of infusion-related reaction.

b. Common signs and symptoms include fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, back or abdominal pain, nausea, vomiting and/or diarrhea, skin rashes.

c. Example of diagnostic criteria for anaphylaxis can be found in Table 2 of the following manuscript – Rosello, et al. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. 2017. Annals of Oncology 28 (Supplement 4): iv 100-iv118.

d. For example, diphenhydramine (1 – 2 mg/kg or 25–50 mg) given slowly via IV in combination with ranitidine (50 mg diluted in 5% dextrose to a total volume of 20 mL) injected IV over 5 min.

e. Additional supportive care measures (e.g.. oxygen supplementation, airway protection) should be provided as needed.

### Management of Potential Toxicities Associated with ART Interruptions

Among chronic HIV-infected participants who undergo an ART interruption and experience viral rebound, a minority experience symptom similar to those of acute HIV disease. This "retroviral rebound syndrome," or RRS, is a mononucleosis-like illness characterized by signs and symptoms that include malaise, fever, headache, lymphadenopathy, rash, sore throat, myalgia or arthralgia, unintentional weight loss, night sweats and diarrhea.[31] Rarely, this RRS may be severe enough to warrant hospitalization.[39,40]

In this study, participants will be monitored continuously for occurrence of adverse events consistent with RRS while undergoing ART interruption. For suspected RRS, prompt and comprehensive evaluation will be performed to confirm RRS or exclude other causes. Participants with RRS Grade 3 or higher (or with any RRS symptom Grade 3 or higher) will immediately restart ART; a supplemental eCRF must also be completed (Section 6.1).

If there is a clinical suspicion or known exposure to STIs during the study, PI should make efforts to confirm the infection. Treatment should be managed as per local guidelines. Counseling on risks of HIV and other STI transmission, particularly during ATI period should be reinforced. The investigator should discuss with the participant if continuing ATI could pose a risk to the participant and/or to participant's partner(s) and assess for ART restart.

# 7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

## 7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and secondary analyses. Complete and specific details of the statistical analysis will be described in the SAP.


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Analyses of eCOAs will be further described in the SAP. Descriptive, summary statistics at each collected visit will be provided for the change from baseline in EQ-5D-5L health index and VAS scores, HIVTSQs and HIVTSQc, and HAT-QoL by treatment arm.

An interim analysis will be conducted after all participants in Arms A to E have completed Week 12 or prematurely discontinued prior to Week 12 (to occur approximately 4 weeks after last participant last dose in Arms A to E). Further details on this interim analysis and additional interim analyses are described in Section 7.6.

The primary analysis for Arms A to E will be conducted after all participants in Arms A to E have completed Week 24 or prematurely discontinued study prior to Week 24 and the database has been locked. The primary analysis will be unblinded to the sponsor.

The final analysis will occur after all participants across all treatment arms (Arms A to F) have completed (at Week 112) or prematurely discontinued from the study and the database has been locked.

Study sites and participants should remain blinded to participant randomization assignment for the duration of the study.

## 7.2 Definition for Analysis Populations

The ITT population will include all randomized participants who receive at least 1 dose of study drug. Participants will be analyzed according to the treatment group as randomized. The ITT population will be used for all efficacy analyses. The 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) and 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.

## 7.3 Handling Potential Intercurrent Events for the Primary and Secondary Endpoints

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.

## 7.4 Statistical Analyses for Efficacy

Efficacy endpoints will be analyzed using the ITT population. The mITT population will be used for supplementary analyses of efficacy. Details on the efficacy analyses will be provided in the SAP.


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### Summary and Analysis of the Primary Endpoint

The difference in the proportion of participants who achieve viral control (viral load < 1000 copies/mL) without ART restart at Week 24 between each active treatment arm and placebo (Arms A to E) will be compared using the Mantel-Haenszel chi-squared test. For the primary analysis, if viral load is missing at Week 24, then available viral load measurements after Week 24 while off ART will be used to impute missing data (backward imputation). If no other viral load measurements are available, then NRI will be used to impute missing viral load data. A supplementary analysis will be conducted on the mITT population. Point estimates of the difference (vs. placebo) in proportions will be provided, along with 90% CIs for the difference and p-values.

Proportions and confidence intervals will also be provided for each individual treatment arm (Arms A to F).

### Summary and Analysis of Secondary Endpoints

The difference in median peak viral load (at rebound, before restarting ART) between each active treatment arm and placebo (Arms A to E) will be analyzed using a Wilcoxon rank sum test. Additionally, 90% CIs and p-values will be provided for each difference, along with means and 90% CIs for each individual treatment arm (Arms A to F).

The median time to rebound to ≥ 1000 copies/mL during ART interruption in each treatment arm will be analyzed using the Kaplan-Meier (KM) method. 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. Kaplan-Meier summaries, including KM curves, with the median, quartiles, and range will be provided for each treatment arm.

### Summary and Analysis of Additional Efficacy Endpoints

- The Mantel-Haenszel chi-squared test will be used to analyze other binary endpoints, for the differences in proportions for Arms A to E.
- The same method (KM) described in the above section "Summary and Analysis of Secondary Endpoints" 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 of ART interruption.
- Descriptive statistics will be presented by treatment arm for the proportion of participants with viral re-suppression after ART restart.

### Subgroup Analysis for Efficacy

Subgroup analyses will be performed on the primary endpoint or other selected endpoints, with details specified in the SAP.

Subgroups of interest include, but are not limited to, the following:

- Age


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- Race
- Country
- Gender identity
- Baseline CD4 count
- Baseline CD4:CD8 ratio
- Baseline ART regimen
- Time since HIV-1 diagnosis
- Time to ART start following diagnosis
- HIV-1 subtype
- Comorbidities

## 7.5 Statistical Analyses for Safety

Safety data will be analyzed using the Safety Analysis Set, where participants will be assigned to a treatment group based on the actual treatment received, regardless of the treatment randomized.

Further details on safety endpoints will be provided in the SAP including:

- Frequency and severity of AEs;
- Drug-related Grade 3 or higher AEs;
- AESIs (irAEs, infusion-related reactions, injection site reactions, and hepatic-related AEs);
- RRS during ATI;
- Hepatic-related laboratory events;
- Virologic failure following ART restart.

## 7.6 Interim Analysis

A planned, unblinded interim analysis will be conducted once all randomized participants in Arms A to E have reached Week 12 or prematurely discontinued. The objective of the interim analysis is to accelerate decisions on future development plans and no decisions regarding study conduct will be made based on this interim analysis. There is no intention of stopping the study early based on efficacy findings from the interim analysis. The intention is to follow all treated participants to the end-of-study (Week 112).

To conduct this unblinded interim analysis, the AbbVie TA MD and TA SD, study designated statisticians, statistical programmers, pharmacokineticist(s), pharmacovigilance representative, and virologist(s) will be unblinded to each participant's treatment assignment and will review unblinded efficacy, safety, and available PK/PD data from this interim analysis.


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An additional interim look will occur when all randomized participants in 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 (e.g., when all enrolled participants in Arm F have reached Week 12 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.

### Population PK and Exposure-Response Analyses

Interim (pre-database lock) 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.

## 7.7 Overall Type I Error Control

As this is a Phase 2 trial, there will be no adjustments for multiplicity. All statistical tests will be 2-sided hypothesis tests performed at a nominal significance level of 0.1. All CIs will be 2-sided 90% CIs, unless stated otherwise.

## 7.8 Sample Size Determination




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# 8 ETHICS

## 8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

## 8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, EU Clinical Trial Regulation, ICH guidelines, other applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

## 8.3 Participant Confidentiality

To protect participants' confidentiality, all participants and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

For the personal data that AbbVie Deutschland GmbH & Co acting as sponsor of the submitted study ("AbbVie") controls and maintains, AbbVie has developed a robust security program focused on due diligence in design, managed change, and information security governance. Information Security policies govern the Information Security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's Information Security policies taking into account the sensitivity of the data.

Before participant data are shared with AbbVie, the study doctor and staff will replace any information that could directly identify a participant (such as name, address, and contact information) with a generic code which AbbVie cannot link to that participant's identity to protect the confidentiality of the data.

AbbVie has a data protection impact assessment program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains and these processing activities respect privacy of clinical trial participants. AbbVie also maintains robust security incident response policies and procedures, including requirements for the containment of any data related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.


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# 9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, EU CTR, ICH Good Clinical Practice (GCP), and other applicable local regulatory requirement(s).

# 10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human participant protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, EU Clinical Trial Regulation, ICH GCP, and other applicable regulatory requirements.

# 11 START AND COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of end-of-study participation by the last participant in the last country where the study was conducted (e.g., Week 112).

For EU CTR submissions, irrespective of the outcome of this study, within 1 year from the end of the clinical trial, the sponsor will submit to the EU database a summary of the trial results. The content of that summary will be done in compliance with the EU Clinical Trials Regulation.

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# APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

| Abbreviation | Definition |
|---|---|
| Ab | antibody |
| ADA | antidrug antibody |
| AE | adverse event |
| AESI | adverse event of special interest |
| AIDS | acquired immunodeficiency syndrome |
| ALT | alanine aminotransferase |
| ANA | antinuclear antibody |
| ART | antiretroviral therapy |
| AST | aspartate aminotransferase |
| ATI | Analytical Treatment Interruption |
| $AUC_{tau}$ | area under the concentration-time curve over the dosing interval |
| CD4+ | cluster of differentiation 4 |
| [redacted] | |
| CI | confidence interval |
| $C_{max}$ | maximum observed concentration |
| COPD | chronic obstructive pulmonary disease |
| DILI | drug induced liver injury |
| DLT | dose-limiting toxicity |
| DMC | Data Monitoring Committee |
| DNA | deoxyribonucleic acid |
| DRESS | drug reaction with eosinophilia and systemic symptoms |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EU CTR | European Union Clinical Trials Regulation |
| FDA | Food and Drug Administration |
| FIH | first-in-human |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| HBc | hepatitis B core |
| HBs | hepatitis B surface Ab |


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| | |
|---|---|
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HIV | human immunodeficiency virus |
| HTLV-1 | human T-cell lymphotropic virus type 1 |
| HTLV-2 | human T-cell lymphotropic virus type 2 |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IgG | immunoglobulin G |
| IgG1 | immunoglobulin G1 |
| IGRA | interferon gamma release assay |
| IMP | Investigational Medicinal Product |
| INR | international normalized ratio |
| irAE | immune-related AE |
| IRB | Institutional Review Board |
| IRR | infusion-related reaction |
| IRT | interactive response technology |
| ISR | injection site reaction |
| ITT | intention-to-treat |
| IU | International Unit |
| KM | Kaplan-Meier |
| LLOQ | lower limit of quantitation |
| mAb | monoclonal antibody |
| mITT | modified ITT |
| MS | multiple sclerosis |
| NIH | National Institutes of Health |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NRI | non-responder imputation |
| OR | odds ratio |
| PBMC | peripheral blood mononuclear cell |
| PD | premature discontinuation |
| PD-1 | programmed cell death 1 |
| PG-DNA | pharmacogenomic deoxyribonucleic acid |
| PG-RNA | pharmacogenomic ribonucleic acid |


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| | |
|---|---|
| PK | pharmacokinetic(s) |
| PLWH | people living with HIV |
| PO | orally (*per os)* |
| PrEP | pre-exposure prophylaxis |
| PRO | patient-reported outcome |
| PTC | post-treatment controllers |
| Q2W | every 2 weeks |
| Q4W | every 4 weeks |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| RNA | ribonucleic acid |
| RRS | Retroviral Rebound Syndrome |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAR | serious adverse reaction |
| SC | subcutaneous |
| SDAC | Statistical Data Analysis Center |
| SISCa | superficially invasive squamous cell carcinoma |
| STI | sexually transmitted infection |
| SUSAR | suspected unexpected serious adverse reactions |
| T4 | thyroxine |
| TA MD | Therapeutic Area Medical Director |
| TA SD | Therapeutic Area Scientific Director |
| TB | tuberculosis |
| TENS | toxic epidermal necrolysis |
| $T_{max}$ | time to maximum observed concentration |
| TSH | thyroid-stimulating hormone |
| ULN | upper limit of normal |
| VCAM-1 | vascular cell adhesion molecule 1 |
| VL | viral load |


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# APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol 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

Protocol Date: 19 July 2024

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP), as well as applicable laws, EU Clinical Trial Regulation, other regulations, and guidelines. Certain laws, regulations, or guidelines may apply to conduct of the study at investigator's site even if such laws, regulations, or guidelines originate in a foreign jurisdiction. The investigator agrees and acknowledges that applicable laws or regulations may require AbbVie to submit inspection reports, instances of significant non-compliance with the study protocol, or other documents regarding conduct of the study at the investigator's site to regulatory authorities, and such documents may be publicly disclosed by such authorities. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the participant from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all participants, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting the following to AbbVie within 1 calendar day of becoming aware:
    - Any unanticipated problems involving risks to human participants
    - Any departure from relevant clinical trial regulation, GCP, or the trial protocol that has affected or is likely to affect to a **significant** degree the following:
        - Rights, safety, physical or mental integrity of the participants in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
10. Where required by local regulation, inform relevant Ethics Committees / Institutional Review Boards and other appropriate individuals (e.g., Co-ordinating Investigator, Institution Director).
11. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

| | |
|---|---|
| Signature of Principal Investigator | Date |
| Name of Principal Investigator (printed or typed) | |


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# APPENDIX C. LIST OF PROTOCOL SIGNATORIES

| Name | Title | Functional Area |
|---|---|---|
| [redacted] | [redacted] | Clinical |
| | | Clinical |
| | | Statistics |


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# APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities. The individual activities are described in detail in the **Operations Manual**.


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## Study Activities Table 1 for Arms A to E from Screening to Week 52

| **Activity**<br>***Indicates no onsite visit required** | Screening<br>Day –35 to Day –1 | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **VISIT TYPE** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Required onsite visits for all participants | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | ✓ | ✓ |
| Required phone call visit (For participants who have re-started ART and have already met viral re-suppression criteria, no labs will be collected. For all other participants, labs will be collected locally or at home visit. Onsite visit allowed if preferred by the participant). | | | | | | | | | | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | | |
| **INTERVIEWS & QUESTIONNAIRES** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eligibility criteria (review on Day 1 visit prior to randomization) | ✓ | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |


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| Activity<br>*Indicates no onsite visit required | Screening<br>Day –35 to Day –1 | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Medical/surgical history (update on Day 1 visit) | ✓ | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Drug, alcohol, and nicotine use | ✓ | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adverse event assessment | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Record prior/concomitant therapy | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Counseling on Prevention of HIV Transmission | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| COVID-19 assessment and counseling | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | | | |
| PRO – HIVTSQ | | ✓ | | | | | | | | | | ✓ | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| PRO – HAT-QoL | | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| PRO – EQ-5D-5L | | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| **LOCAL LABS & EXAMS** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Chest x-ray | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 12-lead ECG | ✓ | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Height (screening only) and weight | ✓ | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |


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| Activity<br>*Indicates no onsite visit required | Screening<br>Day –35 to Day –1 | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vital signs | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | ✓ | ✓ |
| Physical examination | ✓ | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Urine pregnancy test | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | | ✓ | | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **CENTRAL LABS** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatitis B panel, HCV AB, HIV AB | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| FSH Test (postmenopausal women/person assigned female sex at birth) | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Serum pregnancy test | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| IGRA test | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Drug and alcohol screen | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Anti-thyroglobulin and anti-thyroid peroxidase antibody | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Total CK, Troponin-I, Coagulation panel | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |


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| Activity<br>*Indicates no onsite visit required | Screening<br>Day –35 to Day –1 | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
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| Lipid Profile, Hemoglobin A1C (HgbA1c) | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | ✓ | ✓ |
| ACTH and cortisol | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ANA | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinalysis | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Clinical chemistry, Hematology (CBC) | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | ✓ | ✓ |
| TSH, T4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | ✓ | ✓ |
| Plasma HIV-1 RNA | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| TBNK panel (if local only CD4 ± CD4:CD8) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Inflammatory markers: Hs-CRP, LDH, and D-Dimer | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | | ✓ | | ✓ | | | | ✓ | | | ✓ | | | | ✓ | ✓ |
| **PK & BIOMARKERS LABS** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood draw for budigalimab and ABBV-382 PK | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | | ✓ |
| ADA/NAb for budigalimab | | ✓ | | | | ✓ | | | | ✓ | | | | | | ✓ | | ✓ | | ✓ | | | ✓ | | | | | ✓ |
| ADA/NAb for ABBV-382 | | ✓ | | | | ✓ | | | | ✓ | | | | | | ✓ | | ✓ | | ✓ | | | ✓ | | | | | ✓ |


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| Activity<br>*Indicates no onsite visit required | Screening<br>Day –35 to Day –1 | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Whole blood: HIV tropism | | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Whole blood: Plasma HIV Tropism | | | Sample to be collected at the study visit after the first instance of plasma HIV-1 RNA ≥ 1000 cp/mL | | | | | | | | | | | | | | | | | | | | | | | | | |
| Whole blood: Plasma ART resistance | | | Sample to be collected once in each of the following situations: at the study visit after the first instance of plasma HIV-1 RNA ≥ 1000 cp/mL; at subsequent visit at the time the repeat plasma HIV-1 RNA is drawn; at second rebound after viral control and after virological failure if they occur (consult Section 3.18 of the Operations Manual). | | | | | | | | | | | | | | | | | | | | | | | |
| Whole blood: biomarker, PD-1 saturation | | ✓ | | ✓ | | | | | | | | ✓ | | | | | | | | | | | | | | | | ✓ |
| Whole blood: biomarker, a4b7 saturation | | ✓ | | ✓ | | | | | | | | ✓ | | | | | | | | | | | ✓ | | | | | ✓ |
| Whole blood: biomarker, immunophenotyping panel 1 | | ✓ | | | | | | | | ✓ | | | | ✓ | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Whole blood: biomarker, immunophenotyping panel 2 | | ✓ | | | | | | | | ✓ | | | | ✓ | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Whole blood: biomarker serum (cytokine/chemokine panel 1) | | ✓ | | | | | | | | ✓ | | | | ✓ | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Whole blood: biomarker serum (cytokine/chemokine panel 2) | | ✓ | | | | | | | | ✓ | | | | ✓ | | | | | | ✓ | | | | | | | ✓ | ✓ |


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| Activity<br>*Indicates no onsite visit required | Screening | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day –35 to Day –1 | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Whole blood: Biomarker PBMC-1 | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | | ✓ | | | | ✓ | | | ✓ | | | | ✓ | ✓ |
| Whole blood: Biomarker PBMC-2 | | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Whole blood: biomarker serum | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | ✓ | ✓ |
| Whole blood: biomarker plasma | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | ✓ | ✓ |
| Whole blood: biomarker PG-DNA | | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Whole blood: biomarker PG-RNA | | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Stool sample (optional) | | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | ✓ | |
| **STUDY DRUG ADMINISTRATION & PROCEDURES** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Randomization/drug assignment | | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Study drug administration (budigalimab or placebo) | | ✓ | | ✓ | | ✓ | | ✓ | | | | | | | | | | | | | | | | | | | | |
| Study drug administration (ABBV-382 or placebo) | | ✓ | | | | ✓ | | | | ✓ | | | | | | | | | | | | | | | | | | |
| Stop ART | | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |


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| Activity<br>*Indicates no onsite visit required | Screening<br>Day –35 to Day –1 | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Assess for ART restart | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

## Study Activities Table 2 for Arm F from Screening to Week 52

| Activity<br>*Indicates no onsite visit required | Screening<br>Day –35 to Day –1 | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **VISIT TYPE** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Required onsite visits for all participants | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | ✓ | ✓ |


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| Activity<br>*Indicates no onsite visit required | Screening<br>Day –35 to Day –1 | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Required phone call visit (For participants who have re-started ART and have already met viral re-suppression criteria, no labs will be collected. For all other participants, labs will be collected locally or at home visit. Onsite visit allowed if preferred by the participant). | | | | | | | | | | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | | |
| **INTERVIEWS & QUESTIONNAIRES** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eligibility criteria (review on Day 1 visit prior to randomization) | ✓ | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical/surgical history (update on Day 1 visit) | ✓ | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Drug, alcohol, and nicotine use | ✓ | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adverse event assessment | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |


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| Activity<br>*Indicates no onsite visit required | Screening<br>Day –35 to Day –1 | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Record prior/concomitant therapy | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Counseling on Prevention of HIV Transmission | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| COVID-19 assessment and counseling | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | | | |
| PRO – HIVTSQ | | ✓ | | | | | | | | | | ✓ | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| PRO – HAT-QoL | | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| PRO – EQ-5D-5L | | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| **LOCAL LABS & EXAMS** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Chest x-ray | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 12-lead ECG | ✓ | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Height (screening only) and weight | ✓ | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Vital signs | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | ✓ | ✓ |
| Physical examination | ✓ | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Urine pregnancy test | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | | ✓ | | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **CENTRAL LABS** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatitis B panel, HCV AB, HIV AB | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |


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| Activity<br>*Indicates no onsite visit required | Screening<br>Day –35 to Day –1 | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FSH Test (postmenopausal women/person assigned female sex at birth) | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Serum pregnancy test | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| IGRA test | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Drug and alcohol screen | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Anti-thyroglobulin and anti-thyroid peroxidase antibody | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Total CK, Troponin-I, Coagulation panel | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lipid Profile, Hemoglobin A1C (HgbA1c) | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | ✓ | ✓ | |
| ACTH and cortisol | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ANA | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinalysis | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Clinical chemistry, Hematology (CBC) | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | ✓ | ✓ |
| TSH, T4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | ✓ | ✓ |
| Plasma HIV-1 RNA | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |


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| Activity<br>*Indicates no onsite visit required | Screening<br>Day –35 to Day –1 | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TBNK panel (if local only CD4 ± CD4:CD8) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Inflammatory markers: Hs-CRP, LDH, and D-Dimer | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | | ✓ | | ✓ | | | | ✓ | | | ✓ | | | | ✓ | ✓ |
| **PK & BIOMARKERS LABS** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood draw for budigalimab PK | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | | | | | | | | ✓ |
| ADA/NAb for budigalimab | | ✓ | | | | ✓ | | | | ✓ | | | | | | ✓ | | ✓ | | ✓ | | | ✓ | | | | | ✓ |
| Whole blood: Plasma ART resistance | | | **Sample to be collected once in each of the following situations: at the study visit after the first instance of plasma HIV-1 RNA ≥ 1000 cp/mL; at subsequent visit at the time the repeat plasma HIV-1 RNA is drawn; at second rebound after viral control and after virological failure if they occur (consult Section 3.18 of the Operations Manual).** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Whole blood: biomarker, PD-1 saturation | | ✓ | | ✓ | | | | | | ✓ | | ✓ | | ✓ | | ✓ | | | | | | | | | | | | ✓ |
| Whole blood: biomarker, immunophenotyping panel 3 | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Whole blood: biomarker serum (cytokine/chemokine panel 1) | | ✓ | | | | | | | | ✓ | | | | ✓ | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Whole blood: biomarker serum | | ✓ | | | | | | | | ✓ | | | | ✓ | | | | | | ✓ | | | | | | | ✓ | ✓ |


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| Activity<br>*Indicates no onsite visit required | Screening<br>Day –35 to Day –1 | Day 1 (Dose 1) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9* | Week 10 | Week 11* | Week 12 | Week 14* | Week 16 | Week 18* | Week 20 | Week 22* | Week 24 | Weeks 26 and 28* | Weeks 30, 32, and 34* | Week 36 | Weeks 38, 40, and 42* | Week 44* | Weeks 46, 48, and 50* | Week 52 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (cytokine/chemokine panel 2) | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Whole blood: Biomarker PBMC-1 | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | | ✓ | | | | ✓ | | | ✓ | | | | ✓ | ✓ |
| Whole blood: Biomarker PBMC-2 | | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Whole blood: biomarker serum | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | ✓ | ✓ |
| Whole blood: biomarker plasma | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | | | ✓ | ✓ |
| Whole blood: biomarker PG-DNA | | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| Whole blood: biomarker PG-RNA | | ✓ | | | | | | | | | | | | | | | | | | ✓ | | | | | | | ✓ | ✓ |
| **STUDY DRUG ADMINISTRATION & PROCEDURES** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Enrollment/drug assignment | | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Study drug administration (budigalimab SC) | | ✓ | | ✓ | | ✓ | | ✓ | | | | | | | | | | | | | | | | | | | | |
| Stop ART | | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Assess for ART restart | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |


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## Study Activities Table 3 – Visits after Week 52 for Participants in All Arms (A to F)

| **Activity**<br>***Indicates no onsite visit required** | Weeks 54, 56, and 58* | Week 60* | Weeks 62, 64, and 66* | Week 68 | Weeks 70, 72, and 74* | Week 76* | Weeks 78, 80, and 82* | Week 84 | Weeks 86, 88, and 90* | Week 92* | Weeks 94 and 96* | Week 98 | Weeks 100, 102, and 104* | Week 106* | Weeks 108 and 110* | Week 112 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **VISIT TYPE** | | | | | | | | | | | | | | | | | |
| Required onsite visits for all participants | | | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | ✓ |
| Required visits only for participants who have not re-started ART or have restarted ART but have NOT met viral re-suppression criteria. For all other participants those visits are not required. Visits can be done on site or as a phone call with local laboratory testing or as a home health visit. | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | | |
| **INTERVIEWS & QUESTIONNAIRES** | | | | | | | | | | | | | | | | | |
| Assessment of AESIs (including suspect irAEs), SAEs, special situation AEs, and any AE that triggers ART restart | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | ✓ |
| Record new concomitant therapy | | | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | ✓ |
| Counseling on Prevention of HIV Transmission | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Assess for ART restart (only participants OFF ART) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| PRO – HIVTSQ | | | | | | | | ✓ | | | | | | | | ✓ | ✓ |
| PRO – HAT-QoL | | | | | | | | ✓ | | | | | | | | ✓ | ✓ |
| PRO – EQ-5D-5L | | | | | | | | ✓ | | | | | | | | ✓ | ✓ |
| **LOCAL LABS & EXAMS** | | | | | | | | | | | | | | | | | |
| Weight and vital signs | | | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | ✓ |
| Physical examination | | | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | ✓ |
| Urine pregnancy test (can also be collected at home/local lab on phone call visits) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |


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| **Activity**<br>***Indicates no onsite visit required** | Weeks 54, 56, and 58* | Week 60* | Weeks 62, 64, and 66* | Week 68 | Weeks 70, 72, and 74* | Week 76* | Weeks 78, 80, and 82* | Week 84 | Weeks 86, 88, and 90* | Week 92* | Weeks 94 and 96* | Week 98 | Weeks 100, 102, and 104* | Week 106* | Weeks 108 and 110* | Week 112 | Premature Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **CENTRAL LABS** | | | | | | | | | | | | | | | | | |
| Lipid Profile, Hemoglobin A1C (HgbA1c) | | | | | | | | | | | | | | | | ✓ | ✓ |
| Clinical chemistry, Hematology (CBC) | | | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | ✓ |
| TSH, T4 | | | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | ✓ |
| Plasma HIV-1 RNA (can be collected in local lab at phone call visits) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| TBNK panel (can be collected in local lab at phone call visits - if local only CD4 ± CD4:CD8) | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | ✓ |
| Inflammatory markers: Hs-CRP, LDH, and D-Dimer | | | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | ✓ |
| **PK & BIOMARKERS LABS** | | | | | | | | | | | | | | | | | |
| Whole blood: Plasma ART resistance | **Sample to be collected once in each of the following situations: at the study visit after the first instance of plasma HIV-1 RNA ≥ 1000 cp/mL; at subsequent visit at the time the repeat plasma HIV-1 RNA is drawn; at second rebound after viral control and after virological failure if they occur (consult Section 3.18 of the Operations Manual).** | | | | | | | | | | | | | | | | |
| Whole blood: Biomarker PBMC-1 | | | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | ✓ |
| Whole blood: Biomarker PBMC-2 | | | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | ✓ |
| Whole blood: Biomarker serum | | | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | ✓ |
| Whole blood: Biomarker plasma | | | | ✓ | | | | ✓ | | | | ✓ | | | | ✓ | ✓ |


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# APPENDIX E. PROTOCOL SUMMARY OF CHANGES

| Protocol | Date |
|---|---|
| Version 1.0 | 26 June 2023 |
| Version 2.0 | 09 August 2023 |
| Version 3.0 | 06 October 2023 |
| Admin Change 1 (Japan Only) | 07 November 2023 |
| Version 3.1 (United Kingdom Only) | 21 February 2024 |
| Version 3.2 (European Union Only) | 28 February 2024 |

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to, but not limited to, the following:

- Throughout the protocol and the Operations Manual, modified study design to:
  - add a long-term extension to follow all participants in all arms to Week 112, and
  - add a new open-label treatment arm to evaluate budigalimab SC (Arm F).
- Throughout the protocol and the Operations Manual, incorporated safety language regarding PML.
- Throughout the protocol and the Operations Manual, incorporated versions of the protocol that resulted from regulatory interactions (administrative change 1 [Japan only], Version 3.1 [UK only], and Version 3.2 [EU only]).
  - Clarified contraception language as requested by the UK and EU.
  - Clarified conditions for when additional arm(s) may be added to the study as requested by the UK and EU.
  - Clarified ART restart criteria as requested by EU.
  - Added language pertinent to following EU CTR, including addition of Section 5.13 Publication Policy.
  - In Operations Manual, Section 2.1, added decentralized procedures details as requested by EU.
  - Clarified site unblinding details as requested by the EU.
- SYNOPSIS - Removed Denmark and Sweden from study sites in the synopsis.
- Section 2.2 and Section 4.2 – Added results from Study M19-972 (budigalimab SC).
- Section 3.4 – Added additional efficacy endpoint on viral control based on study extension.
- Section 4.1, Section 5.9, and Section 7 – Clarified details on interim analyses.
- Section 5.1 – Updated select eligibility criteria.
- Section 6.2 – Added management of injection site reactions for Arm F.


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- Section 7.6 – Added interim looks based on study extension and new treatment arm (Arm F).
- Appendix D Activity Schedule for Arms A to E from Screening to Week 52 and Operations Manual, Section 2.2:
  - Added Whole blood[a]: HIV tropism and Plasma ART Resistance: **IF** 1st instance HIV VL ≥1,000cps/mL to the appropriate visits.
  - Removed COVID-19 assessments after Week 24.
  - Added lipid profile and Hemoglobin A1C (HgbA1c) to Week 52 and PD visit.
  - Added urinalysis to Weeks 2, 6, and 10.
  - Added clinical chemistry, hematology (CBC) to Week 10.
- Added Activity Schedule for Arm F from Screening to Week 52 and updated Operations Manual, Section 2.2 accordingly.
- Added Activity Schedule for All Arms for Visits after Week 52 and updated Operations Manual, Section 2.2 accordingly.
- Operations Manual, CONTACTS – Added Japan sites and Labcorp Development contact information.
- Operations Manual, Section 3.14, Section 3.16 and Section 3.18 – Added additional vital signs, chest x-ray, and clinical laboratory tests guidance.


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# APPENDIX F. OPERATIONS MANUAL


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# Operations Manual for Clinical Study Protocol M19-965

## HIV: Budigalimab and/or ABBV-382 in People Living with HIV on Stable Antiretroviral Therapy

| | | | |
|---|---|---|---|
| SPONSOR: | AbbVie Inc. | ABBVIE INVESTIGATIONAL PRODUCT: | Budigalimab and ABBV-382 |

FULL TITLE: 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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# 1 CONTACTS

| | | |
|---|---|---|
| Sponsor Contact/Therapeutic Area Scientific Director | [redacted]BSN, MPH<br>AbbVie Inc.<br>1 North Waukegan Road<br>North Chicago, IL 60064 | Office:<br>Mobile:<br>Fax:<br>Email: [redacted] |
| Emergency Medical Contact/Therapeutic Area Medical Director | [redacted] MD<br>AbbVie Inc.<br>1 North Waukegan Road, AP31-1<br>North Chicago, IL 60064<br><br>**EMERGENCY 24-hour Number:**<br>**+1 (973) 784-6402** | Office:<br>Mobile:<br>Fax:<br>Email: [redacted] |
| Safety Questions | Virology Safety Team | Phone: +1 (833) 942-2226<br>Email: SafetyManagement_Virology@abbvie.com |
| SAE Reporting outside of EDC | Email: PPDINDPharmacovigilance@abbvie.com | Fax: +1 (847) 806-2062 |
| Protocol Deviations and Product Complaints | [redacted]<br>AbbVie Inc.<br>1 North Waukegan Road, AP31-1<br>North Chicago, IL 60064 | Phone:<br>Fax:<br>Email: [redacted] |


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| | | |
|---|---|---|
| Certified Clinical Laboratory | North and South American Sites:<br>Labcorp Central Laboratory Services<br>8211 SciCor Drive,<br>Indianapolis, IN 46214 | Phone: +1 (317) 271-1200<br>Fax: +1 (317) 616-2362 |
| | Japan Sites:<br>CB Lab c/o BML General Laboratory<br>1361-1 Matoba, Kawagoe-shi<br>Saitama 350-1101, Japan | Japan Toll Free Line: 0120 123 905<br>Direct Line: +81 3 6837 9536<br>Fax: +81 3 5250 0360 |
| | Labcorp Development (Asia) Pte. Ltd.<br>1, International Business Park<br>#03-14 The Synergy<br>Singapore 609917 | Tel: +65 6560 8793<br>Fax: +65 6565 5901 |
| | All Other Sites:<br>Labcorp Central Laboratory Services S.À.R.L.<br>Rue Moïse-Marcinhes 7<br>CH – 1217 Meyrin/Genève<br>Switzerland | Phone: +41 58 822 7901<br>Fax: +41 58 822 7521 |
| PK Sample Laboratory | Regulated Bioanalysis<br>AbbVie Deutschland GmbH and Co KG<br>Knollstrasse<br>67061 Ludwigshafen, Germany | Phone: +49 621-589-3978<br>Email: [redacted]<br>Email: gprd_lupet@abbvie.com |


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# 2 PROTOCOL ACTIVITIES BY VISIT AND OPTIONAL DECENTRALIZED PROCEDURES

## 2.1 Optional Decentralized Procedures

To alleviate the burden of frequent visits to participants while maintaining close monitoring of HIV viral load and CD4 counts, especially for participants that continue on analytical treatment interruption, this study provides flexibility for certain visits that can be done virtually by phone call with blood collection either at a local certified laboratory or by a qualified home healthcare nurse in a non-hospital/clinic environment (e.g., the participant's home) or at alternative locations.

Offering decentralized visits options were planned considering the rights, safety, dignity and well-being of the study participants. Those visits can also be performed on-site per investigator discretion and/or participant preference.

The activities listed below will be conducted at the following visits at Week 9, Week 11, Week 14, Week 18, Week 22, Week 26, Week 28, Week 30, Week 32, Week 34, Week 38, Week 40, Week 42, Week 44, Week 46, Week 48, and Week 50. In addition, for participants who have not re-started ART or have restarted ART but have NOT met viral re-suppression criteria, the activities listed below may also be conducted at the following visits: Week 54, Week 56, Week 58, Week 60, Week 64, Week 66, Week 70, Week 72, Week 74, Week 76, Week 78, Week 80, Week 82, Week 86, Week 88, Week 90, Week 92, Week 94, Week 96, Week 100, Week 102, Week 104, Week 106, Week 108, and Week 110:

- Adverse Event Assessment (Site Required Phone Call, after Week 50 only required at Weeks 60, 76, 92, and 106)
- Record prior/Concomitant Therapy (Site Required Phone Call – Required only up to Week 50)
- Counselling on Prevention of HIV Transmission (Site Required Phone Call)
- COVID-19 Assessment and Counseling (Site Required Phone Call – Required only up to Week 22)
- Assess for ART restart (Site Required Phone Call)
- Plasma HIV-1 RNA ± TBNK Panel (if local only CD4 ± CD4:CD8) (collected locally or at home visit)
- HIV tropism and ART resistance samples can be collected if requirements for these tests have been met (collected only at home visit)
- Urine Pregnancy Test (Only once a month preferable at Weeks 28, 32, 40, 44, 48, 56, 60, 64, 72, 76, 80, 88, 92, 96, 100, 104, and 108). A serum pregnancy test sample is taken if urine pregnancy test is positive. (collected locally or at home visit)

For participants who have re-started ART and have already met viral re-suppression criteria, no laboratory samples will be collected and decentralized visits.


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**Home Health Care Option**

Prior to home visits being implemented, the site/PI should verify whether the study participant is willing to complete virtual/home visits; whether their home situation (including status disclosure) is suitable to have study related procedures performed at home, whether there are any potential additional risks to study participants in collecting samples at home or at a qualified local laboratory. The participant will be informed during the informed consent process about optional study procedures planned to take place at home. The Home Healthcare option is also documented in the Informed Consent Form.

Home visits would be executed by qualified staff contracted and trained for the study and delegated to perform the established procedures if allowed by local legislation. The Home Nurses will be qualified nurses who will visit the study participant at their home to complete the home procedures. The Home Nurse will collect the laboratory samples, prepare the samples for shipping and ship the samples to the central laboratory for analysis and reporting to the Investigational Site. AbbVie will provide study protocol and study requirement training to the Health Care Manager. The Health Care Manager will provide training to the Home Nurses. Primary nurses will be qualified, credentialed and trained. Back-up nurses will be qualified, credentialed and trained on an as needed basis. Qualified homecare nurses will sign the delegation of activity log prior to any activities being performed.

The investigator will maintain full oversight and will be informed of the laboratory results and any adverse events collected at decentralized visit procedures. The Home Nurse will be trained to check for hospitalizations, potential changes in health and/or concomitant medications at the beginning of and during all study visits. If any potential changes in Health are reported, the Home Nurse will immediately contact the designated contact at the investigator site and place the participant on the telephone with the investigator site staff. If the participant is in acute distress when the home health nurse is there, they will call emergency services and stay until they arrive.

This operational strategy is expected to eliminate physical visits to a clinical trial center for certain visits, reducing the burden on clinical trial participants, if they choose to not visit the clinical trial center. This will give the participants the option to eliminate the need to travel and allows participants more flexibility to fit the trial activities into their daily lives.

The addition of the home procedures does not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice, for subjects who agree to have laboratory samples drawn outside of the clinic. In addition, the home healthcare visit is not thought to significantly impact scientific validity, data integrity, benefit-risk ratio or impact on the protection of trial participants' rights.

Additional details are provided in Section 2.2.

During the ATI period, additional collection of HIV-RNA and/or CD4 count (unscheduled visits) can be performed at any time by participant or investigator request.


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## 2.2 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit and by period (Screening to Week 52 in subsection Visit Activities (Arms A to F from Screening to Week 52) and Week 54 to Week 112 in subsequent subsection.

Visit Activities (Arms A to F from Week 54 to Week 112). The dot pattern on the upper right indicates the place of the visit in the overall study period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3. It is important to note that some activities (as PK and biomarkers collection and drug administration) may differ from study part 1 (Arms A to E) and Arm F (second part of the study). Those differences are highlighted in the table whenever appropriate.

### Visit Activities (Arms A to F from Screening to Week 52)

SCREENING
(-35 to Day -1):



| | | |
|---|---|---|
| INTERVIEW | • Informed consent<br>• Inclusion/Exclusion criteria<br>• Medical/surgical history<br>• Drug, alcohol, and nicotine use<br>• Adverse event assessment | • Record prior/concomitant therapy<br>• Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| EXAM | • Chest x-ray<br>• 12-lead ECG<br>• Height and weight | • Vital signs<br>• Physical examination<br>• Urine pregnancy test |
| CENTRAL LAB | • Hepatitis B panel, HCV-AB, HIV-AB<br>• FSH Test (postmenopausal women/person assigned female sex at birth)<br>• Serum pregnancy test<br>• IGRA<br>• Drug and alcohol screen<br>• Anti-thyroglobulin and anti-thyroid peroxidase antibody<br>• Total CK, Troponin-I, Coagulation panel<br>• Lipid Profile, Hemoglobin A1C (HgbA1c) | • ACTH and cortisol<br>• ANA<br>• Urinalysis<br>• Clinical chemistry, Hematology (CBC)<br>• TSH, T4<br>• Plasma HIV-1 RNA<br>• TBNK panel |


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DAY 1:



| | | |
|---|---|---|
| INTERVIEW | • Inclusion/Exclusion criteria<br>• Medical/surgical history<br>• Drug, alcohol, and nicotine use<br>• Adverse event assessment | • Record prior/concomitant therapy<br>• Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| PRO | • HIVTSQ<br>• EQ-5D-5L | • HAT-QoL |
| EXAM | • 12-lead ECG<br>• Weight<br>• Vital signs | • Physical examination<br>• Urine pregnancy test |
| CENTRAL LAB | • Urinalysis<br>• Clinical chemistry, Hematology (CBC)<br>• TSH, T4 | • Plasma HIV-1 RNA<br>• TBNK panel<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer |
| PK AND BIOMARKERS LAB (Arms A to E) | • Blood draw for budigalimab and ABBV-382 PK<br>• ADA/NAb for budigalimab<br>• ADA/NAb for ABBV-382<br>• Stool sample (optional) | • Whole blood[a]: HIV tropism, PD-1 saturation, a4b7 saturation, immunophenotyping panel 1, immunophenotyping panel 2; biomarker serum (cytokine/chemokine panel 1), biomarker serum (cytokine/chemokines panel 2); PBMC-1, PBMC2, biomarker serum, biomarker plasma, PG-DNA, PG-RNA |


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| | | |
|---|---|---|
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK<br>• ADA/NAb for budigalimab | • Whole blood[a]: PD-1 saturation, immunophenotyping panel 3, biomarker serum (cytokine/chemokine panel 1), biomarker serum (cytokine/chemokines panel 2); PBMC-1, PBMC2, biomarker serum, biomarker plasma, PG-DNA, PG-RNA |
| TREATMENT | • Randomization/drug assignment for Arms A to E or Enrollment/drug assignment for Arm F<br>• Stop ART | **Arms A TO E ONLY:**<br>• Study drug IV administration (budigalimab or placebo)<br>• Study drug IV administration (ABBV-382 or placebo)<br>[redacted] |

a. Whole blood collections should be taken prior to dosing.

WEEK 1
(Day 8 ± 1 day):

| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| EXAM | • Vital signs | |
| CENTRAL LAB | • TSH, T4<br>• Plasma HIV-1 RNA | • TBNK panel |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood[a]: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK | • Whole blood[a]:Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL)* |
| TREATMENT | | • Assess for ART restart |

a. Whole blood collections should be taken prior to dosing.


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WEEK 2
(Day 15 ± 1 day)

| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| EXAM | • Vital signs | • Urine pregnancy test |
| CENTRAL LAB | • Urinalysis<br>• Clinical chemistry, Hematology (CBC)<br>• TSH, T4<br>• Plasma HIV-1 RNA | • TBNK panel<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer |
| PK AND BIOMARKERS LAB (Arms A to E) | • Blood draw for budigalimab and ABBV-382 PK | • Whole blood[a]: PD-1 saturation, a4b7 saturation, Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK | • Whole blood[a]: biomarker PD-1 saturation, Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL))* |
| TREATMENT | **Arms A to E:**<br>• Study drug IV administration (budigalimab or [redacted] | • Assess for ART restart |

a. Whole blood collections should be taken prior to dosing.


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WEEK 3
(Day 22 ± 1 day)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| EXAM | • Vital signs | |
| CENTRAL LAB | • TSH, T4<br>• Plasma HIV-1 RNA | • TBNK panel |
| PK AND BIOMARKERS LAB (Arms A to E) | • Blood draw for budigalimab and ABBV-382 PK | • Whole blood[a]: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK | • Whole blood[a]: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL))* |
| TREATMENT | • Assess for ART restart | |

a. Whole blood collections should be taken prior to dosing.


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WEEK 4
(Day 29 ± 1 day)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| EXAM | • Vital signs | • Urine pregnancy test |
| CENTRAL LAB | • Urinalysis<br>• Clinical chemistry, Hematology (CBC)<br>• TSH, T4 | • Plasma HIV-1 RNA<br>• TBNK panel<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer |
| PK AND BIOMARKERS LAB (Arms A to E) | • Blood draw for Budigalimab and ABBV-382 PK<br>• ADA/NAb for budigalimab<br>• ADA/NAb for ABBV-382 | • Whole blood[a]: PBMC-1; biomarker serum; biomarker plasma; Whole blood[a]: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK<br>• ADA/NAb for budigalimab | • Whole blood[a]: PBMC-1, Biomarker Serum, Biomarker Plasma, biomarker immunophenotyping panel 3, Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL)* |
| TREATMENT | • Assess for ART restart | **Arms A to E:**<br>• Study drug IV administration (budigalimab or placebo) and Study drug IV administration (ABBV-382 or placebo)<br>[redacted] |

a. Whole blood collections should be taken prior to dosing.


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WEEK 5
(Day 36 ± 1 day)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| EXAM | • Vital signs | |
| CENTRAL LAB | • TSH, T4<br>• Plasma HIV-1 RNA | • TBNK panel |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood[a]: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK | • Whole blood[a]: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL)* |
| TREATMENT | • Assess for ART restart | |

a. Whole blood collections should be taken prior to dosing.


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WEEK 6
(Day 43 ± 1 day)

| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| EXAM | • Vital signs | • Urine pregnancy test |
| CENTRAL LAB | • Urinalysis<br>• Clinical chemistry, hematology (CBC)<br>• TSH, T4<br>• Plasma HIV-1 RNA | • TBNK panel<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer |
| PK AND BIOMARKERS LAB (Arms A to E) | • Blood draw for Budigalimab and ABV-382 PK | • Whole blood[a]: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK | • Whole blood[a]: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL)* |
| TREATMENT | • Assess for ART restart | **Arms A to E:**<br>• Study drug IV administration [redacted] |

a. Whole blood collections should be taken prior to dosi


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WEEK 7
(Day 50 ± 1 day)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| EXAM | • Vital signs | |
| CENTRAL LAB | • TSH, T4<br>• Plasma HIV-1 RNA | • TBNK panel |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood[a]: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK | • Whole blood[a]: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL)* |
| TREATMENT | • Assess for ART restart | |

a. Whole blood collections should be taken prior to dosing.


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WEEK 8
(Day 57 ± 1 day)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| EXAM | • Vital signs | • Urine pregnancy test |
| CENTRAL LAB | • Urinalysis<br>• Clinical chemistry, Hematology (CBC)<br>• TSH, T4 | • Plasma HIV-1 RNA<br>• TBNK panel<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer |
| PK AND BIOMARKERS LAB (Arms A to E ) | • Blood draw for Budigalimab and ABBV-382 PK<br>• ADA/NAb for budigalimab<br>• ADA/NAb for ABBV-382 | • Whole blood[a]: biomarker immunophenotyping panel 1; biomarker, immunophenotyping panel 2; biomarker serum (cytokine/chemokine panel 1); biomarker serum (cytokine/chemokine panel 2); PBMC-1; biomarker serum, biomarker plasma; Whole blood[a]: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK<br>• ADA/NAb for budigalimab | • Whole blood[a]: PD-1 saturation, immunophenotyping panel 3, biomarker serum (cytokine/chemokine panel 1), biomarker serum (cytokine/chemokine panel 2), biomarker serum, biomarker plasma, PBMC-1; Whole blood[a]: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL))* |
| TREATMENT | • **Arms A to E:** Study drug IV administration (ABBV-382 or placebo) | • Assess for ART restart |

a. Whole blood collections should be taken prior to dosing.


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WEEK 9
(Day 64 ± 1 day)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| CENTRAL/ LOCAL LAB | • Plasma HIV-1 RNA | • TBNK panel (if local only CD4 ± CD4:CD8) |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |

NOTES: This visit can be done virtually. For participants who are already on ART and have met confirmed viral re-suppression criteria, no labs will be collected. For all other participants, laboratory samples can be collected locally or at home. Local laboratory results should be entered in the appropriate section in EDC as soon as possible. The visit can also be conducted at the site.


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WEEK 10
(Day 71 ± 1 day)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| PRO | • HIVTSQ | |
| EXAM | • Vital signs | |
| CENTRAL LAB | • Urinalysis<br>• Clinical chemistry, Hematology (CBC), TSH, T4<br>• Plasma HIV-1 RNA | • TBNK panel |
| PK AND BIOMARKERS LAB (Arms A to E) | • Blood draw for Budigalimab and ABBV-382 PK | • Whole blood: PD-1 saturation, a4b7 saturation; Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK | Whole blood: PD-1 saturation, Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |


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WEEK 11
(Day 78 ± 1 day)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| CENTRAL/ LOCAL LAB | • Plasma HIV-1 RNA | • TBNK panel (if local only CD4 ± CD4:CD8) |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |

NOTES: This visit can be done virtually. For participants who are already on ART and have met confirmed viral re-suppression criteria, no labs will be collected. For all other participants, laboratory samples can be collected locally or at home. Local laboratory results should be entered in the appropriate section in EDC as soon as possible. The visit can also be conducted at the site.


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WEEK 12
(Day 85 ± 2 days)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| EXAM | • Vital signs | • Urine pregnancy test |
| CENTRAL LAB | • Urinalysis<br>• Clinical chemistry, Hematology (CBC)<br>• TSH, T4 | • Plasma HIV-1 RNA<br>• TBNK panel<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer |
| PK AND BIOMARKERS LAB (Arms A to E) | • Blood draw for Budigalimab and ABBV-382 PK | • Whole Blood: biomarker, immunophenotyping panel 1; biomarker, immunophenotyping panel 2; biomarker serum (Cytokine/chemokine panel 1); Biomarker serum (Cytokine/chemokine panel 2); PBMC-1; biomarker serum; biomarker plasma; Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for Budigalimab PK | • Whole blood: PD-1 saturation; biomarker, immunophenotyping panel 3; biomarker serum (cytokine/chemokine panel 1); biomarker serum (cytokine/chemokine panel 2); PBMC-1; biomarker serum; biomarker plasma; Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure)* |
| TREATMENT | • Assess for ART restart | |


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WEEK 14
(Day 99 ± 2 days)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| CENTRAL/LOCAL LAB | • Plasma HIV-1 RNA | • TBNK panel (if local CD4 and CD4:CD8) |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |

NOTES: This visit can be done virtually. For participants who are already on ART and have met confirmed viral re-suppression criteria, no labs will be collected. For all other participants, laboratory samples can be collected locally or at home. Local laboratory results should be entered in the appropriate section in EDC as soon as possible. The visit can also be conducted at the site.


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WEEK 16
(Day 113 ± 2 days)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| EXAM | • Vital signs | • Urine pregnancy test |
| CENTRAL LAB | • Clinical chemistry, Hematology (CBC)<br>• TSH, T4<br>• Plasma HIV-1 RNA | • TBNK panel (if local only CD4 ± CD4:CD8)<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer |
| PK AND BIOMARKERS LAB (Arms A to E) | • Blood draw for Budigalimab and ABBV-382 PK<br>• ADA/NAb for budigalimab<br>• ADA/NAb for ABBV-382 | • Whole blood: PBMC-1, biomarker serum, biomarker plasma, Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK<br>• ADA/NAb for Budigalimab | • Whole blood: biomarker PD-1 saturation, biomarker PBMC-1; biomarker serum; biomarker plasma; Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |


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WEEK 18
(Day 127 ± 2 days)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| CENTRAL/ LOCAL LAB | • Plasma HIV-1 RNA | • TBNK panel (if local only CD4 ± CD4:CD8) |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |

NOTES: This visit can be done virtually. For participants that are already on ART and have met confirmed viral resuppression criteria, no labs will be collected. For all other participants, laboratory samples can be collected locally or at home. Local laboratory results should be entered in the appropriate section in EDC as soon as possible. The visit can also be conducted at the site.


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WEEK 20
(Day 141 ± 2 days)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| EXAM | • Vital signs | • Urine pregnancy test |
| CENTRAL LAB | • Clinical chemistry, Hematology (CBC)<br>• TSH, T4 | • Plasma HIV-1 RNA<br>• TBNK panel |
| PK AND BIOMARKERS LAB (Arms A to E) | • Blood draw for Budigalimab and ABBV-382 PK<br>• ADA/NAb for budigalimab<br>• ADA/NAb for ABBV-382 | • Whole blood: biomarker serum, biomarker plasma, Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK<br>• ADA/NAb for Budigalimab | • Whole blood: biomarker serum; biomarker plasma; Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |


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WEEK 22
(Day 155 ± 2 days)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| CENTRAL/ LOCAL LAB | • Plasma HIV-1 RNA | • TBNK panel (if local only CD4 ± CD4:CD8) |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |

NOTES: This visit can be done virtually. For participants who are already on ART and have met confirmed viral resuppression criteria, no labs will be collected. For all other participants, laboratory samples can be collected locally or at home. Local laboratory results should be entered in the appropriate section in EDC as soon as possible. The visit can also be conducted at the site.


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WEEK 24
(Day 169 ± 2 days)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission<br>• COVID-19 assessment and counseling |
| PRO | • HIVTSQ<br>• EQ-5D-5L | • HAT-QoL |
| EXAM | • Vital signs<br>• Physical examination | • Urine pregnancy test<br>• Weight |
| CENTRAL LAB | • Urinalysis<br>• Clinical chemistry, Hematology (CBC)<br>• TSH, T4 | • Plasma HIV-1 RNA<br>• TBNK panel<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer |
| PK AND BIOMARKERS LAB (Arms A to E) | • Blood draw for budigalimab and ABBV-382 PK<br>• ADA/NAb for budigalimab<br>• ADA/NAb for ABBV-382<br>• Stool sample (optional) | • Whole blood: biomarker, immunophenotyping panel 1; biomarker, immunophenotyping panel 2; biomarker serum (cytokine/chemokine panel 1), biomarker serum (cytokine/chemokines panel 2); PBMC-1; PBMC-2; biomarker serum; biomarker plasma; PG-DNA; PG-RNA; Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |


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| | | |
|---|---|---|
| PK AND BIOMARKERS LAB (Arm F) | • ADA/NAb for budigalimab | • Whole blood: biomarker, immunophenotyping panel 3; biomarker serum; (cytokine/chemokine panel 1); biomarker serum (cytokine/chemokines panel 2); PBMC-1; PBMC-2; biomarker serum, biomarker plasma; PG-DNA; PG-RNA; Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| Rx TREATMENT | • Assess for ART restart | |


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| WEEKS 26 and 28 (Days 183 and 197 ± 2 days) | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission |
| EXAM | • Urine pregnancy test (Week 28 only) | |
| CENTRAL/ LOCAL LAB | • Plasma HIV-1 RNA | • TBNK panel (if local only CD4 ± CD4:CD8) |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure)* |
| TREATMENT | • Assess for ART restart | |

NOTES: These visits can be done virtually. For participants who are already on ART and have met confirmed viral resuppression criteria, no labs will be collected. For all other participants, laboratory samples can be collected locally or at home. Local laboratory results should be entered in the appropriate section in EDC as soon as possible. The visit can also be conducted at the site.


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| WEEKS 30, 32 AND 34 (Days 211, 225 and 239 ± 2 days) | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission |
| EXAM | • Urine pregnancy test (Week 32 only) | |
| CENTRAL/ LOCAL LAB | • Plasma HIV-1 RNA | • TBNK panel (if local only CD4 ± CD4:CD8) |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure)* |
| TREATMENT | • Assess for ART restart | |

NOTES: These visits can be done virtually. For participants who are already on ART and have met confirmed viral resuppression criteria, no labs will be collected. For all other participants, laboratory samples can be collected locally or at home. Local laboratory results should be entered in the appropriate section in EDC as soon as possible. The visit can also be conducted at the site.


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WEEK 36
(Day 253 ± 2 days)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission |
| EXAM | • Vital signs | • Urine pregnancy test |
| CENTRAL LAB | • Clinical chemistry, Hematology (CBC)<br>• TSH, T4<br>• Plasma HIV-1 RNA | • TBNK panel<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer |
| PK AND BIOMARKERS LAB (Arms A to E) | • Blood draw for budigalimab and ABBV-382 PK<br>• ADA/NAb for budigalimab<br>• ADA/NAb for ABBV-382 | • Whole blood: biomarker, a4B7; biomarker, PBMC-1; biomarker serum; biomarker plasma; Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | • ADA/NAb for budigalimab | • Whole blood: PBMC-1; biomarker serum, biomarker plasma; Whole blood[a]: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |


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| WEEKS 38, 40, AND 42 (Days 267, 281 and 295 ± 3 days) |  | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission |
| EXAM | • Urine pregnancy test (Week 40 only) | |
| CENTRAL/ LOCAL LAB | • Plasma HIV-1 RNA | • TBNK panel (if local only CD4 ± CD4:CD8) |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |

NOTES: These visits can be done virtually. For participants who are already on ART and have met confirmed viral resuppression criteria, no labs will be collected. For all other participants, laboratory samples can be collected locally or at home. Local laboratory results should be entered in the appropriate section in EDC as soon as possible. The visit can also be conducted at the site.


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WEEK 44
(Day 309 ± 3 days)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission |
| EXAM | • Urine pregnancy test | |
| CENTRAL/ LOCAL LAB | • Plasma HIV-1 RNA | • TBNK panel (if local only CD4 ± CD4:CD8) |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |

NOTES: This visit can be done virtually. For participants who are already on ART and have met confirmed viral resuppression criteria, no labs will be collected. For all other participants, laboratory samples can be collected locally or at home. Local laboratory results should be entered in the appropriate section in EDC as soon as possible. The visit can also be conducted at the site.


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| WEEKS 46, 48 AND 50 (Days 323, 337, and 351 ± 3 days) | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission |
| EXAM | • Urine pregnancy test (Week 48 only) | |
| CENTRAL/ LOCAL LAB | • Plasma HIV-1 RNA | • TBNK panel (if local only CD4 ± CD4:CD8) |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood: Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |

NOTES: These visits can be done virtually. For participants who are already on ART and have met confirmed viral resuppression criteria, no laboratory data will be collected. For all other participants, laboratory samples can be collected locally or at home. Local laboratory results should be entered in the appropriate section in EDC as soon as possible. The visit can also be conducted at the site.


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WEEK 52
(Day 365 ± 3 days)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission |
| PRO | • HIVTSQ<br>• EQ-5D-5L | • HAT-QoL |
| EXAM | • Vital signs<br>• Physical examination | • Urine pregnancy test<br>• Weight |
| CENTRAL LAB | • Urinalysis<br>• Clinical chemistry, Hematology (CBC)<br>• TSH, T4 | • Plasma HIV-1 RNA<br>• TBNK panel<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer<br>• Lipid Profile, Hemoglobin A1C (HgbA1c) |
| PK AND BIOMARKERS LAB (Arms A to E) | • Stool sample (Optional) | • Whole blood[a]: biomarker, immunophenotyping panel 1; immunophenotyping panel 2; biomarker serum (cytokine/chemokine panel 1); biomarker serum (cytokine/chemokines panel 2); PBMC-1, PBMC-2, biomarker serum, biomarker plasma, PG-DNA, PG-RNA; Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |


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| | | |
|---|---|---|
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood[a]: biomarker, immunophenotyping panel 3; biomarker serum (cytokine/chemokine panel 1); biomarker serum (cytokine/chemokines panel 2); PBMC-1; PBMC-2; biomarker serum; biomarker plasma; PG-DNA; PG-RNA; Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |

NOTES: Optional stool sample can be provided anytime between Week 48 and Week 52.

## PREMATURE DISCONTINUATION (Before Week 52)



| | | |
|---|---|---|
| INTERVIEW | • Adverse event assessment<br>• Record prior/concomitant therapy | • Counseling on prevention of HIV transmission |
| PRO | • HIVTSQ<br>• EQ-5D-5L | • HAT-QoL |
| EXAM | • Vital signs<br>• Physical examination | • Urine pregnancy test<br>• Weight |
| CENTRAL LAB | • Urinalysis<br>• Clinical chemistry, Hematology (CBC)<br>• TSH, T4 | • Plasma HIV-1 RNA<br>• TBNK panel<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer<br>• Lipid Profile, Hemoglobin A1C (HgbA1c) |


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| | | |
|---|---|---|
| PK AND BIOMARKERS LAB (Arms A to E) | • Blood draw for budigalimab and ABBV-382 PK<br>• ADA/NAb for budigalimab<br>• ADA/NAb for ABBV-382 | • Whole blood[a]: PD-1 saturation; a4b7 saturation; biomarker, Immunophenotyping panel 1, biomarker, immunophenotyping panel 2; biomarker serum (cytokine/chemokine panel 1), biomarker serum (cytokine/chemokines panel 2); PBMC-1; PBMC-2; biomarker serum; biomarker plasm; PG-DNA; PG-RNA; Plasma HIV tropism and Plasma ART Resistance: **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | • Blood draw for budigalimab PK<br>• ADA/NAb for budigalimab | • Whole blood[a]: PD-1 saturation; biomarker, Immunophenotyping panel 3, biomarker serum (cytokine/chemokine panel 1), biomarker serum (cytokine/chemokines panel 2); PBMC-1, PBMC-2, biomarker serum; biomarker plasma; PG-DNA; PG-RNA; Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| TREATMENT | • Assess for ART restart | |


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Visit Activities (Arms A to F from Week 54 to Week 112)

**WEEKS 68, 84, 98, and 112**

(Days 477, 589, 687 and 785 ± 7 days)



| | | |
|---|---|---|
| INTERVIEW | • Assessment of AESIs (including suspect irAEs, SAEs, special situation AEs, and any AE that triggers ART Restart)<br>• Record new concomitant therapy<br>• Assess for ART restart (only for participants who are off ART) | • Counseling on prevention of HIV transmission |
| PRO | • HIVTSQ (Weeks 84 and 112 only)<br>• EQ-5D-5L (Weeks 84 and 112 only) | • HAT-QoL (Weeks 84 and 112 only) |
| EXAM | • Weight and Vital signs<br>• Physical examination | • Urine pregnancy test |
| CENTRAL LAB | • Clinical chemistry, Hematology (CBC)<br>• TSH, T4<br>• Lipid-Profile, Hemoglobin A1C (HgbA1c) (Both Week 112 only) | • Plasma HIV-1 RNA<br>• TBNK panel<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood: biomarker PBMC-1, PBMC-2, serum, plasma; Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood: biomarker PBMC-1, PBMC-2, serum, plasma; Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |

NOTES: These are onsite visits and are required for all participants.


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**WEEKS 54, 56, 58, 62, 64, 66, 70, 72, 74, 78, 80, 82, 86, 88, 90, 94, 96, 100, 102, 104, 108, and 110**

(Days 379, 393, 407, 435, 449, 463, 491, 505, 519, 547, 561, 575, 603, 617, 631, 659, 673, 701, 715, 729, 757, and 771 ±3 days)



| | | |
|---|---|---|
| INTERVIEW | • Assess for ART restart (only for participants who are off ART) | • Counseling on prevention of HIV transmission |
| CENTRAL/ LOCAL LAB | • Plasma HIV-1 RNA<br>• Urine pregnancy test (weeks 56, 64, 72, 80, 88, 96, 100, 104, and 108 only) | |
| PK AND BIOMARKERS LAB | | • Whole Blood: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |

NOTES: These visits can be done virtually. They are required only for participants who are still on ATI (Off ART) or that have not yet met confirmed viral resuppression criteria. Local laboratory results should be entered in the appropriate section in EDC as soon as possible. The visit can also be conducted at the site. TBNK panel (or CD4 ± CD4:CD8) is not required in those visits however can be collected if needed by PI discretion.


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## WEEKS 60, 76, 92, and 106

(Days 421, 533, 645, and 743 ± 2 days)

| | | |
|---|---|---|
| INTERVIEW | • Assessment of AESIs (including suspect irAEs, SAEs, special situation AEs, and any AE that triggers ART Restart)<br>• Assess for ART restart (only for participants who are off ART) | • Counseling on prevention of HIV transmission |
| EXAM | • Urine pregnancy test | |
| CENTRAL/ LOCAL LAB | • Plasma HIV-1 RNA | • TBNK panel (if local only CD4 ± CD4:CD8) |
| PK AND BIOMARKERS LAB | | • Whole Blood: Plasma ART Resistance **IF** *1st instance HIV VL ≥1,000cps/mL or a 2nd rebound HIV VL ≥1,000cps/mL after viral control OR virological failure* |

NOTES: These visits can be done virtually. They are required only for participants who are still on ATI (Off ART) or that have not yet met confirmed viral resuppression criteria. Local laboratory results should be entered in the appropriate section in EDC as soon as possible. The visit can also be conducted at the site.


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PREMATURE DISCONTINUATION (After Week 52):

| | | |
|---|---|---|
| INTERVIEW | • Assessment of AESIs (including suspect irAEs, SAEs, special situation AEs, and any AE that triggers ART Restart)<br>• Record new concomitant therapy<br>• Assess for ART restart (only for participants who are off ART) | • Counseling on prevention of HIV transmission |
| PRO | • HIVTSQ<br>• EQ-5D-5L | • HAT-QoL |
| EXAM | • Weight and Vital signs<br>• Physical examination | • Urine pregnancy test |
| CENTRAL LAB | • Clinical chemistry, Hematology (CBC)<br>• TSH, T4<br>• Lipid-Profile, Hemoglobin A1C (HgbA1c) | • Plasma HIV-1 RNA<br>• TBNK panel<br>• Inflammatory markers: Hs-CRP, LDH, and D-Dimer |
| PK AND BIOMARKERS LAB (Arms A to E) | | • Whole blood: biomarker PBMC-1; PBMC-2; serum; plasma; Plasma ART Resistance ONLY IF: *1st instance HIV VL ≥1,000cps/mL OR second rebound after viral control OR virological failure)* |
| PK AND BIOMARKERS LAB (Arm F) | | • Whole blood: biomarker PBMC-1, PBMC-2, serum, plasma; Plasma ART Resistance ONLY IF: *1st instance HIV VL ≥1,000cps/mL OR second rebound after viral control OR virological failure)* |

# 3 STUDY PROCEDURES

## 3.1 Study Participant Information and Informed Consent

The investigator or their representative will explain the nature of the study to the participant, the benefits and risks anticipated from participation in the study, the potential risks and implications of undergoing ATI, the potential risks of HIV transmission during ATI, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the participant or any medications being discontinued by the participant in order to participate in this study, the informed


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consent statement will be reviewed, signed, and dated by the participant or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the participant and the original will be placed in the participant's medical record. An entry must also be made in the participant's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the participant received a signed copy.

Information regarding benefits for participants and information regarding provisions for treating and/or compensating participants who are harmed because of participation in the study can be found in the informed consent form.

Samples for optional pharmacogenetic analyses, biomarker research, or other exploratory analyses will only be collected if the participant has voluntarily signed and dated a separate written consent form for this testing that has been approved by an IRB/IEC, after the nature of the testing has been explained and the participant has had an opportunity to ask questions. The separate written consent may be part of the main consent form. If the participant does not consent to the testing, it will not impact the participant's participation in the study.

## 3.2 Medical, Surgical, and HIV History

A complete medical history including demographics, history of tobacco, alcohol, and drug/substance use will be taken at screening. This history will include a detailed HIV history with estimated date of infection (if available), date of diagnosis, reported CD4 nadir during chronic stage of infection, history of AIDS-associated opportunistic infections, history of retroviral rebound syndrome, available viral load measurements within a year before initiation of ART, and ART treatment history (including date of first ART initiation, toxicities with ART regimens, details on any known ART drug resistance, ART regimen at screening, duration of viral suppression on ART at time of screening). The participant's medical history will be updated at the Study Day 1 visit. This updated medical history will serve as the baseline for clinical assessment.

## 3.3 Drug and Alcohol Screen

Urine specimens will be tested at the screening visit for the presence of drugs used in substance use disorders (including alcohol) with the objective to support the principal investigators in identifying participants that could be at additional risk of transmitting HIV to their HIV negative partners and/or not adhering to study requirements. Participants with recent substance or alcohol use disorder history and/or positive urine screen for drugs at screening may be included after evaluation by the investigator that the use would not interfere with adherence to study requirements and will not pose additional risks to the participant and their HIV negative partner.

The panel will minimally include the drugs listed below. Any positive result must be assessed for clinical significance and whether the participant is suitable to participate in this study (refer to Protocol, Section 5.1). These analyses will be performed by the certified central laboratory chosen for the study.

- Opiates
- Barbiturates


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- Amphetamines
- Cocaine
- Benzodiazepines
- Alcohol
- Phencyclidine
- Methadone

## 3.4 Prior/Concomitant Therapy

Medication (prescription or over-the-counter, including vitamins, nutritional supplements and herbal supplements) use from 4 weeks prior to study drug administration through the end of the study, including the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use will be recorded.

General guidelines regarding prohibited, cautionary, and allowed medications are summarized in Protocol Section 5.3 and Protocol Section 5.4.

The AbbVie TA MD/SD should be contacted if there are any questions regarding concomitant or prior therapy(ies).

Prior and concomitant HIV-1 antiretroviral therapies should be recorded in the EDC system separately from other prior or concomitant therapies on the appropriate eCRFs.

## 3.5 ART Interruption and ART Restart

As described in Protocol Section 5.7, participants will undergo an interruption of their ART regimen starting on Study Day 1. If a participant's ART regimen requires a morning dose, participants should take their ART regimen on the morning of the scheduled Study Day 1 visit prior to administration (infusion or injection) of the first dose of study drug. Participants must not take any additional doses of any antiretrovirals following first administration of study drug until study Week 112, unless they meet ART restart criteria.

If a participant's ART regimen does not require a morning dose, participants should not take their ART regimen on Study Day 1 visit and must not take any additional doses of any antiretrovirals following first administration of study drug until study Week 112, unless they meet ART restart criteria.

As described in Protocol Section 5.7, during ART interruption, participants meeting ART restart criteria will be required to restart their ART regimen. ART restart criteria should be checked at every visit. The details on the date, time, and exact ART regimen for both the last dose prior to ART interruption and upon ART restart should be collected and recorded in EDC.

For ART restart, participants should be re-initiated on the same ART regimen they were taking prior to ART interruption, and the ART restart reason and timing and ART regimen should be documented in the EDC system on the appropriate eCRFs. If the investigator uses an ART regimen that is different than the


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ART regimen the participant was taking prior to ART interruption or changes the ART regimen for a participant at any time after ART restart, the reasons for this switch must be recorded in the EDC system and discussed with the TA MD/SD.

## 3.6 Adverse Event Assessment

Please refer to Section 4.1.

## 3.7 Counseling on Prevention of HIV Transmission

All participants will be counselled at screening and at all study visits, as specified in Section 2.2, on the risk of transmitting HIV to their HIV negative sexual partner(s) and how to best protect their HIV negative sexual partner(s) from HIV transmission (as per Protocol, Section 5.2). Documentation of counselling at each visit will be provided in the source notes and the eCRF where applicable. To be eligible for the study, participants must agree on taking appropriate measures (that need to be discussed with the investigator) to prevent HIV transmission to their HIV negative partners. Risk of HIV superinfection during ATI in participants receiving immune-based therapy is unknown. Therefore, principal investigators should also discuss and counsel participants on avoiding HIV exposure while they are off ART.

## 3.8 COVID-19 Assessment and Counseling

COVID-19 assessment will be performed prior to any study procedures at each visit as specified in Section 2.2. Site should do an evaluation of signs/symptoms of COVID-19 and potential exposures to SARS-CoV-2, as well as consider current local COVID-19 epidemiology situation to assess the risk of COVID-19 or SARS-CoV-2 infection. If COVID-19/SARS-CoV-2 infection is suspected, the investigator/site should make all efforts to confirm diagnosis and start treatment, if applicable, as per local guidelines.

If COVID-19 is confirmed, the investigator/site should assess and discuss with TA MD/SD on potential risks of starting/continued study drug dosing (if in dosing period) and/or continued ATI (if ART has not yet restarted).

Counseling of participants on measures to help prevent contracting or transmitting SARS-CoV-2 will also be performed at the initial visit and should be reviewed at all subsequent visits.

Documentation of these assessments/counselling at each visit will be provided in the source notes and the eCRF where applicable. Confirmed COVID-19 occurring during the study should be captured as an adverse event in the appropriate eCRF and supplemental eCRF where applicable.

Additional COVID-19 assessments outside of the study protocol may be done and will be per the discretion of the investigator.


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## 3.9 Patient-Reported Outcomes

PROs will be administered on site using digital questionnaires. The investigator or their representative will verify that the digital health tools are received intact. A proof of receipt or similar document will be kept in the site files as a record of what was received.

Participants may be asked to complete the self-administered PRO instrument (when allowed per local regulatory guidelines). Participants should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to participants other than encouragement to complete the tasks. The only exception is that participants who are functionally unable to read any of the instruments may have site personnel read the questionnaire to them. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

The EQ-5D-5L with VAS, HIVTSQ, and HAT-QoL will be collected in this study.

The ePRO instruments should be completed prior to drug administration on Day 1 and prior to any discussion of AEs or any review of laboratory findings.

The participant should complete the questionnaires before site personnel perform any clinical assessments to avoid biasing the participant's response.

The questionnaires will be completed in the following order, when applicable: HAT-QoL, HIVTSQ, and EQ-5D-5L.

## 3.10 Pharmacokinetic Sampling

Blood samples for PK and ADA/NAb analyses of ABBV-382 and budigalimab will be collected as specified in Section 2.2.

### Arms A to E

On study drug administration days, PK samples should be collected immediately before the start of the infusion and immediately after the completion of infusion (≤ 15 minutes), as applicable. Budigalimab (or placebo) infusion time should be at least 30 minutes (0.5 hours) and ABBV-382 (or placebo) infusion time should be at least 90 minutes. Please refer to dose preparation and administration manual for more details on infusion duration/time and minimum/maximum infusion duration/time.

After budigalimab (or placebo) administration is complete (which is defined as the time at which the line flush procedure is completed), a waiting period of approximate 60 minutes must be maintained from the end of budigalimab (or placebo) infusion until the start of the ABBV-382 (or placebo) infusion. On study drug administration days, ADA/NAb samples should be collected prior to the start of the first drug infusion (≤ 1 hour).

Specific time points for blood sample collection for PK samples and ADA/NAb samples are provided in Table 1 and Table 2.


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## Table 1. PK sampling times and analytes (budigalimab IV or ABBV-382 IV) – Arms A to E

| Days/Weeks | Sampling times | Budigalimab concentration will be analyzed | ABBV-382 concentration will be analyzed |
|---|---|---|---|
| Day 1 (Dose 1) | 0 h (Predose budigalimab)[a] | X | X |
| | EOI-budigalimab[b] | X | |
| | EOI-382[b] | X | X |
| Week 2 | 0 h (Predose budigalimab)[a] | X | X |
| | EOI-budigalimab[b] | X | |
| Week 4 | 0 h (Predose budigalimab)[a] | X | X |
| | EOI-budigalimab[b] | X | |
| | Predose 382[a] | X | X |
| | EOI-382[b] | X | X |
| Week 6 | 0 h (Predose budigalimab)[a] | X | X |
| | EOI-budigalimab[b] | X | |
| | 1 h after EOI-budigalimab[c] | X | |
| Week 8 | 0 h (Predose 382)[a] | X | X |
| | EOI-382[b] | X | X |
| Weeks 10, 12, 16, 20, 24, 36 | (no study drug dosing) | X | X |

EOI = end of infusion; EOI-budigalimab = end of infusion of budigalimab (or placebo); EOI-382 = end of infusion of ABBV-382 (or placebo); h = hour(s)

a. PK samples should be collected immediately before the start of the infusion (≤ 15 minutes before the start of the infusion).

b. PK samples should be collected immediately after the end of the infusion (≤ 15 minutes after the end of the infusion).

c. PK sample should be collected within ± 15 minutes.

Note: Weeks 2, 4, 6, 8, and 10 have ± 1 day time window; Weeks 12, 16, 20, 24, and 36 have ± 2 days time window.


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## Table 3. ADA and NAb Sampling Times – Arms A to F

| Sample | Day 1 (Dose 1) | Week 4 | Week 8 | Weeks 16, 20, 24, 36 |
|---|---|---|---|---|
| ADA/NAb for budigalimab | X | X | X | X |
| ADA/NAb for ABBV-382 (Arms A-E only) | X | X | X | X |

Note: On Day 1 (Dose 1) and Week 4, ADA/NAb samples should be collected prior to the start of the infusion for budigalimab/placebo (≤ 1 hour); On Week 8, ADA/NAb samples should be collected prior to the start of the infusion for ABBV-382/placebo (≤ 1 hour). Weeks 4 and 8 have ± 1 day time window; Weeks 16, 20, 24, and 36 have ± 2 days time window.


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Blood samples will be collected by venipuncture from the arm contralateral to the arm used for dose administration. The time that each blood sample is collected will be recorded to the minute.

For subjects in any arm, who discontinue study drug(s) for any reason, PK and ADA/Nab samples should still be collected in specific visits as described in protocol activities Table 1-3, with the exception of EOI and post-injection sampling.

Additional information on the collection, handling/processing, and disposition can be found in the laboratory manual.

Serum concentrations of ABBV-382 and budigalimab (ABBV-181) and relative titers of ABBV-382 ADA and budigalimab ADA will be determined using validated methods at or under the supervision of the Bioanalysis Department at AbbVie (Ludwigshafen, Germany). Any additional analytes may be analyzed using non-validated methods. Serum samples collected for analysis may be used for future assay development or validation activities. ABBV-382 NAb and budigalimab NAb samples may be used for the analysis of NAb.

## 3.11 Biomarker Sampling

Biospecimens (whole blood, plasma, serum, PBMCs, and stool) will be collected as described in Section 2 and Protocol Activity Schedule throughout the study, to evaluate known and/or novel disease-related or drug-related biomarkers in circulation or at tissue sites. Some of these samples may be optional. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. The objective of this research is to analyze samples for biomarkers that will help to understand HIV disease, related conditions, response to treatment with budigalimab, ABBV-382, or similar therapeutic agents. The analyses may include but are not limited to: immune cell profiling, virologic profiling, genomics profiling, microbiome profiling, ART PK or other possible predictors of response. This research is exploratory in nature and the biomarker research results may not be included with the clinical study report.

All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will store the samples and data in a secure storage space with measures to protect confidentiality. The samples may be retained while research on ABBV-382 and budigalimab (or drugs of these classes) continues for up to but no longer than 20 years after study completion, or per local requirement.

## 3.12 12-Lead Electrocardiogram

### 12-Lead Electrocardiogram (Single Only)

Resting 12-lead ECGs will be obtained singly as specified in Section 2.

The ECG acquired prior to dosing will serve as the baseline measurements for clinical assessment. A sign/symptom-directed ECG can be performed at any time post-baseline, as deemed necessary by the investigator.


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When an ECG is scheduled at the same time as a blood collection, the ECG will be obtained prior to the blood collection. ECGs occurring near meals will take place prior to meals.

ECGs will be acquired after the participant has been in the supine position for at least 5 minutes. Participants will be instructed to remain completely stationary (no talking, laughing, deep breathing, sleeping, or swallowing) for approximately 10 seconds during the ECG recording. While ECGs are being acquired, participants and staff are prohibited from having devices (e.g., cellular telephones, fans, heaters, etc.) that emit electrical interference in the room.

### ECG Safety Review

Each ECG will be evaluated by an appropriately trained physician (preferably a cardiologist) at the study site (the "local reader"). The local reading of the ECG will be used by the investigator for participant safety assessments, including adverse event determination and management, and decision on whether a participant will be discontinued from the study.

The local reader will sign and date all the ECGs collected in this study and provide a global interpretation for each ECG using the following categories:

- Normal ECG
- Abnormal ECG – Not clinically significant (NCS)
- Abnormal ECG – Clinically significant (CS)
- Unable to evaluate

All local reader evaluations of ECGs will be entered into the source documents. If the global interpretation is Abnormal (NCS or CS), the local reader will provide further information (e.g., sinus bradycardia, arrhythmia). The QTcF will be calculated and documented for all ECGs.

All ECG source documentation will be retained at the study site. The automatic cardiograph reading (i.e., cardiograph-generated measurements and interpretations) will not be collected for analysis.

## 3.13 Height, Weight, and BMI

Height will be measured at screening only. Body weight will be measured at scheduled visits as specified in Section 2.2. The participant will wear lightweight clothing and no shoes during weighing.

Height and weight will be measured to calculate BMI. BMI is calculated as weight in kg divided by the square of height measured in meters. For amputees, an adjusted BMI calculation may be used after discussion with TA MD/SD.

## 3.14 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be obtained at visits as specified in Section 2.2. Blood pressure and pulse rate should be measured after the participant has been sitting for at least 3 minutes.


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Measurements should be assessed consistently throughout the study. Vital signs measurements determined prior to dosing on Day 1 will serve as baseline.

When measurements of vital signs are scheduled at the same time as a blood collection, the measurements of vital signs will be obtained prior to the blood collection.

Measurements of vital signs occurring near meals will take place prior to meals.

Minimum vital signs measurement requirements for Arms A to E and Arm F are specified below. Vital signs may be measured more frequently, when needed for any sign/symptom directed assessment, during the infusion and/or post-infusion monitoring period, as deemed necessary by the investigator.

### Arms A to E

On Day 1 and at Week 4, vital signs will be measured and monitored before infusion (0-hour, predose, up to 15 minutes prior to administering infusion) of budigalimab/placebo, and approximately every 15 (± 5) minutes during the infusion. During the 1-hour post-budigalimab/placebo infusion monitoring period, vital signs should be monitored approximately every 30 (± 5) minutes until just before the ABBV-382/placebo infusion is started. The last vital signs measurement taken prior to starting the ABBV-382/placebo infusion will serve as the time 0 measurement for ABBV-382/placebo infusion monitoring. During ABBV-382/placebo infusion, vital signs will be monitored approximately every 30 (± 5) minutes until the end of the infusion and through the 1-hour post-ABBV-382/placebo infusion monitoring period.

On Week 2 and Week 6, vital signs will be measured and monitored before infusion (0-hour, predose, up to 15 minutes prior to administering infusion) of budigalimab/placebo, and approximately every 15 (± 5) minutes during the infusion and approximately every 30 (± 5) minutes for 1 hour after the end of the infusion.

On Week 8, vital signs will be measured and monitored before infusion (0-hour, predose, up to 15 minutes prior to administering infusion) of ABBV-382/placebo, and approximately every 30 (± 5) minutes during the infusion and approximately every 30 (± 5) minutes for 1 hour after the end of the infusion.

[redacted]

## 3.15 Physical Examination

A complete physical examination will be performed at the designated study visits as specified in Section 2.2. This examination includes a comprehensive skin examination (including mucosa), neurologic examination, and assessment of current bowel habits and respiratory function. The physical examination performed on Study Day 1 will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted at the baseline visit prior to the first dose of study drug should be recorded in the participant's medical history. Any significant physical examination findings after the first dose will be recorded as AEs. All findings, whether related to an AE or part of each participant's medical history, will be captured on the appropriate eCRF page.


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At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

## 3.16 Chest X-Ray

A chest x-ray (posterior-anterior and lateral views) will be performed at screening to establish a baseline measurement and to provide additional evidence of no clinically significant findings, including tuberculosis. It is particularly important to establish a baseline measurement for clinical assessment and to facilitate differential diagnosis of potential pneumonitis, which is a reported immune-related adverse event in trials for anti-PD1 agents in Oncology indications and can be a potential risk to the participant.

A plain PA chest radiograph has approximately 0.02 mSv effective dose of radiation which is equivalent to approximately 3 days of natural background radiation or to the radiation exposure during a 6-7 hour flight. The additional lifetime risk of cancer would be approximately 1:1 million and it is considered very low.

A radiologist must perform an assessment of the chest x-ray. The investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the chest x-ray for presence of TB, the investigator or his/her delegate must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB.

The results of the chest x-ray will be retained at the site as the original source documentation and may not be transferred to the clinical database.

## 3.17 Tuberculosis Screen

The TB screening tests are diagnostic test results to be interpreted in the context of the participant's epidemiology, history, examination findings, etc., and it is the responsibility of the investigator to determine if a participant has previous, active, or latent TB.

All participants will be tested for TB infection by an IGRA by a certified local or central laboratory as applicable. If a participant had a negative IGRA within 90 days prior to screening and source documentation is available, the test may not need to be repeated, provided nothing has changed in the participant's medical history to warrant a repeat test. These cases may be discussed with the AbbVie TA MD/SD. The results of the TB test(s) will be retained at the site as the original source documentation and may not be transferred to the clinical database.

Participants with documented or previous history of active TB or latent TB, even if treated, will be excluded. Participants with current clinical suspicion of TB should also be excluded.

## 3.18 Clinical Laboratory Tests

Clinical laboratory tests to be performed during the study are presented in Table 4 and described further below. Clinical laboratory tests will be collected at the designated study visits as specified in Section 2.2.


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A central laboratory will be utilized to process and provide results for the clinical laboratory test (unless otherwise noted). The laboratory must be certified and must provide laboratory reference ranges prior to the initiation of the study. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug. Follow-up safety laboratory values may be performed by a certified laboratory other than the central laboratory. In unexpected situations where there is a logistic and/or operational issue that could significantly impact a central laboratory test, specific tests could be performed by a certified laboratory other than central laboratory following approval of the TA SD/TA MD. Exceptions for that are: HIV RNA, CD4/CD8 cells counts, and tuberculosis IGRA testing that can be performed in a local certified laboratory as specified further in this operations manual.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or
- discontinue the participant from the study or require the participant to receive treatment; in this case, the laboratory result will be recorded as an adverse event.

Discuss with TA MD/SD for other tests not listed in Table 4, that are considered necessary by the investigator for a safety evaluation.


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## Table 4. Clinical Laboratory Tests

| Clinical Laboratory Tests | | |
|---|---|---|
| **Hematology** | **Clinical Chemistry** | **Other Tests** |
| Hematocrit<br>Hemoglobin<br>Red blood cell (RBC) count<br>White blood cell (WBC) count<br>Neutrophils<br>Bands<br>Lymphocytes<br>Monocytes<br>Basophils<br>Eosinophils<br>Platelet count (estimate not acceptable)<br>Mean corpuscular hemoglobin (MCH)<br>Mean corpuscular volume (MCV)<br>Mean corpuscular hemoglobin concentration (MCHC) | Blood urea nitrogen (BUN/Urea)<br>Creatinine<br>Total bilirubin<br>Direct and indirect bilirubin<br>Gamma-glutamyl transferase (GGT)<br>Lactate dehydrogenase (LDH)<br>Albumin<br>Alanine aminotransferase (ALT)<br>Aspartate aminotransferase (AST)<br>Alkaline phosphatase<br>Sodium<br>Potassium<br>Calcium<br>Magnesium<br>Inorganic phosphorus<br>Uric acid<br>Cholesterol[a]<br>Total protein<br>Glucose<br>High-density lipoprotein (HDL)[a]<br>Low-density lipoprotein (LDL)[a]<br>Triglycerides[a]<br>Bicarbonate/$CO_2$<br>Chloride<br>Creatinine clearance (Cockcroft-Gault calculation)<br>Thyroid-stimulating hormone (TSH)<br>Free thyroxine (Free T4)<br>Total creatinine phosphokinase (CK)[a]<br>Troponin-I[a]<br>Anti-thyroglobulin antibody[a]<br>Anti-thyroid peroxidase antibody[a]<br>Cortisol[a]<br>Adrenocorticotropic hormone (ACTH)[a]<br>Hemoglobin A1C (HgbA1C)[a]<br>High sensitivity C-Reactive protein (hs-CRP)<br>Anti-nuclear antibody (ANA)[a] | Interferon gamma release assay (IGRA)[a,d]<br>Urine pregnancy test[b,d]<br>Serum human chorionic Gonadotropin (hCG)[b]<br>FSH (postmenopausal females only)[a,c]<br>HIV Ab[a]<br>HIV-1 RNA[g]<br>HIV tropism<br>ART resistance test<br>TBNK panel or CD4 count and CD4/CD8 ratio[g]<br>Hepatitis B panel (Anti-HBc Total, Anti-HBs and HBsAg)[a]<br>Anti-HCV Ab[a]<br>HBV DNA[e]<br>HCV RNA[f]<br>D-dimer |
| **Urinalysis** | | **Coagulation**[a] |
| Specific gravity<br>Ketones<br>pH<br>Protein<br>Blood<br>Glucose<br>Bilirubin<br>Leukocytes<br>Nitrite<br>Microscopic examination (as applicable)<br>Urine drug screen[a] | | Prothrombin time (PT)<br>International Normalized Ratio (INR)<br>Activated partial thromboplastin time (aPTT) |

a. Required only at screening.

b. Required only for females of childbearing potential.

c. If needed to determine postmenopausal status.

d. Can be done as a local laboratory test for select visits as indicated in Section 2.

e. Done at screening as a reflex test in participants with isolated positive anti-hepatitis B core (HBc) antigen.

f. Done at screening as a reflex test in participants with positive anti-HCV.


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g. At visits indicated in Section 2, those tests are only required for participants that have not yet restarted ART or have restarted ART but have not yet met re-suppression criteria. Those tests can be performed in a local certified lab or home collection. When done by a local laboratory, if the full TBNK panel is not available, only CD4 count with or without CD4/CD8 ration will be accepted.

## Pregnancy Tests (Serum and Urine)

Pregnancy testing should not be performed for postmenopausal women/person assigned as female sex at birth.

A qualitative serum pregnancy test will be performed at Screening and may be performed on Day 1 (per local guidelines). A urine pregnancy test will be performed at Screening and at baseline (prior to first dose) for all female participants of childbearing potential.

The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive the participant is considered a screen failure. If the serum pregnancy test is borderline, the serum pregnancy test should be repeated ≥ 3 days later to determine eligibility.

If the repeat serum pregnancy test is:

- Positive, the participant is considered a screen failure;
- Negative, the participant can be enrolled into the trial;
- Still borderline, ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the participant can be enrolled into the study (unless prohibited per local requirements) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

Additional urine pregnancy tests will be performed at visits indicated in Section 2 and Protocol Activity Schedule (Appendix D). Urine pregnancy tests must be conducted and evaluated prior to dosing on dosing days. More frequent pregnancy tests can be performed throughout the study at the investigator's discretion or if required per local/country requirements.

- If the baseline urine pregnancy test is negative, then dosing with study drug may begin.
- If the baseline or postbaseline urine pregnancy test is positive, dosing with study drug must be withheld and a serum pregnancy test is required (as stated above). Depending on the results of the serum pregnancy test, ART restart criteria (Protocol Section 5.7) may also apply.

At virtual visits specified in Section 2.2, a pregnancy test is required. A report from a urine pregnancy test done in a local lab or performed by the participant at home on the day of the visit will be acceptable.

## Hepatitis Testing

HIV Ab, hepatitis B panel (hepatitis B surface antigen [HBs Ag], hepatitis b core antibody [anti-HBc], anti-HBs) and hepatitis C antibody (anti-HCV Ab) tests will be performed at screening by the central laboratory. HBV DNA and HCV RNA testing will be performed as indicated (Table 4 and exclusion criteria).


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## Flow Cytometry, HIV RNA, and HIV Genotypic Resistance Testing

Samples for plasma HIV-1 RNA levels and flow cytometry (TBNK panel including but not limited to CD4+ T-cell and CD8+ T-cell counts [absolute and percent]) will be obtained at the times specified in Section 2.2 and in the Protocol Activity Schedule. Plasma HIV-1 RNA will be measured by the central laboratory; on visits performed virtually as specified in Section 2.2, a local certified laboratory may be used for measuring plasma HIV-1 RNA.

Plasma HIV-1 RNA results below the LLOQ from the central laboratory are reported as: "No HIV-1 RNA Detected" or "< 20 copies/mL, HIV-1 RNA Detected."

At visits performed virtually as specified in Section 2.2, plasma HIV-RNA and CD4+ T-cell count with or without CD4:CD8 ratio are required in participants who have NOT restarted ART or who have restarted ART but have not yet met viral re-suppression. Those tests can be performed in a local certified laboratory. Test results need to be retained by the site and information included in the appropriate eCRF page.

Additional plasma HIV-RNA and/or CD4+ T-cell count with or without CD4:CD8 ratio can be done anytime in participants who have not restarted ART at the discretion of the principal investigator, including per participant's request. Those tests can also be performed in a local certified laboratory. Also, local HIV-1 RNA and/or CD4 tests can be performed at required onsite visits, per PI discretion, when there is a need for turnaround <48 hours, in addition to central laboratory tests that are mandatory on those visits.

Following ART interruption, a sample should be obtained for HIV-1 genotypic ART resistance testing and HIV-1 tropism testing as soon as possible after the first instance of a plasma HIV-1 RNA ≥ 1000 copies/mL; this sample will be analyzed for HIV-1 genotypic resistance and HIV-1 tropism analysis. A sample should also be obtained for HIV-1 genotypic resistance testing at the time the repeat plasma HIV-1 RNA is drawn. If the participant's repeat HIV-1 RNA is ≥ 500 copies/mL, the sample obtained for HIV-1 genotypic resistance testing will be analyzed.

In participants that have not restarted ART therapy and have a confirmed second rebound (plasma HIV-1 RNA ≥ 1000 copies/mL) following at least 8 weeks of viral control, an additional sample for HIV-1 genotypic ART resistance testing may be performed after discussion with the TA MD.

An additional sample for HIV-1 genotypic ART resistance testing will also be collected and performed in case of virologic failure following re-initiation of ART (as defined in the Protocol, Section 5.4). This sample should be collected as soon as virologic failure is confirmed and plasma HIV-1 RNA is ≥ 500 copies/mL.

Please note that HIV-1 genotypic ART resistance testing and HIV-1 tropism testing can only be processed by the central lab. Therefore, if any of the above situations happened and participant do not have a on site visit scheduled with a window of less than 7 days of the date the test result becomes available, participant will need to come to site for an unscheduled visit to collect those labs OR labs could be collected virtually through a schedule home health visit.


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Specific instructions for preparation and storage of flow cytometry (PD-1 saturation, α4β7 saturation, immunophenotyping panels 1 and 2), plasma HIV-1 RNA, HIV resistance, HIV-1 tropism, and cytokine/chemokine samples will be provided by the central laboratory, AbbVie, or its designee.

### Hematology and Coagulation

In conjunction with a complete blood count, a coagulation panel will be evaluated at Screening. A complete blood count will also be evaluated at the scheduled visits as specified in Section 2.2. At any time, symptom-driven assessments may be performed, at the discretion of the investigator.

### Clinical Chemistry

Participants are not required to fast prior to having blood samples drawn for clinical chemistry. If an abnormal result is obtained, the investigator may request that a participant return in a fasting state to repeat the test.

Hgb A1c, ANA, anti-thyroglobulin antibody, ACTH, and cortisol will be evaluated at screening. Blood collection for ACTH and cortisol should be performed in the morning (e.g., 8 AM – 10 AM). Creatinine phosphokinase, troponin-I, and total lipid panel (cholesterol, triglycerides, HDL, LDL) will be collected at baseline (prior to dose).

TSH and Free T4 will be performed at Screening and at visits indicated in the Section 2 and Protocol Activity Schedule.

At any time, symptom-driven assessments may be performed, at the discretion of the investigator.

As biotin supplement can lead to the false measurement of thyroid hormone in commonly used assays, participants that use biotin (alone or as part of a multivitamin) should be recommended to stop taking biotin for at least 2 days before thyroid testing collection on Day 1, weekly for the first 8 weeks, and at Weeks 12, 16, 20, 24, 36, 52, 68, 84, 98, and 112 to avoid the risk of having a misleading test.

### Urinalysis

Dipstick urinalysis will be completed by the central laboratory at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

At any time, symptom-driven assessments may be performed, at the discretion of the investigator.

## 3.19 Participant Withdrawal

All attempts must be made to determine the primary reason for premature discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the participant's condition. Following discontinuation of study drug, the participant will be treated in accordance with the investigator's best clinical judgment, irrespective of whether the participant decides to continue participation in the study.


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## 3.20 Meals and Dietary Requirements

There are no dietary requirements for study drug (budigalimab, ABBV-382, or placebo) dosing. Participants who restart ART should follow the food requirements per the prescribing information for their respective antiretroviral regimen.

## 3.21 Retesting and Rescreening

Participants who at Screening have any of the following are not eligible to rescreen or retest:

- A positive HBsAg;
- Detectable HCV RNA;
- A positive HIV-2 test;
- A positive serum pregnancy test (if female).
- A positive IGRA test.
- An HIV RNA above 200 copies/mL.

Otherwise, each specific test or panel may be retested or rescreened only once following approval from the AbbVie TA MD/SD.

Participants who have exclusionary laboratory parameter(s) per criterion in Protocol Section 5.1 are allowed to retest on the related panel(s) (e.g., exclusionary ALT requires a repeat chemistry panel) within the same screening period and must meet all inclusion and none of the exclusion criteria on the panel that is repeated. If the retest result(s) are also exclusionary, the participant may not be rescreened or retested again.

Participants who are outside of the initial 35-day Screening period at the time of rescreen must be rescreened for all laboratory, inclusion and exclusion criteria. The Chest X-ray does not need to be repeated if the previous Chest X-ray was completed within 90 days prior to the rescreening visit. For participants who rescreen or participants who do not meet all inclusion and none of the exclusion criteria upon retest/rescreen, the site personnel must register the participant as a screen failure in both the IRT and EDC systems.

## 3.22 Unscheduled Visits

Visits in addition to those described in Section 2.2 will be allowed in this study. An unscheduled visit should be performed when the participant comes in for a medical visit for evaluation and assessment. During unscheduled visits, blood and urine samples may be obtained for the laboratory tests listed in Section 3, at the investigator's discretion. Discuss with TA MD/SD for other tests not listed in Section 3, that are considered necessary by the investigator for a safety evaluation.

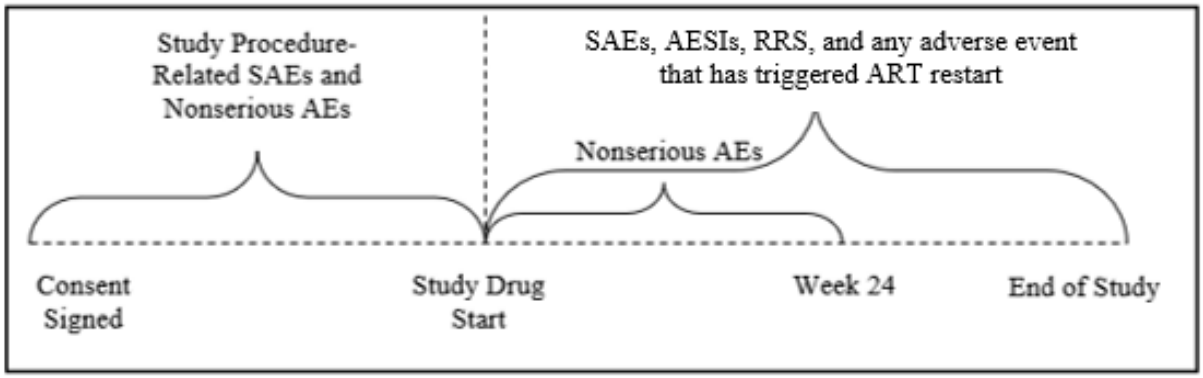
Visits to only retest a lab will not be considered an Unscheduled Visit.


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# 4 SAFETY MANUAL

## 4.1 Methods and Timing of Safety Assessment

All serious and nonserious AEs which could be related to study procedures (e.g., blood collection, ECG) will be collected from the time the participant signed the study-specific informed consent until study drug administration. From the time of study drug administration until Week 24, all nonserious AEs will be collected whether solicited or spontaneously reported by the participant. All SAEs, AESIs (including irAEs), RRS and any adverse event that has triggered ART restart will be collected from the time of study drug administration until the end of the study.




## 4.2 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the EDC system. SAEs that occur prior to the site having access to the EDC system, or if EDC is not operable, should be documented on the SAE non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 806-2062 Backup: +1-847-935-2844

### For safety questions, contact the Antiviral Safety Team at:

Virology Safety Team
Email: SafetyManagement_Virology@abbvie.com


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For any participant safety concerns, please contact the physician listed below:

**Primary Therapeutic Area Medical Director**
**EMERGENCY MEDICAL CONTACT:**
[redacted] **MD**
**AbbVie Inc.**
**1 North Waukegan Road**
**North Chicago, IL 60064**

Contact Information:

**Office:** [redacted]
**Mobile:**
**Fax:**
**Email:**

In emergency situations involving study participants when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

| HOTLINE: +1 (973) 784-6402 |
|---|

The sponsor will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements.

# 5 COUNTRY-SPECIFIC REQUIREMENTS

## 5.1 SUSAR Reporting

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with EU Clinical Trial Regulation, global and local requirements, and Appendix A of the Investigator Brochure will serve as the RSI. The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

## 5.2 Treatment After End of Study

Continued treatment for trial participants to AbbVie treatment will not be available for participants in this study as this study is testing a finite treatment of 8 weeks.


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# 6 STUDY DRUG

## 6.1 Treatments Administered

The study drugs, budigalimab (ABBV-181) or placebo and ABBV-382 or matching placebo, will be administered intravenously for treatment Arms A to E and open label budigalimab (ABBV-181) will be administered subcutaneously for Arm F at the visits listed in Section 2.2.

Budigalimab (ABBV-181) for infusion (Arms A to E) and for injection (Arm F) will be supplied as [redacted] mg of lyophilized powder for reconstitution. Placebo for budigalimab will be a solution of 0.9% sodium chloride for infusion. Budigalimab IV or placebo IV will be taken Q2W for 4 doses total. Open label Budigalimab [redacted] will be taken Q2W for 4 doses total.

ABBV-382 will be supplied as [redacted] mg [redacted] mL solution for infusion; matching placebo will be supplied as solution for infusion. ABBV-382 or matching placebo will be taken Q4W for 3 doses total.

Dose preparation and administration instructions for budigalimab infusion (ABBV-181), ABBV-382 infusion or placebo infusion (Arms A to E), including blinding of the study drugs, infusion duration/time, minimum/maximum infusion duration/time; suggested modifications of infusion times for IRR, etc. will be provided in a separate dose preparation and administration manual. Infusion time for budigalimab/placebo, ABBV-382/placebo should respect the minimum time established in the Pharmacy Manual.

For Arm F, dose preparation and administration instructions for open label budigalimab injection (ABBV-181) are also provided in a separate dose preparation and administration manual. The injections per quadrant will be administered in the following order (as needed):

1. Left upper quadrant of the abdomen
2. Right upper quadrant of the abdomen
3. Left lower quadrant of the abdomen
4. Right lower quadrant of the abdomen

Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to participants enrolled in the study through the IRT system. At the end of the treatment period or at the premature discontinuation visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

All doses of study drug (budigalimab [ABBV-181] infusion or injection, ABBV-382, or placebo) will be administered at the clinic by qualified staff with appropriate medical training and support equipment and medication available as needed.

Refer to Protocol Section 6.2 for managing infusion-related and injection site reactions.


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## 6.2 Packaging and Labeling

Study drug for budigalimab (ABBV-181), ABBV-382, and matching placebo for ABBV-382 will be supplied as a vial in a carton. Placebo for budigalimab infusion (0.9% sodium chloride) will be supplied with commercially available material in either bags or bottles.

Each vial, bag, and carton will be labeled as required per country requirements.

The labels must remain affixed to the vials and cartons. All blank spaces should be completed by site staff prior to dispensing to participant.

## 6.3 Storage and Disposition of Study Drug

Study drug must be stored refrigerated (2° to 8°C/36° to 46°F). For additional storage conditions, please refer to the clinical study label. Placebo for budigalimab IV (0.9% sodium chloride) will be stored according to the commercial label.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for participant use or destroyed on site as appropriate.

Sites are responsible for maintaining the investigational study drug according to the storage conditions specified on the clinical label and monitoring for temperature excursions with the use of a calibrated continuous temperature monitoring device (e.g., chart recorders and/or acceptable calibrated min/max thermometers) or continuous monitoring systems. Specific guidance on appropriate temperature monitoring and temperature excursions reporting requirements will be provided separately.

## 6.4 Method of Assigning Participants to Treatment Groups

This is a 2-part, Phase 2, proof-of-concept study, with a randomized, double-blind, placebo-controlled study part followed by a single arm, open-label study part.

A central randomization scheme will be utilized. All eligible participants will be centrally randomized (Arms A to E) or enrolled (Arm F) using an IRT.

At the screening visit, all participants will be assigned a unique participant number using the IRT. For participants who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the participant as a screen failure.

Participants who are enrolled will retain their participant number assigned at the screening visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.


*No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.*

## 6.5 Selection and Timing of Dose for Each Participant

Selection of the doses for this study is discussed in Protocol Section 4.2.

## 6.6 Preparation/Reconstitution of Dosage Form

Written instructions for the preparation of budigalimab and/or ABBV-382 and placebo solutions for infusion will be provided as a separate document from the protocol.


CONFIDENTIAL INFORMATION
*No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.*

# Document Approval

Study M19965 - 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 - Operations Manual for Protocol Version 4-0 - 19Jul2024

**Version:** 2.0 **Date:** 19-Jul-2024 **Company ID:** 20240719-0900f9f687f52e06-2.0-en

| Signed by: | Date: | Meaning of Signature: |
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