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HIV

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Markowitz M, Lalezari JP, DeJesus E, et al. Safety, pharmacokinetics, and antiviral activity of a combination of TMB-365 and TMB-380 in people living with HIV suppressed with antiretroviral therapy in the USA: a phase 1b/2a, open-label, dose-escalation study. *Lancet HIV* 2026; published online Nov 10. https://doi.org/10.1016/S2352-3018(26)00148-7.

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Rashes leading to participant discontinuation in Phase 2a

One participant developed an erythematous pruritic papular rash which began on both upper extremities and became generalized 32 days after the first infusion. No mucosal involvement was present. There were no systemic symptoms, no laboratory correlates including eosinophilia or abnormal liver enzymes. Punch biopsy one week after the onset of rash revealed superficial and deep perivascular to interstitial lymphoid infiltrates with eosinophils consistent with a hypersensitivity reaction. The causality of the rash was due to TMB-365/TMB-380. Treatment included a 6-day course Medrol pack and antihistamines followed by Prednisone 20mg orally for 7 days. The duration of the rash was 27 days. It was considered unwise to proceed with further treatment with TMB-365 and TMB-380.

A second participant developed a pruritic rash in his axillae and groin bilaterally 14 days after his initial infusion of TMB-365/380. There were no associated symptoms, mucosal involvement, liver function test abnormalities, or laboratory correlates such as eosinophilia. The Principal Investigator concluded that the rash was due to fungal dermatitis and initiated clotrimazole/betamethasone cream twice daily. Two weeks later, the participant reported improvement in the rash. However, 21 days later the participant reported atypical papules on the neck and was referred to a dermatologist who confirmed the presence of erythematous papules on the left central lateral neck and the left inferior lateral neck. Biopsy of an inferior lateral neck lesion revealed urticarial hypersensitivity dermatitis with slight spongiosis. The differential diagnosis included an urticarial hypersensitivity reaction due to a drug, virus, or arthropod. The subject made the decision to withdraw from the study despite the investigator's willingness to continue treatment with TMB-365/380.

Table S1. All reported TEAEs

	Sentinel Groups (Single dose)			Core Group (Single dose)
	2400 mg (n=10)	3200 mg (n=10)	4800 mg (n=10)	4800 mg q8wks (n=20)
	Number of events	Number of events	Number of events	Number of events
Total number of events	11	14	7	48
Oropharyngeal pain	1 (G1, unrelated)	1 (G1, unrelated)	0	0
Sneezing	0	1 (G1, probable)	0	0
Asthma	0	0	0	1 (G2, unrelated)
Cough	0	0	0	1 (G1, unrelated)
Nasal congestion	0	0	0	1 (G1, unrelated) 1 (G2, unrelated)
Papule	1 (G1, unrelated)	1 (G1, unrelated)	0	3 (G1, unrelated) 2 (G2, unrelated)
Eczema	1 (G2, unrelated)	0	0	0
Dermatitis	0	1 (G2, unrelated)	0	1 (G2, probable)
Rash	0	1 (G1, unrelated)	1 (G2, unrelated)	1 (G2, unrelated) 2 (G2, probable)
Rash papular	0	0	1 (G1, unrelated)	0
Pruritus	0		0	2 (G1, unrelated)
Urticaria	0	0	0	1 (G2, probable)
Macule	0	0	0	1 (G1, unrelated)
COVID-19	2 (G1, unrelated) 1 (G2, unrelated)	1 (G1, unrelated)	0	1 (G1, unrelated)
Tinea cruris	1 (G1, unrelated)	0	0	0
Prostatitis	0	1 (G2, unrelated)	0	0
Conjunctivitis	0	1 (G1, unrelated)	0	0
Upper respiratory tract infection	0	1 (G1, unrelated)	0	2 (G2, unrelated)
Syphilis	0	0	1 (G1, unrelated)	0
Viral upper respiratory tract infection	0	0	1 (G1, unrelated)	0
Viral infection	0	0	1 (G1, unrelated)	0
Pharyngitis streptococcal	0	0	1 (G1, unrelated)	0
Tonsillitis	0	0	0	1 (G2, unrelated)
Fungal infection	0	0	0	2 (G2, unrelated)
Folliculitis	0	0	0	2 (G1, unrelated)

Oropharyngeal gonococcal infection	0	0	0	1 (G1, unrelated)
Nasopharyngitis	0	0	0	1 (G2, unrelated)
Lymphadenopathy	1 (G1, unrelated)	0	0	0
Peripheral coldness	1 (G2, probable)	0	0	0
Flushing	0	0	0	2 (G1, probable)
Fatigue	1 (G1, probable)	2 (G1, unrelated)	0	1 (G1, unrelated) 2 (G1, probable) 2 (G1, definite)
Chills	0	0	0	1 (G1, probable)
Pyrexia	0	0	0	1 (G2, probable)
Peripheral swelling	0	0	0	1 (G1, unrelated)
Pain	0	0	0	1 (G1, definite)
Nephropathy toxic	1 (G2, unrelated)	0	0	0
Type IV hypersensitivity reaction	0	1 (G1, probable) 1 (G2, definite)	0	0
Headache	0	1 (G1, unrelated)	0	2 (G1, probable) 1 (G2, probable)
Somnolence	0	0	0	1 (G1, unrelated)
Dizziness	0	0	0	1 (G1, unrelated)
Basal cell carcinoma	0	0	1 (G1, unrelated)	0
Depression	0	0	0	1 (G1, unrelated)
Attention deficit hyperactivity disorder	0	0	0	1 (G2, unrelated)
Diarrhoea	0	0	0	1 (G1, unrelated)
Oesophageal stenosis	0	0	0	1 (G2, unrelated)
Joint swelling	0	0	0	1 (G1, unrelated)

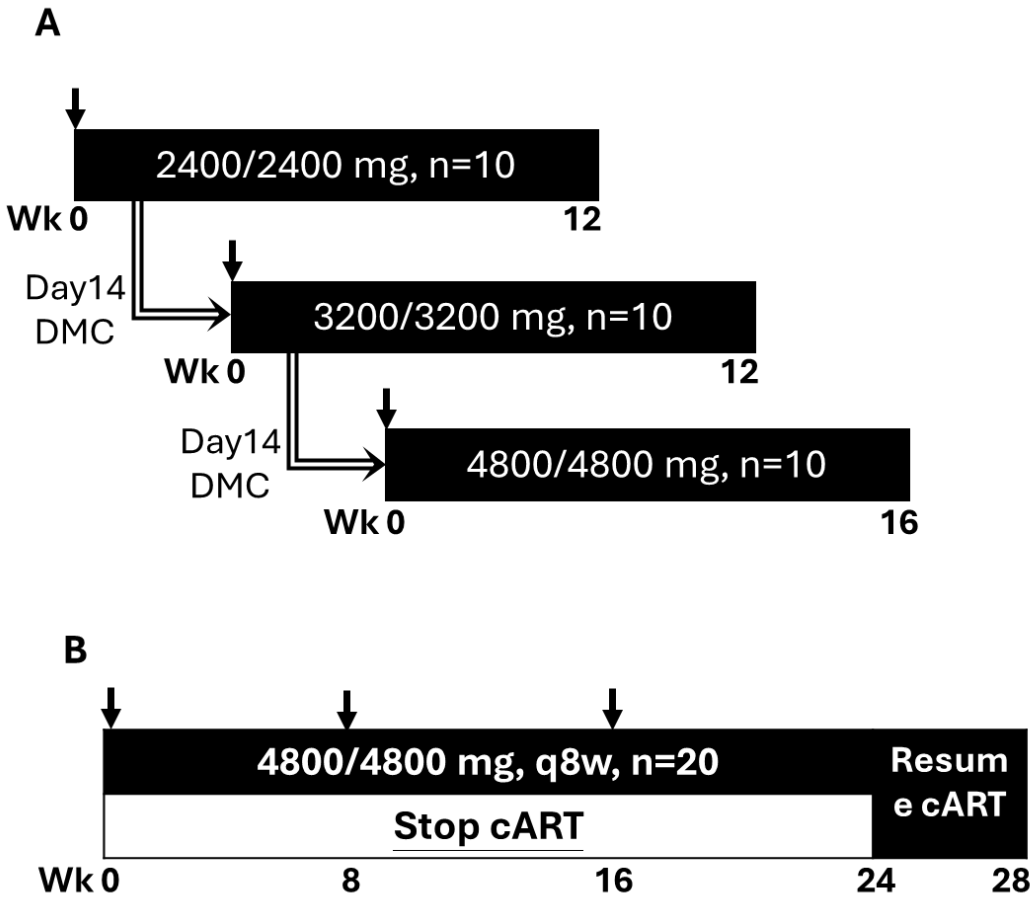
G1 = Grade 1 (Mild) TEAE, G2 = Grade 2 (Moderate) TEAE

Unrelated: The AE is unrelated to the study drug.

Probable: The AE is probably related to the study drug.

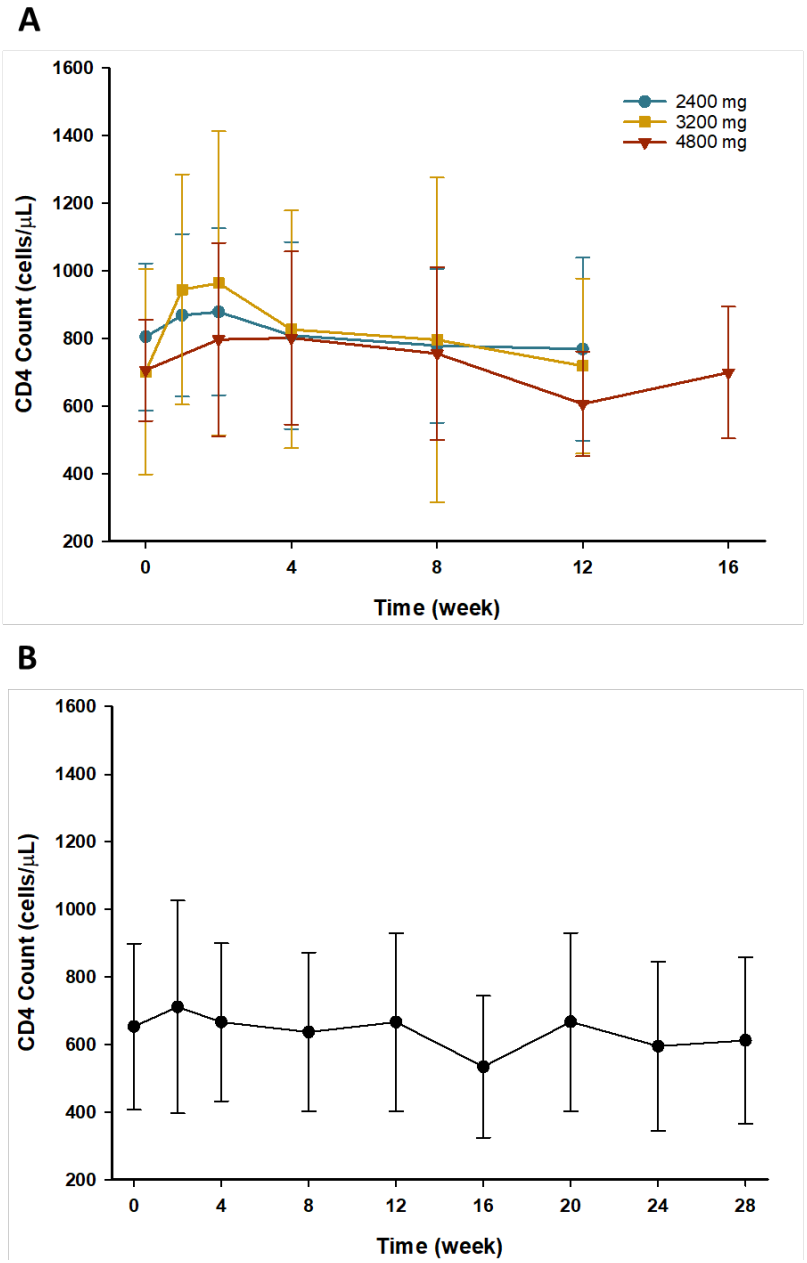
Definite: The AE is definitely related to the study drug.

Figure S1. Study schema



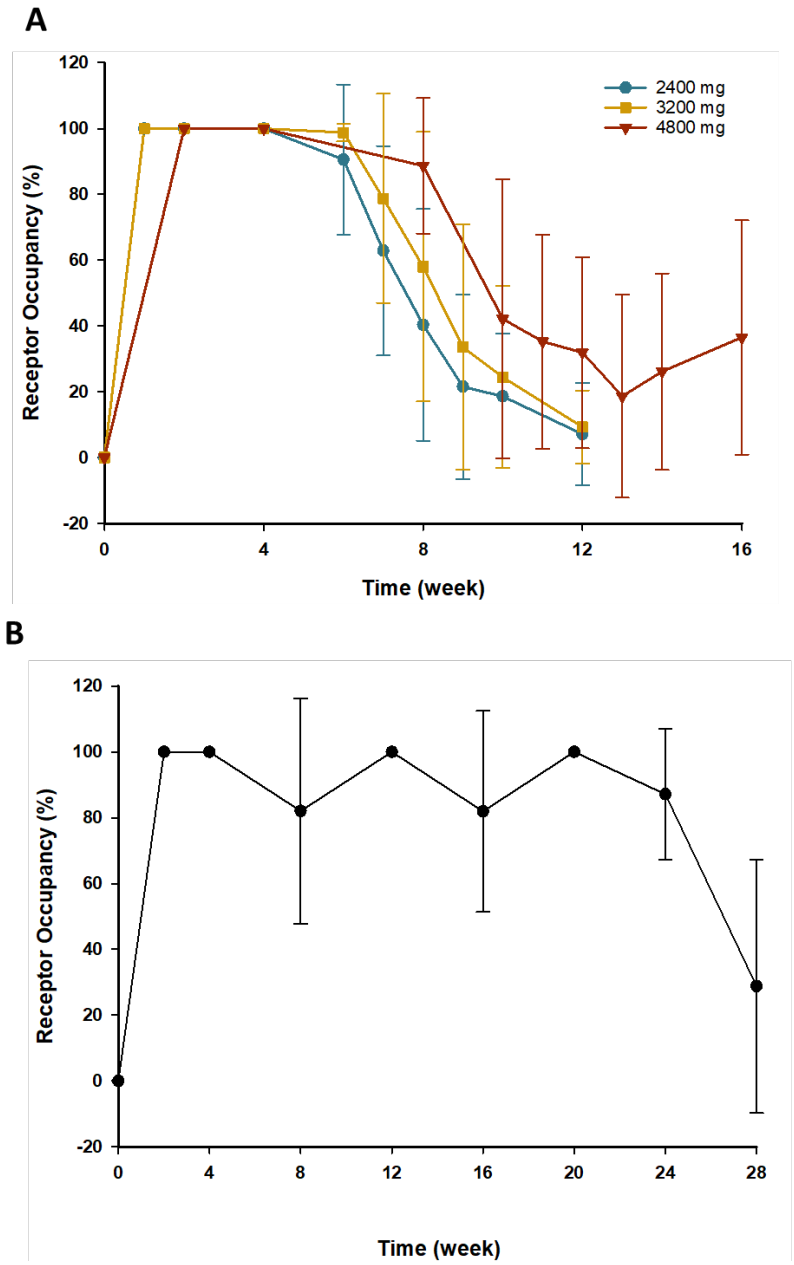
Overview of the TMB-a21 study design. (A) The Sentinel Groups (Phase 1b) evaluated safety and pharmacokinetics of single-dose, dose-escalating TMB-365/TMB-380. (B) The Core Group (Phase 2a) was initiated after the conclusion of the Sentinel Group to assess the safety and efficacy of repeat dosing in a single-arm study. Arrows indicate dosing time points. DMC= data monitoring committee. cART= combination antiretroviral therapy.

Figure S2. CD4 counts over time



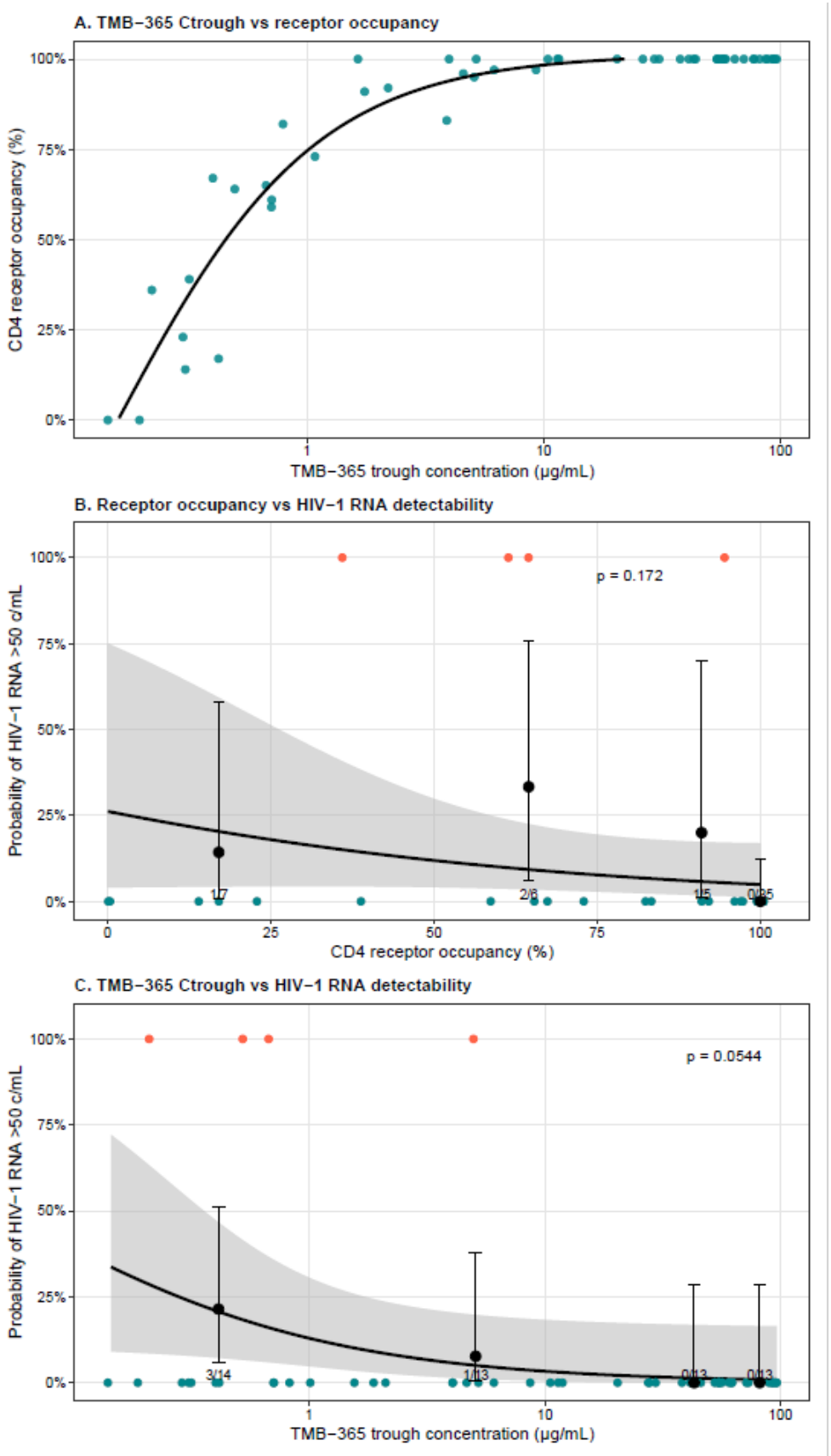
Mean CD4 counts with error bars indicating the SD following a single administration of TMB-365 and TMB-380 (A) in the Sentinel Group and following repeat administrations of TMB-365 and TMB-380 (B) at weeks 0, 8, and 16 in the Core Group.

Figure S3. Receptor occupancy over time



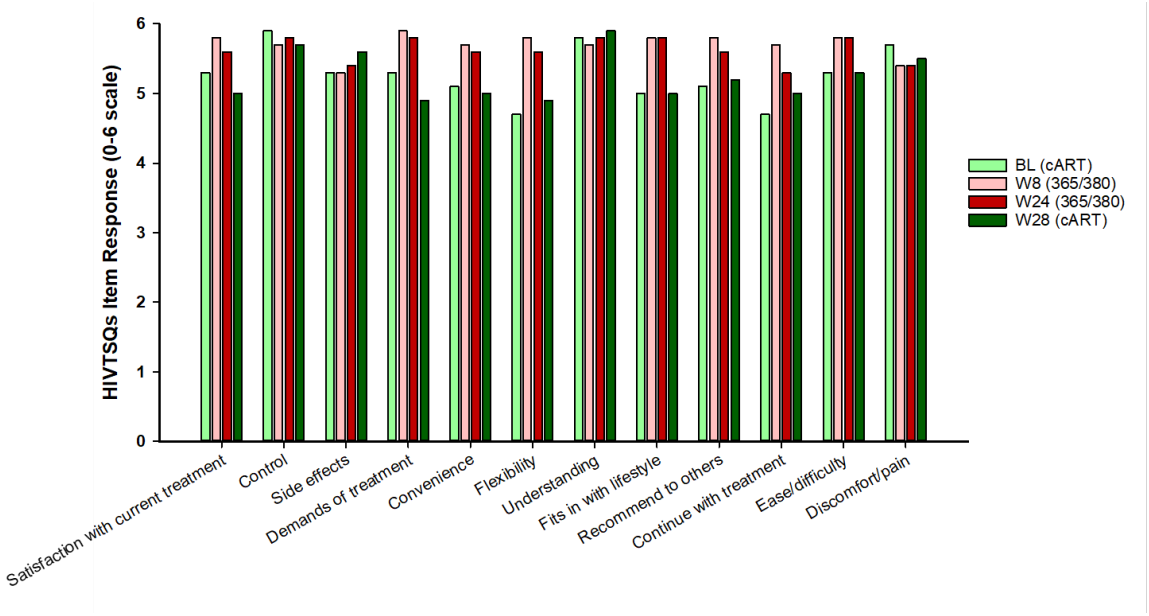
Mean CD4 receptor occupancy with error bars indicating the SD following a single administration of TMB-365 and TMB-380 (A) in the Sentinel Group and following repeat administrations of TMB-365 and TMB-380 (B) at weeks 0, 8, and 16 in the Core Group.

Figure S4. Exposure-response relationships for TMB-365



(A) Relationship between TMB-365 trough concentration (Ctrough) and CD4 receptor occupancy (RO), described using an Emax model.
(B) Relationship between RO and probability of detectable HIV-1 RNA (>50 copies/mL).
(C) Relationship between TMB-365 Ctrough and probability of detectable HIV-1 RNA (>50 copies/mL).
In panels B and C, individual observations at Week 8, 16, and 24 are shown as dots (detectable: red; undetectable: teal). Black circles are the observed proportions of participants with detectable HIV-1 RNA within predefined bins (clinical RO categories in panel B; quartiles of Ctrough in panel C), also shown as numerical values above the x-axis. Black vertical lines are 95% confidence intervals of the probability of detectable HIV-1 RNA. Black curve line represents the logistic regression fit, with shaded areas indicating 95% confidence intervals. The p value is a likelihood ratio test comparing the logistic regression fit against the null hypothesis that the probability of response is independent of exposures.

Figure S5. Participant reported outcomes



Participants in the Core group completed the HIV Treatment Satisfaction Questionnaire-Status (HIVTSQs) at Baseline, Week 8, 24, and 28 prior to any study procedures. Responses for each question ranged from 6 (e.g. very satisfied) to 0 (e.g. very dissatisfied), with higher scores representing greater satisfaction, flexibility, etc.

cART= combination antiretroviral therapy. HIVTSQs=HIV Treatment Satisfaction Questionnaire-Status

Appendix. TMB-a21 Study protocol (NCT05275998)

STUDY PROTOCOL

A Phase 1b/2a Dose Escalation Study of the Safety, Pharmacokinetics, and Efficacy of the Combination of TMB-365 and TMB-380 in HIV-1 Infected Individuals Suppressed with Combination Antiretroviral Therapy

PROTOCOL NUMBER: TMB-a21

AMENDMENT 4

Version:	5.1
Date of Protocol:	23 JAN 2024
Sponsor:	TaiMed Biologics, USA Corp. 4790 Irvine Blvd. STE 105-697 Irvine, CA 92620

Sponsor Contact:	YingAn Lai TaiMed Biologics 4790 Irvine Blvd. STE 105-697 Irvine, CA 92620 Email: ylai@taimedbio.com
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Serious Adverse Event Reporting:	Westat 1600 Research Blvd. Rockville, MD 20850 Phone : 888-464-5246 Fax : 888-865-1983 Email : Regulatory@westat.com
Proprietary Notice:	This document contains mainly unpublished data and is the sole property of TaiMed Biologics. Therefore, it is provided to you in strict confidence as an investigator, potential investigator, or consultant. The information may be reviewed by you, your staff, and your institutional review board/independent ethics committee. It is understood that this information will not be disclosed to others without written authorization from TaiMed Biologics, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.
Ethics Statement:	The study will be completed according to the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) and E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

INVESTIGATOR'S STATEMENT

I agree to conduct the study as outlined in the protocol entitled, "A Phase 1b/2a dose escalation study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of the combination of TMB-365 and TMB-380 as maintenance therapy in HIV-1 infected patients suppressed on combination antiretroviral therapy" in accordance with the guidelines and all applicable government regulations.

I have read and understand all sections of the protocol, including the section on administrative considerations (Section 12).

Principal Investigator's Name

Principal Investigator's Institution

Principal Investigator's Signature

Date

SPONSOR APPROVAL

Approved by



23 January 2024

Martin Markowitz, M.D.

Date

Medical Director

TaiMed Biologics

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PROTOCOL SYNOPSIS

Protocol Number:	TMB-a21
Title:	A Phase 1b/2a Dose Escalation Study of the Safety, Pharmacokinetics, and Efficacy of the Combination of TMB-365 and TMB-380 in HIV-1 Infected Individuals Suppressed with Combination Antiretroviral Therapy
Sponsor:	TaiMed Biologics
Study Phase:	1b / 2a
Participants and Investigator Sites:	Up to 70 participants from approximately 6-8 sites in North America
Study Drug, Dosage, and Route of Administration and Controls:	The investigational products, TMB-365 and TMB-380 are monoclonal antibodies (MAbs) to be administrated via intravenous (IV) infusion. Doses to be tested include – 2400 mg, 3200 mg and 4800 mg for each antibody in the Sentinel Groups of 10 subjects. 4800 mg of each antibody will be tested every 8 weeks in a Core Group. If indicated by safety, PK, and efficacy, an amendment may be made to the current protocol to test higher doses of either antibody in consultation with the Data Monitoring Committee and the FDA. There are no controls.
Objectives:	The primary objectives of this study are to: ■ Evaluate the safety and tolerability of various doses and dosing regimens of IV infusions of TMB-365 and TMB-380 given q8wks in suppressed, cART treated HIV-1 infected participants. ■ Define the pharmacokinetic (PK) profile of TMB-365 and TMB-380 when given q8wks in suppressed, cART treated HIV-1 infected participants ■ Evaluate the antiviral activity of TMB-365 in combination with TMB-380 as maintenance therapy in suppressed HIV-infected individuals. (Core only) Exploratory objectives of this study are to: ■ Determine the immunogenicity of TMB-365 and TMB-380 in HIV-1 infected suppressed participants ■ Determine the resistance profiles of TMB-365 and TMB-380 *in vivo*.
Study Population:	Males and females aged between 18-70 years who are HIV-1 seropositive, suppressed on continuous cART for at least 6 months with documentation of HIV-1

	RNA levels below the limit of detection on at least one occasion within 3 months prior to screening.
Inclusion Criteria:	Participants must meet all of the following criteria to be included in the study: 1. Male or female at least 18 years of age and no greater than 70 years on the day of Screening. 2. Asymptomatic HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by Geenius™ or a second antibody test by a method other than the initial rapid HIV and/or E/CIA test, or by HIV-1 antigen, plasma HIV-1 RNA viral load at or prior to screening. 3. On continuous suppressive cART for 6 months prior to Screening with one documented HIV-1 RNA level below the level of detection within 3 months of Screening. Continuous cART is defined as no interruptions greater than 3 consecutive days. cART is defined as a DHHS recommended regimen. Study participants should be on a stable regimen for at least 3 months. 4. Screening plasma HIV-1 RNA below the limit of detection. 5. CD4+ T cell count $\geqq 350$ cells/mm^3 6. Laboratory values obtained within 30 days prior to the first dose: • Hemoglobin ≥ 10.0 g/dL; • Platelet count $\geq 100{,}000/mm^3$; • Absolute neutrophil count $\geq 1{,}000/mm^3$; • Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 1.5 x upper limit of normal (ULN); and • Creatinine clearance (CrCl) of ≥ 50 mL/min. 7. Willing to comply with the requirements of the protocol and available for follow-up for the planned duration of the study. 8. In the opinion of the principal investigator or designee, has understood the information provided; written informed consent needs to be given before any study-related procedures are performed. 9. Females of childbearing potential, sexually active with a male sex partner, must agree to use one effective method of contraception from the time of signing the consent to completion of the study, and agree to pregnancy testing as per the Schedule of Events and Procedures. Females of childbearing potential are female participants who

	are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy), are not postmenopausal (at least one year without menses), and are not otherwise sterile by medical evaluation.
Exclusion Criteria:	Participants having or meeting any of the following conditions or characteristics will be excluded from the study: 1. Suppressed subjects who have not been on a stable DHHS recommended cART regimen for at least 3 months. 2. Receipt of any monoclonal antibody for the treatment or prevention of HIV infection except for receipt of TMB-365 and TMB-380 by Sentinel subjects eligible for enrollment into Core groups. 3. Suppressed subjects receiving cabotegravir and rilpivirine intramuscularly as maintenance therapy for HIV-1 infection. 4. Pregnant, planning a pregnancy during the trial period, or lactating. 5. Known allergy/sensitivity or any hypersensitivity to components of the study drug or its formulation, or known allergy to a MAb. 6. History of severe allergic reactions to medications, vaccinations or monoclonal antibody therapy for other conditions such as COVID. 7. Major psychiatric illness including any history of schizophrenia or severe psychosis, uncontrolled bipolar disorder requiring acute therapy, or suicide attempt in the previous three years. 8. Serious illness requiring systemic treatment and/or hospitalization within 21 days prior to the first dose. 9. Receipt of immunomodulatory agents (e.g., interleukins, interferons, cyclosporine, high dose systemic corticosteroids), HIV vaccine, systemic cytotoxic chemotherapy, or investigational therapy within 180 days prior to the first dose. 10. Any chronic or acute medical condition, including chronic Hepatitis B infection, chronic and Hepatitis C infection with viremia, drug use and alcohol abuse, which in the opinion of the investigator would interfere with evaluation of the study drug.

	11. Lack of adequate venous access. 12. Individuals who have experienced virologic failure during treatment with two or more cART treatment regimens and those being treated with regimens containing either ibalizumab, enfuvirtide, maraviroc, or fostemsavir. Note that a change in treatment regimen for intolerance does not meet criteria for treatment failure.
Study Design and conduct:	This is an adaptive dose-escalation study of various dosing regimens of TMB-365 and TMB-380 administered intravenously to HIV-1 infected individuals suppressed on combination antiretroviral therapy (cART). This adaptive study design will be comprised of Sentinel Groups (N=10) and Core Groups (N=20). Study participants must be on a continuous DHHS-recommended suppressive cART regimen for at least 6 months and have documented viral suppression below the limit of detection within the 3 months prior to Screening. Study participants should be on a stable regimen for at least 3 months. Switches of components of regimens may be allowed for intolerance and other adverse events, both anticipated and unanticipated. **<u>Sentinel Groups:</u>** Sentinel Groups will be comprised of 10 cART suppressed HIV-1 infected volunteers who receive a single IV dose of the combination of TMB-365 and TMB-380 while continuing cART. <u>Sentinel group dosing:</u> Single intravenous doses of 2400 mg, 3200 mg, 4800 mg of each antibody. <u>Sentinel group dose escalation</u>: 1. Sentinel group 1 will dose both antibodies at 2400 mg. Sentinel group 2 will dose both antibodies at 3200 mg. The third sentinel group will dose both antibodies at 4800 mg. 2. An independent Data Monitoring Committee (DMC) will review all available 14-day post dose safety data for at least 7 of 10 subjects in a Sentinel group before a request for dose escalation to the next Sentinel group will be approved.

	Core Groups: Safety and PK results obtained in Sentinel Group participants will inform the conduct of Core Groups. Core Groups will be comprised of 20 cART suppressed HIV-1 infected volunteers who receive multiple IV doses of the combination of TMB-365 and TMB-380 as a stand-alone maintenance regimen. Criteria for initiation of Core Group enrollment based on Sentinel group results: Safety: No SAEs probably or definitely due to TMB-365/380. No more than **one** Grade 3 or 4 adverse event possibly or definitely due to the monoclonal antibody infusions within 14 days of treatment. PK: Target trough concentrations are achieved in approximately 80% of Sentinel participants at 8 weeks. Asymmetric doses of TMB-365 and TMB-380 may be used in Core groups should safety and PK results support such an approach. Core group dosing: TMB-365: 4800 mg q 8 weeks (3 infusions). TMB-380: 4800 mg q 8 weeks (3 infusions). If indicated by safety, PK, and efficacy, an amendment may be made to the current protocol to test higher doses of either antibody in consultation with the Data Monitoring Committee and the FDA. Participants in the Core Groups will discontinue cART during antibody infusions and restart cART at Week 24. If there is evidence of virologic rebound defined as 2 consecutive HIV-1 RNA levels above 50 copies/mL at least 2 weeks apart in any Core subject, then oral cART must be restarted. Stopping criteria for an individual subject within a Core Group: Safety: Any SAE or Grade 3 or 4 adverse event probably or definitely due to the monoclonal antibody infusions within 14 days of treatment. Antiviral activity: Documented virologic failure in an individual. Resistance analysis including phenotype and genotype will be performed in subjects in whom

	virologic failure is documented. <u>Stopping criteria for dosing of a Core Group:</u> Safety: An SAE probably or definitely due to the monoclonal antibody infusions. More than one Grade 3 or 4 adverse event probably or definitely due to the monoclonal antibody infusions. Antiviral activity: Documented virologic failure in more than two individuals in a Core Group who have received scheduled infusions of the combination of TMB-365 and TMB-380. Resistance analysis including phenotype and genotype will be performed in subjects in whom virologic failure is documented. To ensure participant safety: ▪ All Grade 3, Grade 4, SAEs, and cases of virologic failure will be reviewed by the DMC. ▪ The DMC may terminate enrollment and dosing in the Core Group at any time. **<u>Study duration</u>**: Screening period: 6 weeks/45 days – Sentinel Groups; 8 weeks/60 days – Core Group Sentinel Groups: 12 to 16 weeks (4 weeks follow-up post infusions) Core Groups: 28 weeks (4 weeks follow-up post infusions and cART reinstitution) Dose escalation in the Sentinel groups will require approval of an independent Data Monitoring Committee based on 14-day safety data collected on 7/10 Sentinel Group subjects. Initiation of a Core group will require approximately 80% of Sentinel Group subjects at the selected dose level having met the safety and PK criteria. Toxicity evaluations will be guided by the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events Version 2.1. The Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0 scale will be used for assessment of any infusion reactions, or anaphylactic events.

Safety Assessments:	■ Physical examinations; ■ Vital sign measurements; ■ Clinical laboratory parameters (hematology, serum chemistry, lipid panel, and urinalysis); ■ Pregnancy tests; ■ Adverse events (AEs); and ■ Serious adverse events (SAEs)
Pharmacokinetic, Pharmacodynamic Antiretroviral Assessments and Patient Reported Outcomes Measurements:	■ Quantification of TMB-365 and TMB-380 levels at varying time points in order to characterize the PK profile; ■ In vitro quantification of the number of CD4 receptors and the percentage of CD4 T-cell receptors bound by TMB-365; ■ HIV-1 RNA (viral load) assessment in Core subjects; ■ HIVTSQs and HIVTSQc at various time points in Core subjects;
Statistical Considerations:	Sample Size: Up to 70 HIV-positive participants will be enrolled into the study. The sample size is not statistically driven. Individuals who discontinue the study for reasons other than adverse events may be replaced. Analysis Populations: The full analysis set (FAS) includes all participants who are administered any fraction of study drug. The PK population consists of all participants in the FAS. The analysis of study data will be primarily descriptive, with emphasis on tabular and graphical displays. Summary descriptive statistics will be calculated, along with point and interval estimates of solicited and unsolicited AEs. This study is exploratory, and any statistical inferences will be hypothesis generating, and not confirming. Statistical Analyses: All data collected at each visit will be summarized by dose group and overall where applicable. Continuous variables (e.g., age, weight) will be summarized using descriptive statistics consisting of number of participants, mean, standard deviation, minimum, median, and maximum values. Categorical variables (e.g., gender) will be summarized using the number and percentage of participants in each category. If there are unscheduled assessments between visits or repeat assessments at a visit, the one closest to the scheduled time of the visit will be used in the summaries. The association of data collected with a visit (i.e., whether it is scheduled, unscheduled, or a repeat) will be unambiguous in the Case Report Form

	(CRF). All data collected will be included in the data listings.

ABBREVIATIONS

ABBREVIATION	TERM
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
cART	combination antiretroviral therapy
CD4	glycoprotein expressed on the surface of T-helper cells
$CD4^+$	type of white blood cell, also called T-lymphocytes, T-cells, or T-helper cells
CDC	complement dependent cytotoxicity
Cmax	maximum serum concentration
CrCl	Creatinine clearance
CRF	Case Report Form
DAIDS	Division of Acquired Immunodeficiency Syndrome
DHHS	Department of Health and Human Services
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
EDTA	ethylenediaminetetraacetic acid
EI	entry inhibitor
ELISA	enzyme-linked immunosorbent assay
ERC	ethics review committee
FAS	full analysis set
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
HEENT	head, eyes, ears, nose, throat
HIV-1	human immunodeficiency virus type-1
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IgG	immunoglobulin G
IM	Intramuscular
INI	integrase inhibitor
IRB	institutional review board
IV	Intravenous

ABBREVIATION	TERM
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
Mab	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NRTI	nucleoside reverse transcriptase inhibitor
PBMC	peripheral blood mononuclear cell
PCS	potentially clinically significant
PD	Pharmacodynamic
PI	protease inhibitor
PK	Pharmacokinetic
PT	preferred term
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	system organ class
TEAE	treatment-emergent adverse event
Tmax	the time taken to reach the maximum concentration
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia

1 INTRODUCTION

1.1 Background

In 2019, 38 million people worldwide were living with HIV infection and 690,000 people died from HIV/AIDS[1]. Africa remains most severely affected, accounting for around 67% of the people living with HIV worldwide.

Many infected patients have been successfully treated with combination antiretroviral therapy (cART). Patients treated with cART have experienced profound and continuous viral suppression, often associated with substantial immune system recovery and halt of progression to clinical disease.

That said, there remain individuals with the need for novel therapies. There is interest in the use of long acting antiretroviral agents[2] and broadly neutralizing antibodies (bNAbs) to HIV and receptors required for viral entry[3, 4] for both the treatment and prevention of HIV-1 infection.

Long acting therapies provide advantage in that HIV-infected patients do not have the burden of daily pill taking. Agents given intravenously, particularly bNAbs may be associated with less side effects. Long acting agents may also reduce the risk of the emergence of resistance as oral regimes require high levels of adherence over time.

In this study we are proposing to use the combination of 2 bNAbs, TMB-365 and TMB-380, to maintain virologic suppression in HIV-1 infected participants suppressed on daily oral therapy.

1.2 TMB-365 and TMB-380

TMB-365 is a second generation CD4-directed post-attachment inhibitor with the same binding specificity as Trogarzo® (ibalizumab), but with modifications to improve its stability, pharmacokinetics and drug resistance profiles. The improved breadth of inhibition, stability and half-life of TMB-365 make it a promising candidate for future use in treatment of human immunodeficiency virus type 1 (HIV-1) infections. TMB-365 is being developed by TaiMed and the phase 1 clinical trial has been concluded.

TMB-380 (VRC07-523LS) is a potent and broadly neutralizing monoclonal antibody (bNAb) directed against the CD4-binding site of the HIV-1 glycoprotein 120 (gp120). TMB-380 is being developed by the Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH). The clinical experience with TMB-380 to date includes 15 clinical studies (three completed and 12 ongoing) conducted in the United States, the Republic of South Africa and/or Switzerland.[5]

With different yet complementary mechanisms against HIV-1 entry, combining TMB-365 and TMB-380 is proposed as a safe and potent non-oral maintenance therapy for virologically suppressed HIV-1 infected individuals on standard orally administered cART.

1.3 Preclinical Studies

1.3.1 TMB-365

TMB-365 is a humanized MAb and a member of an emergent class of HIV therapies

known as post-attachment inhibitors. It is the second generation of a US FDA approved HIV medicine, TROGARZO® (ibalizumab-uiyk), with an improved PK profile in cynomolgus monkeys [6] and broader viral strain coverage in vitro [7, 8]. As with TROGARZO®, TMB-365 binds to CD4, the primary receptor for HIV infection, thereby interfering with virus entry[9]. TMB-365 preserves the sequence and binding specificity of the ibalizumab variable region and therefore as with the parent antibody, likely binds to a unique epitope in domain 2 of the extracellular portion of the CD4 receptor and blocks HIV entry by steric hindrance after attachment[10]. Antibody binding to this epitope has also been shown to prevent viral transmission via cell-cell fusion[11]. As was shown for TROGARZO®, the TMB-365 binding site on CD4 domain 2 is likely to be distinct from the binding site required for interaction of CD4 with major histocompatibility complex (MHC) proteins, which map to CD4 domain 1. Because of this, TMB-365 is not expected to interfere with immunologic functions involving antigen presentation.

TMB-365 incorporates modifications, relative to TROGARZO®, including an IgG1 backbone with mutations in the Fc region to block effector functions, a glycan addition to the light chain variable region to improve breadth of inhibition, and amino acid substitutions to improve PK, including substitutions in the neonatal Fc receptor (FcRn) binding site and histidine substitutions in the variable region. The Fc mutations largely eliminate effector functions such as antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC).[12] With the glycan addition to the light chain variable region, TMB-365 has potent antiretroviral activity against diverse HIV strains, including ibalizumab-resistant isolates, regardless of HIV subtype, coreceptor tropism, or resistance to approved antiretroviral agents (PI, NRTI, NNRTI, INI, and EI), including TROGARZO®.[7, 8] Amino acid substitutions in the FcRn binding site and histidine substitutions in the variable region were designed to prolong the serum half-life of TMB-365 with enhanced recycling from acidic endosomes to plasma and reduced lysosomal degradation[9]. The pH-dependency of TMB-365 was demonstrated in vitro[9] and the prolonged half-life of TMB-365 was demonstrated in vivo as compared with ibalizumab. [6]

Three single dose PK studies and two repeated dose toxicity studies of intramuscular (IM) and IV TMB-365 have been conducted in cynomolgus monkeys.[6, 13, 14, 15, 16] In the single dose PK studies, at the dose range of 15-150 mg/kg, the elimination half-lives were 4.5-12.8 days and 4.4-9.1 days for IM and IV administration, respectively. The T_{max} was one day for IM administration. The C_{max} increased in approximately a dose proportional manner and the area under the curve (AUC) increased in a close to or more than dose proportional manner from 15 mg/kg to 150 mg/kg dose following IM and IV administration. The apparent volume of distribution was 36.6-51.4 mL/kg. It was less than the total body water, 0.7 L/kg, indicating that TMB-365 was mainly confined to the bloodstream. The bioavailability of TMB-365 following IM administration in monkeys was 78-88%. In the repeated dose toxicity studies, there was accumulation of drug in the serum, indicated by increased systemic exposure (C_{max} and AUC). No gender differences in the systemic exposure were observed at any dose level for both IM and IV TMB-365. Curve fitting of paired concentration and receptor occupancy data suggested that TMB-365 concentrations greater than 3.9 µg/mL supported 85% CD4 receptor occupancy, which is expected to be associated with significant virologic responses and is a good indicator for efficacy.

In the repeated dose toxicity studies, administration of TMB-365 at doses up to 80 mg/kg/week once weekly for total four injections by IM and IV administration to cynomolgus monkeys was well-tolerated and did not result in any treatment-related mortality or morbidity. No test article-related adverse effects were observed in terms of clinical signs, body weight, food consumption, ophthalmology, safety pharmacology, clinical pathology, and pathology. The median T_{max} was observed at one day post-dose following IM injection. The dose-normalized systemic exposure (C_{max} and AUC) was comparable for all three dose groups and the values were consistent with the PK study results for IM and IV administration. Drug accumulation was observed with a 2-3-fold increase in C_{max} and AUC with repeated dosing over time. The systemic exposure (C_{max} and AUC) appeared to be similar in both sexes at any dose level. The no observed adverse effect level (NOAEL) was suggested and projected to be 80 mg/kg/week for IM and IV administration. The corresponding AUC and C_{max} of IM TMB-365 following the last dose at NOAEL were 10,083 day*µg/mL and 1,840 µg/mL for males, and 11,542 day*µg/mL and 2,150 µg/mL for females, respectively. The corresponding AUC and C_{max} of IV TMB-365 following the last dose at NOAEL were 22,470 day*µg/mL and 5,178 µg/mL for males, and 18,306 day*µg/mL and 4,294 µg/mL for females, respectively. In a tissue cross-reactivity study against human tissues, no unexpected specific staining was observed.

1.3.2 TMB-380

TMB-380 is a recombinant human immunoglobulin G1 (IgG1) antibody produced in the Chinese Hamster Ovary (CHO) DG44 cell line. It was initially developed by the Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID) and manufactured at the VRC Pilot Plant. The nonclinical and clinical data presented in the protocol were obtained using the drug product manufactured by the VRC. The drug supply used in this protocol and in the future clinical studies will be manufactured by TaiMed, and has demonstrated comparability with the drug product manufacture by the VRC based on the physical, chemical and functional properties.

TMB-380 is an engineered variant of VRC01, which was originally discovered in a subject infected with HIV-1 for more than 15 years and whose immune system controlled the virus without antiretroviral therapy (ART).[17] Through advances in B-cell immunology, cloning, and structure-guided optimization techniques, numerous HIV-1 neutralizing monoclonal antibodies (mAb), including VRC07-523LS, were isolated with potency and breadth greater than those of early antibodies.

An *in vitro* neutralization activity results showed that TMB-380 neutralized 96% of strains with an IC_{50} of less than 50 µg/mL and 92% of strains with an IC_{50} of less than 1 µg/mL.[18] The overall breath (96% versus 89%) and potency (5- to 8-fold increase) are improved compared to VRC01. An *in vivo* challenge study showed that TMB-380 was >5-fold more potent than VRC01LS, a VRC01 variant conferring an increased plasma half-life. It was consisted with the *in vitro* neutralization activity results.

A pharmacokinetic study has been conducted male rhesus macaques.[18] Following 10 mg/kg TMB-380 intravenously (IV) administration, the half-life was 9.8 days. The concentrations of TMB-380 in rectal secretions were detectable for at least 14 days (last collection point).

A GLP repeat dose toxicity study with TMB-380 IV and subcutaneously (SC) was performed in male and female Sprague-Dawley rats.[19] Treatment with TMB-380, at

doses up to 400 mg/kg IV or 40 mg/kg SC with three doses at 10-day intervals was generally well tolerated as most findings were reversible and no longer seen at the end of the recovery period. IV administration of either 40 or 400 mg/kg TMB-380 had peak concentrations within one hour post-dose, whereas SC administration of 40 mg/kg TMB-380 resulted in a slower absorption at either 24 or 48 hours post-dose. Exposure (AUC) values were approximately 4-fold higher after the first dose in the 400 mg/kg IV group compared to the 40 mg/kg IV group. AUC values after the third IV dose were higher compared to the first dose, whereas the AUC values after the third SC dose were lower compared to the first SC dose. The SC bioavailablity is 36-42%. No large or consistent gender differences in exposure were noted between males and females within each dosing route. Additionally, histologic changes were not observed in the GLP repeat dose toxicology study in the cell types with staining observed in the GLP tissue cross reactivity study.[20]

1.3.3 Determination of the Antiviral Activity of TMB-365/TMB-380 in Combination

The i*n vitro* antiviral activity of TMB-380 in combination with TMB-365 or with ibalizumab (TMB-355) was evaluated in TZM-bl cell based, HIV-1 pseudovirus neutralization assays. The antiviral activity of the antibodies was determined by the Combinational Index (CI), which is the sum of fold changes of the IC_{50} under combination treatment relative to that of individual antibody. A CI > 1 is consistent with antagonism. If the CI is $\geq$ 0.5 and $\leq$ 1 the antibody effects are additive, and if the CI is < 0.5 then the combination is synergistic.

The in vitro antiviral activity of the combination TMB-365/TMB-380 was 0.007 ug/ml in comparison to 0.006 ug/ml of antiviral activity in the combination of ibalizumab (TMB-355) and TMB-380 (ibalizumab/TMB-380, TMB-355/TMB-380); the individual antibody antiviral activities are 0.010 ug/ml for TMB-365, 0.009 µg/mL for ibalizumab (TMB-355), and 0.025 µg/mL for TMB-380. The results demonstrate that combinations of TMB-365/TMB-380 and ibalizumab/TMB-380 are highly similar to each other. The combination index (CI) of TMB-365/TMB-380 is 1.0, whereas the CI value of ibalizumab/TMB-380 is 0.9. These data are consistent with the additive antiviral activity of TMB-365 and TMB-380 when used combination.[21,22] Additive antiviral activity is also demonstrated between ibalizumab and TMB-380.

1.4 Previous Human Experience

Both TMB-365 and TMB-380 have been developed independently under various INDs with documented safety and efficacy in humans, including healthy subjects and HIV-1 infected patients.

1.4.1 TMB-365

The completed first-in-human clinical study of TMB-365 is a phase 1, randomized, double-blinded, placebo-controlled, sequential single dose escalation study in HIV-1 infected patients (protocol TMB-365-101, IND 141891). In this trial, three groups of 8-9 patients each received intravenously administered TMB-365 at 400, 800 and 1600 mg, respectively, or matching placebo (active:placebo = 6:2). The study populations for 400 and 800 mg dose groups were HIV-1 seropositive and had not received antiretroviral therapy (ART) for at least 4 weeks prior to the first dose, with HIV-1 RNA ≥1,000 copies/mL and <100,000 copies/mL. Protocol amendment 3 was submitted to the FDA

on March 18, 2021 (S-0013, IND 141891) to allow for the rapid recruitment and treatment of 8 HIV-1 infected and cART-suppressed participants for the 1600 mg dose group – the identical target population for this clinical trial.

A total of 17 viremic and 8 aviremic, suppressed HIV-1-infected participants were enrolled in this study. The pharmacokinetics (PK) parameters were calculated by non-compartmental analysis (Table 1). Total exposure (C_{max} and AUC) was dose-dependent and increased disproportionately to dose. Systemic clearance (CL) decreased and half-life ($T_{1/2}$) increased with increasing dose. Such nonlinear effects in clearance are common for monoclonal antibody targeting cell surface molecules, such as CD4. The behavior is characteristic of saturable (capacity-limited) elimination kinetics. At the higher doses, tri-phasic kinetics were observed: a rapid distribution phase followed by a slower terminal elimination phase and then a rapid final elimination. Therefore, $T_{1/2,s}$ and $T_{1/2,b}$ were estimated to describe the slow elimination rate at saturation and rapid elimination rate below saturation, respectively. During the saturated elimination phase, the effective half-life was on the order of roughly 6 to 11 days. As the TMB-365 concentration fell to levels associated with uncoating of $CD4^+$ T-cells, elimination was more rapid, on the order of 2-4 days.

As shown in Figure 1, robust virologic responses were observed after 400 mg or 800 mg TMB-365 administration. There was no virologic response with placebo treatment. The maximum mean change from baseline in HIV viral load occurred at Day 15 post-dose and was -1.55 (±0.29) and -1.57 (± 0.32) $\log_{10}$ HIV RNA copies/mL for the subjects received 400 and 800 mg, respectively. Viral load rebound occurred after 2 and 4 weeks post-dose for the 400 and 800 mg dose group, respectively. This timing coincided with the loss of measurable serum TMB-365 levels.

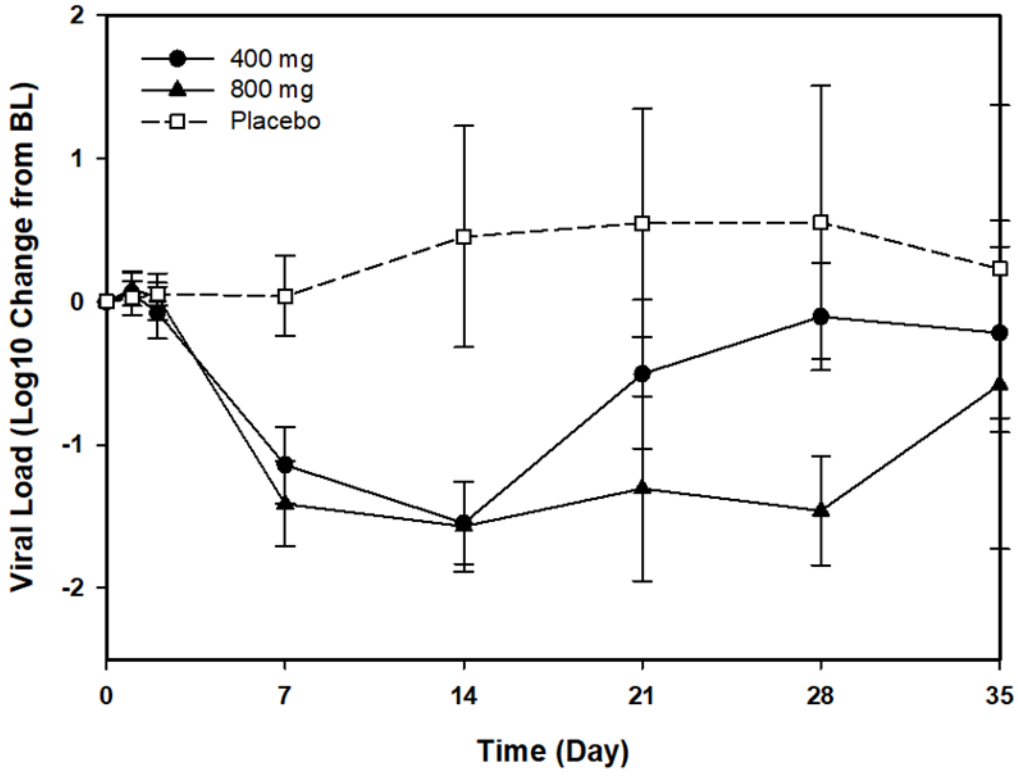
A single dose of TMB-365 at 400 mg, 800 mg, and 1600 mg was well tolerated, with no serious adverse events (SAEs) or grade 3 or 4 treatment emergent adverse events (TEAEs). Eleven participants (44%) experienced one or more TEAEs. Two of them received placebo. The number and percentage of participants experiencing TEAEs did not increase with increasing dose. The majority of TEAEs were mild in severity. Moderate events included headache in 2 participants (8%), suspected COVID-19, urticarial and periorbital oedema in 1 participant each (4%). The most frequent TEAEs were headache and orpharyngeal pain in 2 participants (8%). Three participants (12%) reported at least one TEAE that was possibly related to the study drug. The possible related TEAEs included headache, pyrexia, oropharyngeal pain, wheezing, urticarial and periorbital oedema. There was no evidence of immunogenicity from the study drug.

Table 1 Pharmacokinetics Parameters of TMB-365

Dose (mg)	T_{max} (day)	C_{max} (µg/mL)	AUC (day*µg/mL)	Vd (L)	CL (L/day)	$T_{1/2}$ (day)	$T_{1/2,s}$ (day)	$T_{1/2,b}$ (day)
400	0.20 ± 0.40	138.22 ± 45.27	469.45 ± 121.02	2.84 ± 1.28	0.89 ± 0.21	2.17 ± 0.76	NA	NA
800	0.20 ± 0.36	441.43 ± 79.65	2173.19 ± 1318.47	2.14 ± 1.33	0.45 ± 0.22	3.39 ± 1.48	6.34 ± 1.28	2.43 ± 1.36
1600	0.02 ± 0.02	705.67 ± 67.36	7471.84 ± 1691.80	1.97 ± 0.91	0.22 ± 0.04	6.39 ± 3.02	10.59 ± 2.01	3.67 ± 1.04

NA: Not available; T_{max}: time to maximum concentration; C_{max}: maximum concentration; AUC: area under curve; Vd: volume of distribution; CL: clearance; $T_{1/2}$: half-life; $T_{1/2,s}$: half-life at saturation; $T_{1/2,b}$: half-life below saturation

Figure 1 TMB-365-101 Single Dose Viral Load Reductions



1.4.2 TMB-380

The clinical experience with TMB-380 is derived from 16 clinical trials (5 completed/terminated and 11 ongoing) conducted in the United States, the Republic of South Africa and Switzerland (as of February 2022).

Based on the available results from 2 studies (Studies VRC605 and VRC607/A5378), TMB-380 has been administered IV or SC to 25 HIV-uninfected adults and 9 HIV-infected patients. Single dose regimens of TMB-380 ranging from 1 to 40 mg/kg IV or

5 mg/kg SC and repeat-dose regimens of 20 mg/kg IV have been shown to be well tolerated. All reported local and systemic reactogenicity was mild to moderate in severity. There have been no SAEs assessed as related to TMB-380. For the 26 participants who received TMB-380 IV, the most commonly reported systemic reactions were malaise in 5 participants (19%), myalgia in 4 participants (15%) and headache in 3 participants (12%). Four (15%) participants reported local reactions, including pain/tenderness and bruising. For the 8 participants who received TMB-380 SC, the most commonly reported symptoms were pain and tenderness in four participants (50%) and malaise or headache in three (38%) participants.

TMB-380 showed excellent PK with half-life of 38 and 33 days after IV and SC administrations in the HIV-uninfected participants (n=25).[23] Maximum (C_{max}) and 12-week (C_{84D}) serum concentrations increased proportionally with IV doses from 5-40 mg/kg. The time after infusion where the maximum serum concentration (T_{max}) was measured occurred within the first few hours after IV administration, and approximately 10 days following SC administration.

In the HIV-infected participant (n=9), a single IV dose of TMB-380 at 40 mg/kg achieved a 1.7 log_{10} viral load reduction within 14 days.[5] The PK parameters are shown in Table 2.

Table 2 Pharmacokinetic parameters after 40 mg/kg TMB-380 IV administration (Mean (SD))

C_{max} (µg/mL)	T_{max} (days)	C_{28D} (µg/mL)	C_{84D} (µg/mL)	AUC (µg*day/mL)	CL (mL/day)	$T_{1/2}$ (day)
1295.2 (375.9)	0.06 (0.05)	162.6 (42.7)	60.7 (20.8)	17967 (4563)	188.7 (55.8)	56.5 (13.2)

2 STUDY OBJECTIVES

The primary objectives of this study are to:

- Evaluate the safety and tolerability of various doses and dosing regimens of IV infusions of TMB-365 and TMB-380 given q8wks in suppressed, cART treated HIV-1 infected participants.
- Define the pharmacokinetic (PK) profile of TMB-365 and TMB-380 when given q8wks in suppressed, cART treated HIV-1 infected participants.
- Evaluate the antiviral activity of TMB-365 in combination with TMB-380 as maintenance therapy in suppressed HIV infected individuals. (Core only)

Exploratory objectives of this study are to:

- Determine the immunogenicity of TMB-365 and TMB-380 in HIV-1 infected suppressed participants.
- Determine the resistance profiles of TMB-365 and TMB-380 *in vivo*.

3 STUDY PLAN

3.1 Overall Design

This study is a phase 1b / 2a adaptive open-label dose escalation study of the combination of TMB-365 and TMB-380. This adaptive study design will be comprised of Sentinel Groups (N=10) and Core Groups (N=20). Safety and pharmacokinetic (PK) data obtained from Sentinel group participants will guide the conduct of Core Group execution.

Participants will be HIV-infected and suppressed for at least 6 months on continuous daily oral combination antitretroviral therapy (cART). Continuous is defined as no more than 3 consecutive days of missed cART. There are three doses of each antibody being explored, 2400 mg, 3200 mg, and 4800 mg.

3.1.1 Sentinel Groups

Sentinel Groups will be comprised of 10 cART suppressed HIV-1 infected volunteers who receive a single IV dose of the combination of TMB-365 and TMB-380 while continuing cART.

Sentinel Group 1 will be dosed with 2400 mg of each antibody and will continue daily oral cART throughout the screening, infusion, and post-infusion observation period of 12 weeks and be assessed for safety and pharmacokinetics.

Sentinel group 2 will dose both antibodies at 3200 mg. The third sentinel group will dose both antibodies at 4800 mg.

Criteria for safety of a dose of either TMB-365 or TMB-380 include:

i) No SAEs probably or definitely due to TMB-365 or TMB-380

ii) No more than one Grade 3 or Grade 4 adverse event probably or definitely related to TMB-365 or TMB-380 at any dose level.

Toxicity evaluations will be guided by the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events Version 2.1. The Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0 scale will be used for assessment of any infusion reactions, or anaphylactic events.

PK targets:

i. TMB-365: serum levels $\geq$0.3 μg/mL

ii. TMB-380: serum levels $\geq$65 μg/mL

Should a dose of either antibody prove safe and approximately 80% of subjects studied in a given Sentinel dose group meet specified safety and PK criteria, then a Core group of 20 subjects will be enrolled and treated with that dose of TMB-365 and TMB-380 as a stand-alone complete maintenance regimen for 24 weeks (see below).

Safety must be established prior to any request for dose escalation to the next higher Sentinel dose group. A review of 14-day safety data in 7 of 10 subjects after infusion must be available for review prior to any request for dose escalation. Dose escalation may only occur with the approval of an independent Data Monitoring Committee

(DMC) as described in Section 9.9.

The maximum dose of TMB-365 and TMB-380 that will be tested in Sentinel groups is 4800 mg.

The first 3 subjects in each Sentinel group will be treated at designated sites selected for demonstration of expertise in the use of monoclonal antibody therapy. Subjects will remain at the study site for at least 3 and up to 5 hours post-infusion for monitoring of vital signs every 15 minutes beginning 15 minutes prior to the infusion of TMB-365 and TMB-380 as well as observation for the presence of infusion reactions. It is at the discretion of the Principal Investigator at the study site to determine the duration of observation.

Should the infusions be well tolerated and no Grade 3 or 4 AEs, or SAE's occur due to study drugs within 7 days of infusion, then the remaining 7 subjects in that group may be recruited/treated. These subjects will remain at study sites for at least 1 hour and up to 3 hours post-infusion for monitoring of vital signs and the presence of infusion reactions. It is at the discretion of the Principal Investigator at the study site to determine the duration of observation.

3.1.2 Core Group Subjects

Core Groups will be comprised of 20 cART suppressed HIV-1 infected volunteers and will receive multiple IV doses of the combination of TMB-365 and TMB-380 as a stand-alone maintenance regimen for 24 weeks. Oral cART will be restarted in the clinic at the Week 24 visit.

Core group participants will complete the study at Day 196 / Week 28, 4 weeks after reinstituting oral cART.

Sentinel group participants may be enrolled in a Core group if infusions are well tolerated and the subject is willing to discontinue oral cART.

Dosing of Core participants is based on safety and PK findings in the Sentinel Group and include

TMB-365: 4800 mg q 8 weeks.

TMB-380: 4800 mg q 8 weeks.

If indicated by safety, PK, and efficacy, an amendment may be made to the current protocol to test higher doses of either antibody in consultation with the Data Monitoring Committee and the FDA.

Asymmetric doses of TMB-365 and TMB-380 may be used in Core groups should safety and PK results support such an approach. Sentinel Group participants that wish to participate in Core Groups must repeat all screening procedures including signing a second Informed Consent Form.

3.2 Dose Selection and Rationale for Sentinel Groups

TMB-365 has demonstrated *in vitro* antiviral activity superior to its parent compound, ibalizumab.[7,24] The exposure-response relationship of ibalizumab showed the response rate (the percentage of patients with HIV-1 RNA levels <50 copies/mL at Week 24) achieved a plateau when ibalizumab concentrations were >0.3 µg/mL.[25] Therefore the target effective concentration of TMB-365 is set to 0.3 µg/mL. Results in the Phase 1

study revealed that TMB-365 demonstrates antiviral activity at 0.3 μg/mL supporting this target effective concentration.

In the Phase 1 study, a direct relationship between TMB-365 concentrations and viral load reduction for 400 and 800 mg doses was demonstrated. A direct relationship between TMB-365 concentrations and RO for 800 and 1600 mg doses was also demonstrated. This suggests that TMB-365 concentrations can be used as a surrogate to predict the antiviral activity for dose selection.

Simulations based on the available 400 mg, 800 mg, and 1600 mg pharmacokinetic results suggest that the proposed dosing regimens can maintain concentrations above the target concentration during the treatment period in this study.

The proposed TMB-380 dose is based on the ongoing clinical study designs. In the IGHID 11802 (NCT03803605) and A5357 (NCT03739996) studies, the TMB-380 dose is 40 mg/kg every 60 days and 8 weeks, respectively. The antiviral activity has been demonstrated in a single dose study (Study VRC607-A5378, NCT02840474). A single 40 mg/kg dose reduced HIV viral RNA levels by 1.7 $\log_{10}$ copies/mL and the mean time to the nadir was 9 days. Along these lines, a 3200 mg dose (40 mg/kg for an 80 kg person) is promising for bimonthly dosing.

In a post-hoc analysis of a Phase 1 clinical trial of TMB-380, neutralization coverage over the first 24 weeks after a single administration was predicted.[23] With the predicted coverage as 90%, the correlate concentration is ~65 μg/mL, which is the target effective concentration in this study. Simulations were performed based on the available PK data from study VRC607-A5378. The results suggest that the proposed q8wk and q12wk dosing regimens can maintain concentration above the target effective concentration during the treatment period. The dose of 3200 mg (~40 mg/kg) of TMB-380 every 8 weeks has been studied in several completed and ongoing clinical trials for HIV treatment and demonstrated antiviral activity when the concentration is greater than the target effective concentration.

3.3 Dose selection and rationale for the Core Group

3.3.1 Safety

Thirty subjects from Sentinel groups received one of 3 doses of both TMB-365 and TMB-380 as detailed above and were followed for 12-16 weeks. One Group 3 subject (4800 mg/4800 mg) was erroneously dosed with 1600 mg of each antibody. No SAEs, Grade 3 or 4 adverse events, or acute infusion events were observed. Treatment emergent AEs (N=32) were mild to moderate. Five were probably or definitely attributed to infusions with the study drug bNAbs. Two subjects experienced the delayed onset of fatigue and chills, one moderate and one mild, interpreted as hypersensitivity. Other AEs included sneezing (N=1), fatigue (N=1), and cold feet (N=1).

3.3.2 Pharmacokinetics/Pharmacodynamics

Nine subjects received 4800 mg/4800 mg TMB-365 and TMB-380 in Sentinel Group 3. At Week 8, the mean TMB-365 and TMB-380 concentrations were 15.1 (± 13.5) and 86.4 (± 24.1) μg/ml, respectively, and approximately 80% (7/9) of participants met pre-defined trough targets. In addition, TMB-365 CD4 receptor occupancy was above 80%,

which is an indicator of good efficacy, in 8/9 of Group 3 participants at Week 8. Therefore, 4800 mg/4800 mg q8wk was selected for the Core Group.

If indicated by safety, PK, and efficacy, an amendment may be made to the current protocol to test higher doses of either antibody in consultation with the Data Monitoring Committee and the FDA.

3.3 Study Events and Procedures

Table 3 through Table 5 below provide the schedules of events and procedures for the study.

Table 3 Schedule of Events and Procedures for Sentinel Groups receiving 2400 mg or 3200 mg of TMB-365 and TMB-380

Study Visit	Screening	Day 0 Baseline	Day 7 Week 1	Day 14 Week 2	Day 28 Week 4	Day 42 Week 6	Day 49 Week 7	Day 56 Week 8	Day 63 Week 9	Day 70 Week 10	Day 84 Week 12	Failure Confirmation or Premature Discontinuation
Visit window (days)	(-45 days)	N/A	± 1	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	N/A
Visit Number	1	2	3	4	5	6	7	8	9	10	11	UV
Consent	X											
Inclusion/Exclusion Criteria	X											
History	X											
Demographics	X											
Physical Exam	X										X	
Concomitant Medications	X	X	X	X	X			X			X	X
Interim History		X	X	X	X			X			X	X
Directed Physical Exam		X	X	X	X			X				X
Adverse Event Monitoring		X	X	X	X			X			X	X
Vital Signs	X	X	X	X	X			X			X	X
Weight		X									X	X
Enrollment		X										
TMB-365 and TMB-380 infusion[1]		X										
Serum PK TMB-365 (pre-dose if drug administered on this day)		X[2]	X	X	X	X	X	X	X	X	X	X
Serum PK TMB-380 (pre-dose if drug administered on this day)		X[2]	X	X	X	X	X	X	X	X	X	X
Serum PK TMB-365 post-dose 10 min		X										
Serum PK TMB-380 post-dose 10 min		X										

Study Visit	Screening	Day 0 Baseline	Day 7 Week 1	Day 14 Week 2	Day 28 Week 4	Day 42 Week 6	Day 49 Week 7	Day 56 Week 8	Day 63 Week 9	Day 70 Week 10	Day 84 Week 12	Failure Confirmation or Premature Discontinuation
Visit window (days)	(-45 days)	N/A	± 1	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	N/A
CD4 RDRO (receptor density and occupancy)		X	X	X	X	X	X	X	X	X	X	X
Archive samples		X	X	X	X	X	X	X	X	X	X	X
HIV EIA and Confirmatory Testing	X											
HIV RNA PCR	X	X									X	X
CD4 and CD8 Lymphocyte Count	X	X	X	X	X			X			X	X
Complete Blood Count	X	X	X	X	X			X			X	X
Blood Chemistry	X	X	X	X	X			X			X	X
Creatinine	X	X	X	X	X			X			X	X
Fasting lipid profile[3]		X									X	X
HBV Screening	X											
HCV Screening	X											
Serum Pregnancy[4]	X											
Urine HCG[4]		X									X	X
Urinalysis	X	X						X			X	X
Serum collection for immunogenicity		X		X				X			X	X

NOTE: All specimens other than post-dose serum concentrations are collected pre-dose on the days of study drug administration

[1] The first 3 participants in each Sentinel dose group will be closely observed for at least 180 minutes (3 hours) and up to 300 minutes (5 hours) after IP administration with the duration to be at the discretion of the site PI according to Protocol procedures (see Section 6.3). The remaining Sentinel group participants will be observed anywhere from 60 minutes (1 hour) to 180 minutes (3 hours) after IP administration with the duration to be at the discretion of the site PI.

[2] Pre-Dose specimens to be collected within 1 hour before the start of study drug infusion.

[3] Lipid profile should be a fasting specimen, that is, 8 hours after eating. Water, black coffee or tea are permissible. Medication may be taken prior to blood draw with water.

[4] Pregnancy testing will be performed only for participants of childbearing potential.

Table 4 Schedule of Events and Procedures for Sentinel Group receiving 4800 mg of TMB-365 and TMB-380

Study Visit	Screening	Day 0 Baseline	Day 14 Week 2	Day 28 Week 4	Day 56 Week 8	Day 70 Week 10	Day 77 Week 11	Day 84 Week 12	Day 91 Week 13	Day 98 Week 14	Day 112 Week 16	Failure Confirmation or Premature Discontinuation
Visit window (days)	(-45 days)	N/A	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	N/A
Visit Number	1	2	3	4	5	6	7	8	9	10	11	UV
Consent	X											
Inclusion/Exclusion Criteria	X											
History	X											
Demographics	X											
Physical Exam	X										X	
Concomitant Medications	X	X	X	X	X			X			X	X
Interim History		X	X	X	X			X			X	X
Directed Physical Exam		X	X	X	X			X				X
Adverse Event Monitoring		X	X	X	X			X			X	X
Vital Signs	X	X	X	X	X			X			X	X
Weight		X									X	X
Enrollment		X										
TMB-365 and TMB-380 infusion[1]		X										
Serum PK TMB-365 (pre-dose if drug administered on this day)		X[2]	X	X	X	X	X	X	X	X	X	X
Serum PK TMB-380 (pre-dose if drug administered on this day)		X[2]	X	X	X	X	X	X	X	X	X	X
Serum PK TMB-365 post-dose 10 min		X										
Serum PK TMB-380 post-dose 10 min		X										
CD4 RDRO (receptor density and occupancy)		X	X	X	X	X	X	X	X	X	X	X
Archive samples		X	X	X	X	X	X	X	X	X	X	X

Study Visit	Screening	Day 0 Baseline	Day 14 Week 2	Day 28 Week 4	Day 56 Week 8	Day 70 Week 10	Day 77 Week 11	Day 84 Week 12	Day 91 Week 13	Day 98 Week 14	Day 112 Week 16	Failure Confirmation or Premature Discontinuation
Visit window (days)	(-45 days)	N/A	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	N/A
HIV EIA and Confirmatory Testing	X											
HIV RNA PCR	X	X									X	X
CD4 and CD8 Lymphocyte Count	X	X	X	X	X			X			X	X
Complete Blood Count	X	X	X	X	X			X			X	X
Blood Chemistry	X	X	X	X	X			X			X	X
Creatinine	X	X	X	X	X			X			X	X
Fasting lipid profile[3]		X									X	X
HBV Screening	X											
HCV Screening	X											
Serum Pregnancy[4]	X											
Urine HCG[4]		X									X	X
Urinalysis	X	X			X			X			X	X
Serum collection for immunogenicity		X	X		X						X	X

NOTE: All specimens other than post-dose serum concentrations are collected pre-dose on the days of study drug administration

[1] The first 3 participants in each Sentinel dose group will be closely observed for at least 180 minutes (3 hours) and up to 300 minutes (5 hours) after IP administration with the duration to be at the discretion of the site PI according to Protocol procedures (see Section 6.3). The remaining Sentinel group participants will be observed anywhere from 60 minutes (1 hour) to 180 minutes (3 hours) after IP administration with the duration to be at the discretion of the site PI.

[2] Pre-Dose specimens to be collected within 1 hour before the start of study drug infusion.

[3] Lipid profile should be a fasting specimen, that is, 8 hours after eating. Water, black coffee or tea are permissible. Medication may be taken prior to blood draw with water.

[4] Pregnancy testing will be performed only for participants of childbearing potential.

Table 5 Schedule of Events and Procedures for Core Groups receiving every 8-week dosing

Study Visit	Screening	Day 0 Baseline	Day 14 Week 2	Day 28 Week 4	Day 56 Week 8	Day 84 Week 12	Day 112 Week 16	Day 140 Week 20	Day 168 Week 24	Day 196 Week 28	Failure Confirmation or Premature Discontinuation
Visit window (days)	(-60 days)	N/A	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	N/A
Visit Number	1	2	3	4	5	6	7	8	9	10	UV
Consent	X										
Inclusion/Exclusion Criteria	X										
History	X										
Demographics	X										
Physical Exam	X					X			X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Interim History		X	X	X	X	X	X	X	X	X	X
Directed Physical Exam		X	X	X	X		X	X			
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Weight		X								X	X
Enrollment		X									
Discontinue cART Therapy[1]		X									
Restart cART Therapy[1]									X		
TMB-365 and TMB-380 infusion[2]		X			X		X				
Serum PK TMB-365 (pre-dose if drug administered on this day)		X[3]	X	X	X[3]	X	X[3]	X	X	X	X
Serum PK TMB-380 (pre-dose if drug administered on this day)		X[3]	X	X	X[3]	X	X[3]	X	X	X	X
Serum PK TMB-365 post-dose 10 min		X			X		X				
Serum PK TMB-380 post-dose 10 min		X			X		X				
CD4 RDRO (receptor density and occupancy)		X	X	X	X	X	X	X	X	X	X

Study Visit	Screening	Day 0 Baseline	Day 14 Week 2	Day 28 Week 4	Day 56 Week 8	Day 84 Week 12	Day 112 Week 16	Day 140 Week 20	Day 168 Week 24	Day 196 Week 28	Failure Confirmation or Premature Discontinuation
Visit window (days)	(-60 days)	N/A	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	N/A
Archive samples		X	X	X	X	X	X	X	X	X	X
HIV EIA and Confirmatory Testing	X										
HIV RNA PCR	X	X	X	X	X	X	X	X	X	X	X
CD4 and CD8 Lymphocyte Count	X	X	X	X	X	X	X	X	X	X	X
Complete Blood Count	X	X	X	X	X	X	X	X	X	X	X
Blood Chemistry	X	X	X	X	X	X	X	X	X	X	X
Creatinine	X	X	X	X	X	X	X	X	X	X	X
Fasting lipid profile[4]		X							X		X
HBV Screening	X										
HCV Screening	X										
Serum Pregnancy[5]	X										
Urine HCG[5]		X		X	X	X	X	X	X	X	X
Urinalysis[6]	X	X			X				X	X	X
Serum collection for immunogenicity		X	X				X			X	X
Plasma Storage for Resistance Testing		X	X	X	X	X	X	X	X	X	X
HIVTSQs administration[7]		X			X				X	X	
HIVTSQc administration[8]									X		

NOTE: All specimens other than post-dose serum concentrations are collected pre-dose on the days of study drug administration

[1] Record the time of cART dose which should be taken in the clinic, and prior to study drug administration at the Baseline visit
[2] Core group participants will be observed for 60 minutes (1 hour) after IP administration per protocol procedures (See Section 7.3)
[3] Pre-Dose specimens to be collected within 1 hour before the start of study drug infusion.
[4] Lipid profile should be a fasting specimen, that is, 8 hours after eating. Water, black coffee or tea are permissible. Medication may be taken prior to blood draw with water.
[5] Pregnancy testing will be performed only for participants of childbearing potential.
[6] Urinalyses are performed on site by dipstick and should reflex to a complete urinalysis sending the sample to the central laboratory if the dipstick result is abnormal
[7] HIVTSQs is the HIV Treatment Satisfaction Questionnaire - status version to be completed by study subject. The questionnaire should be completed prior to any other study procedures at visits where it is administered, including the restarting of oral cART at Week 24.
[8] HIVTSQc is the HIV Treatment Satisfaction Questionnaire - change version to be completed by study subject. The questionnaire should be completed after completing the

HIVTSQs and prior to any other study procedures at visits where it is administeredincluding the restarting of oral cART at Week 24.

3.4 Safety Assessments

Safety assessments will include the results of the following measurements:

- Physical examinations;
- Vital sign measurements;
- Patient weight at baseline and end-of-study;
- Anti-TMB-365 and TMB-380 antibody levels (immunogenicity of TMB-365 and TMB-380);
- Clinical laboratory parameters (hematology, serum chemistry, lipid panel, and urinalysis);
- Pregnancy tests;
- AEs;
- SAEs;
- Infusion reactions

3.5 Pharmacokinetic and Antiviral Assessments

Pharmacokinetic and antiviral assessments will include the results of the following measurements:

- Quantification of serum TMB-365 and TMB-380 levels at varying time points in order to characterize the PK profile;
- *In vitro* quantification of the number of CD4 receptors and the percentage of CD4 T-cell receptors bound by TMB-365;
- HIV-1 RNA (viral load) assessments to assess maintenance of suppression in Core subjects.

3.6 Patient Reported Outcome Measures

Patient reported outcome measures (PROM) will be assess at various time points using the following validated questionnaires (see Appendix C):

- HIV Treatment Satisfaction Questionnaire-status (HIVTSQs)
- HIV Treatment Satisfaction Questionnaire-change (HIVTSQc)

4 STUDY TREATMENT

4.1 Study Drug Dosage and Administration

Study drugs TMB-365 and TMB-380 will be administered together in one IV bag of 250 mL normal saline by IV infusion. Potential doses and dosing regimens include:

Sentinel groups (N=10 for each group):
TMB-365: 2400 mg, 3200 mg, 4800 mg x single dose
TMB-380: 2400 mg, 3200 mg, 4800 mg x single dose

Anticipated Core groups (N=20 for each group):
TMB-365: 4800 mg q8wks for 24 weeks
TMB-380: 4800 mg q8wks for 24 weeks

If indicated by safety, PK, and efficacy, an amendment may be made to the current protocol to test higher doses of either antibody in consultation with the Data Monitoring Committee and the FDA.

Study drug will be provided in single-use vials containing 16 mL of TMB-365 or TMB-380 at a concentration of 100 mg/mL.

The site research pharmacist or designee will prepare the study drug.

Study drugs will be thawed by the following steps.

1. Thaw vial(s) for a minimum of 2 hours until no ice is observed at controlled room temperature (maximum 27°C), or overnight (e.g., 6 pm to 8 am) in the refrigerator after removing from the freezer.
2. The refrigerated product must be equilibrated at controlled room temperature (maximum 27°C) for a minimum of 30 minutes before preparation.
3. The thawed drug can be kept at controlled room temperature (maximum 27°C) for 24 hours and in the refrigerator (2-8°C) for two weeks.
4. Before preparation for administration, vials should be swirled for 30 seconds, yet avoid foaming. DO NOT SHAKE THE VIALS.

TMB-365 and TMB-380 will be mixed and diluted in one IV bag for infusion. The study drug should be administered using sterile technique within four hours after the time of preparation. The IV infusion should be administered with an 1.2 Micro in-line filter infusion set in the cephalic vein of the participant's right or left arm. If this vein is not accessible, an appropriate vein located elsewhere can be used.

Antibodies will be administered over 60 minutes to all participants.

The first 3 subjects in each Sentinel group will be treated at designated sites selected for demonstration of expertise in the use of monoclonal antibody therapy. Subjects will remain at the study site for at least 3 hours and up to 5 hours post-infusion for monitoring of vital signs every 15 minutes beginning 15 minutes prior to the infusion of TMB-365 and TMB-380 as well as observation for the presence of infusion reactions. The duration of observation post-infusion is at the discretion of the site PI. Should the infusions be well tolerated and no Grade 3 or 4 AEs, or SAE's occur due to study drugs within 7 days of infusion, then the remaining 7 subjects in that group may be recruited/treated. These subjects will remain at study sites at least 1 hour and up to 3 hours post-infusion for monitoring of vital signs and the presence of infusion reactions. The duration of observation post-infusion is at the discretion of the site PI.

See Section 6.3 for details regarding monitoring the period pre-, post- and during infusion.

4.2 Concomitant Medications and Restrictions

Use of and changes in concomitant medications will be recorded in the participant's source documents. All prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications are to be recorded.

Any concomitant medication with the exception of those listed below may be given at the

discretion of the investigator. However, the investigator has the responsibility of ensuring that details regarding the concomitant medication are recorded for the participant in the Case Report Form (CRF). Complete information is expected for any medication prescribed during the trial.

The prescribing information for all concomitant medications should be reviewed carefully. The guidance provided in the respective contraindications, warnings, and precautions section for any medication must be followed to prevent any potentially serious or life-threatening drug interactions.

The following medications are not to be administered:

- Vaccines other than for influenza and COVID-19.
- All investigational drugs.

Participants in all Sentinel groups are expected to continue suppressive combination antiretroviral therapy with the same medications being taken at the time of the screening throughout study participation. Participants in Core groups will discontinue cART on day 0, the day of first infusion, through the Week 24 week visit unless they are instructed to reinitiate cART in the event of virologic failure or intolerance.

First-dose, generalized, self-limiting skin rash has been described with therapeutic MAbs[26, 27]. Any participant that experiences anaphylactoid symptoms during monoclonal antibody infusion should have the drug administration stopped immediately. Severe post-administration reaction management may include use of corticosteroids, antihistamines, oxygen, and IV fluids based on the severity and symptoms[28]. Refer to Appendix B for further information on the management of suspected anaphylactoid reactions. Participants should be followed until any such symptoms resolve.

4.3 Measurement of Participant Compliance

Participant compliance will require the availability of the participant at the study site to receive the combination of TMB-365 and TMB-380 and the participant's willingness/ability to receive the dose. Participants who fail to receive the administration of study drug may be withdrawn from the study at the discretion of the Sponsor or designee or the principal investigator.

4.4 Study Drug Description

The Sponsor or designee will provide the Research Pharmacists at the sites with open-label vials containing TMB-365 and TMB-380. TMB-365 is provided as a parenteral formulation in a 20 mL, clear-glass vial. The drug product contains TMB-365 at a concentration of 100 mg/mL, polysorbate 80, sucrose, and water for injection USP at pH 4.5 with acetate buffer. Each vial contains 16 mL of fluid to be withdrawn. TMB-380 is provided as a parenteral formulation in a 20 mL, clear-glass vial. The drug product contains TMB-380 at a concentration of 100 mg/mL, histidine, sodium chloride, sucrose, sorbitol, and water for injection at pH 6.8. Each vial contains 16 mL of fluid to be withdrawn.

TMB-365 solution is brownish-yellow, and TMB-380 solution is yellow.

4.5 Study Drug Packaging, Storage, and Disposal

TMB-365 is provided as a single-use parenteral formulation in a 20 mL, clear-glass vial containing 16 mL of study drug. The stability of the TMB-365 drug product at -20ºC is

evaluated in on-going studies. Study drug will be shipped under frozen conditions with a temperature-monitoring device. TMB-365 should be stored frozen at -20ºC and protected from light during storage (not during the preparation and administration).

TMB-380 is provided as a single-use parenteral formulation in a 20 mL, clear-glass vial containing 16 mL of study drug. The stability of the TMB-380 drug product at -20ºC is evaluated in on-going studies. Study drug will be shipped under frozen conditions with a temperature-monitoring device. TMB-380 should be stored frozen at -20ºC and protected from light during storage (not during the preparation and administration).

Investigator sites must store the investigational product in a secure location and maintain a temperature log of the storage conditions. The temperature must be continuously monitored with a continuous-monitoring temperature device. Temperature logs must be available for review at each site monitoring visit. Temperature excursions outside the required limits should be reported promptly to the Sponsor or designee and the affected study drug should not be administered to any participants until further instruction. The Sponsor or designee will investigate temperature excursions and adjudicate disposition of affected study drug.

Any spent vials or remaining contents of used vials (TMB-365 or TMB-380) should be destroyed, according to the site's procedures for spent vial destruction and disposal, after reconciliation of the study drug, and the destruction should be recorded.

4.6 Study Drug Accountability

The research pharmacist will maintain accurate records of the disposition of the entire supply of study drugs, including when, how much, and the condition under which the study drugs are received, dispensed, and destroyed by site personnel. In addition, the Research Pharmacist should maintain accurate records of the administration of each study drug to each participant at the vial level for each administration (i.e. lot number of every vial for that administration, number of vials, time of administration preparation, study ID number, and initials of the participant for whom the prepared dose is intended).

The study personnel should maintain accurate records of the study ID number and initials of the participant receiving the dose, date and time of administration, and site(s) of administration(s) for each participant and dose.

Drug accountability will be reviewed and documented. Reconciliation and accountability of study drugs will be done throughout the study during the monitoring visits. After the completion of the study, the Sponsor or designee may authorize the site to dispose of unused supplies of the investigational drugs, provided this alternative disposition does not expose humans to risks from the drugs. The Sponsor or designee shall maintain written records of all drug disposition, which will include the name of the investigator, the date, quantity, batch or code of each vial, and method of disposal.

4.7 Infusion Reactions

Study drugs should be administered in an area that allows for rapid access to emergency cardiopulmonary support services in the event of a life threatening infusion reaction. The Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0 scale will be used for assessment of any infusion reactions, or anaphylactic events (see Section 9.6)

5 PARTICIPANT ENROLLMENT

5.1 Inclusion Criteria

Participants must meet all of the following criteria to be included in the study:

1. Male or female at least 18 years of age and no greater than 70 years on the day of Screening.
2. Asymptomatic HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by Geenius™ or a second antibody test by a method other than the initial rapid HIV and/or E/CIA test, or by HIV-1 antigen, plasma HIV-1 RNA viral load at or prior to screening.
3. On continuous suppressive cART for 6 months prior to screening with one documented HIV-1 RNA level below the level of detection within 3 months of screening. Continuous cART is defined as no interruptions greater than 3 consecutive days. cART is defined as a DHHS recommended regimen. Study participants should be on a stable regimen for at least 3 months.
4. Screening plasma HIV-1 RNA below the limit of detection.
5. CD4+ T cell count $\geq$350 cells/mm^3
6. Laboratory values obtained within 30 days prior to the first dose:
   - Hemoglobin > 10.0 g/dL;
   - Platelet count $\geq$ 100,000/mm^3;
   - Absolute neutrophil count $\geq$ 1,000/mm^3;
   - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 1.5 x upper limit of normal (ULN); and
   - Creatinine clearance (CrCl) of $\geq$ 50 mL/min.
7. Willing to comply with the requirements of the protocol and available for follow-up for the planned duration of the study.
8. In the opinion of the principal investigator or designee, has understood the information provided; written informed consent needs to be given before any study-related procedures are performed.
9. Females of childbearing potential, sexually active with a male sex partner, must agree to use one effective method of contraception from the time of signing the consent to completion of the study, and agree to pregnancy testing as per the Schedule of Events and Procedures. Females of childbearing potential are female participants who are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy), are not postmenopausal (at least one year without menses), and are not otherwise sterile by medical evaluation.

5.2 Exclusion Criteria

Participants having or meeting any of the following conditions or characteristics will be excluded from the study:

1. Suppressed subjects who have not been on a stable DHHS recommended cART

regimen for at least 3 months.

2. Receipt of any monoclonal antibody for the treatment or prevention of HIV infection except for receipt of TMB-365 and TMB-380 by Sentinel subjects eligible for enrollment into Core groups.
3. Suppressed subjects receiving cabotegravir and rilpivirine intramuscularly as maintenance therapy for HIV-1 infection.
4. Pregnant, planning a pregnancy during the trial period, or lactating.
5. Known allergy/sensitivity or any hypersensitivity to components of the study drug or its formulation, or known allergy to a MAb.
6. History of severe allergic reactions to medications, vaccinations, or monoclonal antibody therapy for other conditions such as COVID.
7. Major psychiatric illness including any history of schizophrenia or severe psychosis, uncontrolled bipolar disorder requiring acute therapy, or suicide attempt in the previous three years.
8. Serious illness requiring systemic treatment and/or hospitalization within 21 days prior to the first dose.
9. Receipt of immunomodulatory agents (e.g., interleukins, interferons, cyclosporine, high dose systemic corticosteroids), HIV vaccine, systemic cytotoxic chemotherapy, or investigational therapy within 180 days prior to the first dose.
10. Any chronic or acute medical condition, including chronic Hepatitis B infection, chronic and Hepatitis C infection with viremia, drug use and alcohol abuse, which in the opinion of the investigator would interfere with evaluation of the study drug.
11. Lack of adequate venous access.
12. Individuals who have experienced virologic failure during treatment with two or more cART treatment regimens and those being treated with regimens containing either ibalizumab, enfuvirtide, maraviroc, or fostemsavir. Note that a change in treatment regimen for intolerance does not meet criteria for treatment failure.

5.3 Participant Withdrawal and Discontinuation

5.3.1 Reasons for Withdrawal

Participants may withdraw consent to participate at any time during the study though this should be strongly discouraged by the site study team.

A Medical Monitor designated by the Sponsor, along with the investigator, will routinely review safety data, including lab results, AEs, and SAEs.

Participants are encouraged to continue participation throughout the study period in the event that they decide or it is decided that they discontinue infusions with TMB-365 and TMB-380.

A participant may be withdrawn from the study if the participant:

- Is in violation of the protocol including non-adherence to study visits;
- Requires a medication that is prohibited by the protocol;
- Requests an early discontinuation for any reason;

- Is intolerant to infusions of TMB-365 or TMB-380 (safety);
- Is in a Core group and has evidence of documented virologic rebound defined by 2 consecutive HIV-1 RNA levels above 50 copies/mL plasma at least two weeks apart. Note that any participant with an HIV-1 RNA value above 50 copies/mL will be asked to return to clinic for an unscheduled visit at least 2 weeks later for a repeat value. If virologic failure is documented then participants should be immediately started on the same combination antiretroviral regimen that was being administered at the time of screening. Participants who demonstrate virologic rebound should be encouraged to complete the clinic visits as outlined in the Schedule of Events (Table 3 through Table 5).

A participant will be withdrawn if the Sponsor or the local regulatory agency terminates the study. Upon occurrence of an SAE, the principal investigator will notify the Sponsor or designee of these events via the SAE hotline. Any participant may withdraw his/her consent at any time.

5.3.2 Stopping Rules

Stopping criteria for an individual subject within a Core Group:

Safety: Any SAE, or Grade 3 or 4 adverse event probably or definitely due to the monoclonal antibody infusions within 14 days of treatment.

Antiviral activity: Documented virologic failure in an individual. Resistance analysis including phenotype and genotype will be performed in subjects in whom virologic failure is documented.

Stopping criteria for dosing a Core Group:

Safety: An SAE probably or definitely due to the monoclonal antibody infusions.

More than one Grade 3 or 4 adverse event probably or definitely due to the monoclonal antibody infusions..

Antiviral activity: Documented virologic failure in more than two individuals in a Core Group who have received scheduled infusions of the combination of TMB-365 and TMB-380.

Resistance analysis including phenotype and genotype will be performed in subjects in whom virologic failure is documented.

To ensure participant safety all SAEs, Grade 3 and Grade 4 AEs will be reviewed by the Data Monitoring Committee (DMC) (Section 9.9) to assess causality. All cases of virologic failure will be similarly reviewed. The DMC may elect to terminate enrollment and dosing of individuals in the Core Group at any juncture based on the assessment of safety and antiviral activity.

Should the study be halted due to safety concerns of lack of efficacy then all enrolled subjects will cease dosing with bNAbs and resume oral cART as per the week 24 and week 28 visits in the Schedule of Events (Table 5).

5.3.3 Handling of Withdrawals and Discontinuations

Study withdrawals and premature discontinuations should be strongly discouraged. It is preferable that participants who insist on withdrawing from the study or meet criteria as

outlined in Section 5.3.1 be offered an opportunity to return to clinic less frequently than outlined in the Schedule of Events and Procedures. The reason for any change in the planned visit schedule must be clearly stated in the source documents.

If the participant refuses then whenever possible, all participants who withdraw, or are discontinued from the study prematurely, will undergo all Premature Discontinuation Visit procedures as described in the Schedule of Events and Procedures (see Table 3 through Table 5). Participants who fail to return for final assessments will be contacted by the site personnel in an attempt to have the participant comply with the protocol. A minimum of two documented phone calls should be made over the course of one week. If the site personnel receive no response, they should send a certified letter requesting that the participant contact the site regarding his/her status in the study. If the participant does not respond at this point, the date the certified letter was mailed will be considered the date of study withdrawal.

In the event of a participant death during the study, the date of death (as listed on the death certificate) will be used for the date of study discontinuation.

It is vital to obtain follow-up data on any participant withdrawn because of an AE or SAE. In such cases, the participant will be followed to satisfactory resolution or until the principal investigator deems the event to be chronic/stable. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures.

5.3.4 Replacements

Participants who prematurely discontinue for reasons other than safety or virologic rebound may be replaced.

5.3.5 Sponsor or Regulatory Agency Termination of Study

Although the Sponsor intends to complete the study, the right is reserved to discontinue the study at any time for clinical or administrative reasons, or if required by the local regulatory authority.

6 STUDY PROCEDURES: SENTINEL GROUPS

6.1 Pre-Screening

Potential participants will first undergo pre-Screening to assess medical history and qualification for the study. They will have the opportunity to discuss the study and ask questions of the study recruiter at this time. Those who are eligible and interested in participation will attend a Screening Visit. No study-specific procedures are to be performed prior to review and signature of an approved informed consent document.

6.2 Screening Visit

During the Screening Visit, study personnel will answer all questions posed about the study. Written site-specific informed consent, including information provided to the participant in case there is an allergic reaction, will be obtained prior to conducting any study procedures. To ensure informed consent, the principal investigator or designee will discuss the following information individually with each potential participant:

- That all study participants must agree to use one effective method of contraception if engaging in sexual activity that may result in pregnancy at any time throughout the

study and the follow-up period. Acceptable methods of birth control for this study are: oral contraceptives, barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or vasectomy.
- To watch for any signs of an allergic reaction and the steps to take to follow up.

If the participant consents to participate, site personnel will:

- Perform complete medical history (including concomitant medications).
- Record demographics.
- Record vital signs as per Section 8.1.4.
- Perform a complete physical examination as detailed in the Schedule of Events and Procedures including confirmation of venous access for study drug infusion.
- Collect blood and urine specimens for all tests as indicated in the Schedule of Events and Procedures.
- Perform a blood pregnancy test for all female participants with reproductive potential.

The Screening Visit may be performed at two separate visits. There will be no participants entered into the study who do not meet all inclusion criteria and who meet any of the exclusion criteria unless a waiver is granted by the Medical Monitor after discussion with the Site PI. Laboratory testing may be repeated once within the 45 day Screening window at the discretion of the site investigator, should laboratory values alone result in exclusion.

No more than 45 days may elapse between signing of the informed consent and study drug administration. If this occurs, then study procedures for the Screening Visit must be repeated unless a waiver is issued by the Medical Monitor. However, the complete medical history may be replaced by an interim medical history and the informed consent form may be reviewed without signing again.

6.3 Day 0 (Study Drug Administration)

Prior to the administration, site personnel will:

- Review the informed consent form administered at the Screening Visit with the participant and answer any questions about the study.
- Review interim medical history (including concomitant medications).
- Review safety laboratory data from the Screening Visit(s).
- Vital signs measurements as per Section 8.1.4 within 15 minutes of study drug administration.
- Perform a directed physical examination as per the Schedule of Events and Procedures.
- Confirm participant is fasting.
- Collect blood and urine specimens for all tests pre-dose as indicated in the Schedule of Events and Procedures, including PK, CD4RO, immunogenicity, fasting lipids and $CD4^+$ cell count samples.
- Perform a urine pregnancy test for all female participants with reproductive potential and obtain results prior to study drug administration.
- Sentinel group subjects will be educated as to the importance of maintaining oral cART regimens.
- At the discretion of the site PI, participants may be dosed with 2 tablets of 325 mg of acetaminophen or 2 tablets of 200 mg of ibuprofen combined with 10 mg of loratadine or cetirizine.

Dosing:

Sentinel groups (N=10 for each group)

Sentinel group 1:

TMB-365: 2400 mg x single dose
TMB-380: 2400 mg x single dose

Sentinel group 2:

TMB-365: 3200 mg x single dose
TMB-380: 3200 mg x single dose

Sentinel group 3:

TMB-365: 4800 mg x single dose
TMB-380: 4800 mg x single dose

Administration Procedure

Study drugs will be administered via IV infusion in the cephalic vein of a study participant. Using a sterile syringe, a corresponding volume of NS for each dose arm is withdrawn from a 250 mL infusion bag of NS and discarded. Then the appropriate dose of each antibody will be added to the infusion bag and the contents of the bag infused over 60 minutes. Low sorb IV lines or equivalent with a 1.2 Micron filter, and an infusion pump and saline lock should be used for the IV IP administration. The clinician/physician/Research Nurse will attach the IV line to the 250mL IV saline bag with added IP and prime the IV line with IP from the IV saline bag.

The infusion rate and volume will be programmed in to the pump so that the IP is infused over a period of approximately 60 minutes. The calculation of the flow rate must be the total volume in the IP bag, as received from the Pharmacy, over 60 minutes. Both the dose and the infusion rate calculations will be checked by a second staff member and must be documented by the staff administering the IP in the participant's source documents. At the end of the infusion of IP, the empty IV saline bag containing IP will be replaced with a normal 0.9% saline bag to flush the IV line with 30 mL of normal saline at the same infusion rate, to ensure all the remaining IP is administered to the participant. The stop time will then be recorded.

After completing the infusion(s), the physician/clinical designee/Research Nurse will record the start time, duration, end time, and date of IP administration on the Participant-Specific IP Accountability Log or site-specific chain of custody document.

- Start time for the infusion is defined as the time that the IP starts flowing from the IV saline bag containing the IP.
- Stop time for the infusion is defined as the point when the normal saline flush post IP infusion has completed and the pump alarm sounds.

Any infusion reaction or adverse event during study drug administration will be recorded. Vital signs should be recorded every 15 minutes beginning 15 minutes prior to the IP infusion and through completion of the required observation times of either 180 minutes or 60 minutes. Participants should be monitored in an area where immediate treatment for any hypersensitivity reaction can be administered. Any local and systemic immunogenicity events, as well as any other event that occurs, will be recorded.

Post-Administration Procedures

The first 3 participants in each Sentinel dose group will be closely observed for at least 180 minutes (3 hours) and up to 300 minutes (5 hours) after IP administration with the duration of post-infusion observation at the discretion of the site PI. The remaining Sentinel group participants at that dose level will be observed for at least 60 minutes (1 hour) and up to 180 minutes (3 hours) with the duration of post-infusion observation at the discretion of site PI after IP administration unless there are safety issues identified, specifically Grade 3 or greater adverse events observed within 7 days in the first 3 subjects treated with IP. Safety issues identified during these infusions will result in the temporary cessation of dosing at that dose level and will result in an adhoc meeting of the Data Monitoring Committee and the Medical Monitor to discuss modifications to the administration procedure and additional dosing. Vital signs (pulse, respiratory rate, blood pressure, and temperature) will be monitored at 15 minute (±5 minutes) intervals after administration and recorded. Participants should be monitored in an area where immediate treatment for any hypersensitivity reaction can be administered. Any local and systemic immunogenicity events, as well as any other event that occurs, will be recorded.

PK samples will be collected at 10 minutes after the end of IP infusion.

The investigator will remind the participant to watch for signs and symptom of any allergic reactions once he/she leaves the study site, and to contact study personnel as appropriate.

6.4 Pharmacokinetic Assessments for Sentinel Group Subjects

Sentinel group participants receiving either 2400 mg or 3200 of either antibody will return to clinic for blood draws for serum levels of TMB-365 and 380 and CD4 receptor occupancy levels of TMB-365 as follows:

Days 0, 7 (± 1d), 14 (± 2d), 28 (± 2d), 42 (± 2d), 49 (± 2d), 56 (± 2d), 63 (± 2d), 70 (± 2d), 84 (± 2d).

Sentinel group participants receiving 4800 mg of either antibody will return to clinic for blood draws for serum levels of TMB-365 and 380 and CD4 receptor occupancy levels of TMB-365 as follows:

Days 0, 14 (± 2d), 28 (± 2d), 56 (± 2d), 70 (± 2d), 77 (± 2d), 84 (± 2d), 91 (± 2d), 98 (± 2d), 112 (± 2d).

6.5 Sentinel Groups Comprehensive Safety Visits:

Participants receiving 2400 mg or 3200 mg of either antibody will be scheduled for safety visits on Days 7 (week 1), 14 (week 2), 28 (week 4) and every 28 days (4 weeks) until Day 84 (week 12)

Participants receiving 4800 mg of both antibodies will be scheduled for safety visits on Days 14 (week 2), Day 28 (week 4) and every 28 days (4 weeks) until Day 112 (week 16).

Visits will include:

- Review of interim medical history and use of concomitant medications.
- Assess AEs by asking open ended questions.
- Perform a directed physical examination and vital signs as per Section 8.1.4 and as per the Schedule of Events and Procedures.

- Collect blood and urine specimens for all tests as indicated in the Schedule of Events and Procedures (Table 3 and Table 4).

6.6 Early Discontinuation

Participants who withdraw from the study at any time before the Day 168 / Week 24 visit will be asked to complete all Premature Discontinuation Visit procedures to ensure safety and to collect as much data as possible (Table 3 and Table 4).

Participants may be asked to complete a Premature Discontinuation Visit and be replaced for non-adherence to the study visit schedule. Critical visits include Day 0, Day 14, and PK assessments Days 49-70 for dose groups 1 and 2 and Day 0, Day 14, and PK assessments days 70-91 for dose group 3.

6.7 Unscheduled Visits

Unscheduled Visits may be completed for the following reasons:

- To perform confirmatory laboratory testing for clinically significant abnormal values.
- If in the judgement of the investigator or his/her designee it is determined that a visit is in the best interest of the participant's safety and required clinical evaluation.

Findings during these Unscheduled Visits must be reported in the CRF in the Unscheduled Visit section.

7 STUDY PROCEDURES: CORE GROUPS

The decision to initiate screening of Core Group participants in each arm will be based on achieving pharmacokinetic (PK) targets in Sentinel Group participants as well as establishing safety. The rationale for dose groups and PK targets can be found in Sections 3.2.and 3.3. To initiate the enrollment of a Core group, approximately 80% of participants in Sentinel groups should meet PK criteria as well as safety criteria as outlined above. Should safety criteria and PK targets not be met then enrollment into a Core group at that dose will not occur.

Asymmetric dosing of Core groups participants may occur should doses of TMB-365 and TMB-380 meet specified safety criteria and PK targets as outlined above.

7.1 Pre-Screening

Potential participants will first undergo pre-Screening to assess medical history and qualification for the study. They will have the opportunity to discuss the study and ask questions of the study recruiter at this time. Those who are eligible and interested in participation will attend a Screening Visit. No study-specific procedures are to be performed prior to review and signature of an approved informed consent document.

7.2 Screening Visit

During the Screening Visit, study personnel will answer all questions posed about the study. Written site-specific informed consent, including information provided to the participant in case there is an allergic reaction, will be obtained prior to conducting any study procedures. To ensure informed consent, the principal investigator or designee will discuss the following information individually with each potential participant:

- All participants should understand that oral cART will be discontinued on the day of the first infusion and restarted at the Day 168 (Week 24) visit, 4 weeks (28 days) prior

to the end of study visit.
- That all study participants must agree to use one effective method of contraception if engaging in sexual activity that may result in pregnancy at any time throughout the study and the follow-up period. Acceptable methods of birth control for this study are: oral contraceptives, barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or vasectomy.
- To watch for any signs of an allergic reaction and the steps to take to follow up.

If the participant consents to participate, site personnel will:

- Perform complete medical history (including concomitant medications).
- Record demographics.
- Record vital signs as per Section 8.1.4
- Perform a complete physical examination as detailed in the Schedule of Events and Procedures including confirmation of venous access for study drug infusion.
- Collect blood and urine specimens for all tests as indicated in the Schedule of Events and Procedures.
- Perform a blood pregnancy test for all female participants with reproductive potential.

The Screening Visit may be performed at two separate visits. There will be no participants entered into the study who do not meet all inclusion criteria and who meet any of the exclusion criteria unless a waiver is granted by the Medical Monitor after discussion with the Site PI. Laboratory testing may be repeated once within the 60 day Screening window at the discretion of the site investigator, should laboratory values alone result in exclusion.

No more than 60 days may elapse between signing of the informed consent and study drug administration. If this occurs, then study procedures for the Screening Visit must be repeated unless a waiver is issued by the Medical Monitor. However, the complete medical history may be replaced by an interim medical history and the informed consent form may be reviewed without signing again.

7.3 Day 0 (Study Drug Administration)

Prior to the administration, site personnel will:

- Review the informed consent form administered at the Screening Visit with the participant and answer any questions about the study.
- Review interim medical history (including concomitant medications).
- Review safety laboratory data from the Screening Visit(s).
- Vital signs measurements as per Section 8.1.4 within 15 minutes of study drug administration.
- Perform a directed physical examination as per the Schedule of Events and Procedures.
- Confirm participant is fasting.
- Collect blood and urine specimens for all tests pre-dose as indicated in the Schedule of Events and Procedures, including PK, CD4RO, immunogenicity, fasting lipids and $CD4^+$ cell count samples.
- Perform a urine pregnancy test for all female participants with reproductive potential and obtain results prior to study drug administration.
  Core group participants will be asked to take their last dose of oral cART in the clinic prior to infusion. Clinic personnel will record the time of the last dose of antiretroviral medications.

7.4 Pharmacokinetic Assessments for Core Group Subjects

Core group participants receiving 4800 mg of TMB-365/TMB-380 will return to clinic for

blood draws for serum levels of TMB-365 and 380 and CD4 receptor occupancy levels of TMB-365 as follows:

Days 0, 14 (± 3d), 28 (± 3d), 56 (± 3d), 84 (± 3d), 112 (± 3d), 140 (± 3d), 168 (± 3d), 196 (± 3d).

7.5 Additional Infusion Schedule: Core Participants

Core group participants will receive study drug at Day 0, Day 56 (Week 8) and Day 112 (Week 16) as described in Section 6.3.

Administration Procedure

Study drugs will be administered via IV infusion in the cephalic vein of a study participant. Using a sterile syringe, corresponding volume of NS for each antibody is withdrawn from a 250 mL infusion bag of NS and discarded. Then the appropriate dose of each antibody will be added to the infusion bag and the contents of the bag infused over 60 minutes. Low sorb IV lines or equivalent with a 1.2 Micron filter, and an infusion pump and saline lock should be used for the IV IP administration. The clinician/physician/Research Nurse will attach the IV line to the 250mL IV saline bag with added IP and prime the IV line with IP from the IV saline bag.

The infusion rate and volume will be programmed in to the pump so that the IP is infused over a period of approximately 60 minutes. The calculation of the flow rate must be the total volume in the IP bag, as received from the Pharmacy, over 60 minutes. Both the dose and the infusion rate calculations will be checked by a second staff member and must be documented by the staff administering the IP in the participant's source documents. At the end of the infusion of IP, the empty IV saline bag containing IP will be replaced with a normal 0.9% saline bag to flush the IV line with 30 mL of normal saline at the same infusion rate, to ensure all the remaining IP is administered to the participant. The stop time will then be recorded.

After completing the infusion(s), the physician/clinical designee/Research Nurse will record the start time, duration, end time, and date of IP administration on the Participant-Specific IP Accountability Log or site-specific chain of custody document.

- Start time for the infusion is defined as the time that the IP starts flowing from the IV saline bag containing the IP.
- Stop time for the infusion is defined as the point when the normal saline flush post IP infusion has completed and the pump alarm sounds.

Any infusion reaction or adverse event during study drug administration will be recorded. Vital signs should be recorded every 15 minutes beginning 15 minutes prior to the IP infusion and through completion of the required observation times of 60 minutes. Participants should be monitored in an area where immediate treatment for any hypersensitivity reaction can be administered. Any local and systemic immunogenicity events, as well as any other event that occurs, will be recorded.

Post-Administration Procedures

Core group participants will be observed for 60 minutes (1 hour) after IP administration.

Vital signs (pulse, respiratory rate, blood pressure, and temperature) will be monitored at 15 minute (±5 minutes) intervals after administration and recorded. Participants should be monitored in an area where immediate treatment for any hypersensitivity reaction can be administered. Any local and systemic immunogenicity events, as well as any other event that occurs, will be recorded.

PK samples will be collected at 10 minutes after the end of IP infusion.

The investigator will remind the participant to watch for signs and symptom of any allergic reactions once he/she leaves the study site, and to contact study personnel as appropriate.

Study Procedures Days 14, 28 and every 28 days through Day 196:

Visits will include:

- Review of interim medical history and use of concomitant medications.
- Assess AEs by asking open ended questions.
- Perform a directed physical examination and vital signs as per Section 8.1.4 and as per the Schedule of Events and Procedures.
- Collect blood and urine specimens for all tests, which include safety and PK/PD assessments at each scheduled visit, as indicated in the Schedule of Events and Procedures (Table 5).
- Restart the oral cART regimen being taken at the time of screening in clinic at the Day 168 (Week 24) visit. Clinic personnel should record the time of dosing.

7.6 Early Discontinuation

Participants who withdraw from the study at any time before the Day 168 / Week 24 visit will be asked to complete all Premature Discontinuation Visit procedures to ensure safety and to collect as much data as possible (Table 5). Study subjects who fail to complete the first 8 weeks of participation due to non-adherence to the schedule may be replaced.

7.7 Unscheduled Visits

Unscheduled Visits may be completed for the following reasons:

- To perform confirmatory laboratory testing for clinically significant abnormal values.
- To confirm virologic failure, defined as 2 consecutive viral load determinations above 50 copies/mL plasma at least 2 weeks apart.
- If in the judgement of the investigator or his/her designee it is determined that a visit is in the best interest of the participant's safety and required clinical evaluation.

Findings during these Unscheduled Visits must be reported in the CRF in the Unscheduled Visit section.

7.8 Stopping Criteria

Stopping criteria for an individual subject within a Core Group:

Safety: Any SAE, Grade 3 or 4 adverse event probably or definitely due to the monoclonal antibody infusions within 14 days of treatment.

Antiviral activity: Documented virologic failure in an individual. Resistance analysis including phenotype and genotype will be performed in subjects in whom virologic failure is documented.

Stopping criteria for dosing of a Core Group:

Safety: An SAE probably or definitely due to the monoclonal antibody infusions.

More than one Grade 3 or 4 adverse event probably or definitely due to the monoclonal antibody infusions..

Antiviral activity: Documented virologic failure in more than two individuals in a Core Group who have received scheduled infusions of the combination of TMB-365 and TMB-380. Resistance analysis including phenotype and genotype will be performed in subjects in whom virologic failure is documented.

To ensure participant safety all SAEs, Grade 3 and Grade 4 AEs will be reviewed by the Data Monitoring Committee (DMC) (Section 9.9) to assess causality. All cases of virologic failure will be similarly reviewed. The DMC may elect to terminate dosing of individuals in the Core Group at any juncture based on their assessment of safety and antiviral activity.

Should the study be halted due to safety concerns of lack of efficacy then all enrolled subjects will cease dosing with bNAbs and resume oral cART as per the week 24 and week 28 visits in the Schedule of Events (Table 5).

8 STUDY ASSESSMENTS

8.1 Activities to Be Completed

The following assessments will be conducted at the times indicated in the Schedule of Events and Procedures (Table 3 through Table 5) and recorded in source documents as per the standard operating procedures of the clinical site. Samples will be processed using standard procedures as described in the laboratory procedures manual, and will be analyzed by a central laboratory unless otherwise noted.

8.1.1 Demographic Data, Medical History, and Concomitant Medications

Demographic data, a complete medical history (per participant report), and documentation of prior medications used within 30 days of the Screening Visit and all prior ART will be collected at Screening; information about concomitant medications will be obtained at each visit.

8.1.2 Complete Physical Examination

A complete physical examination will include the following assessments: skin, head, eyes, ears, nose, throat (HEENT), chest including breasts and lungs, heart, abdomen, extremities, and neurological exam.

8.1.3 Directed Physical Examination

Directed physical examination will be limited to assessment of HEENT, chest, heart, abdomen, and assessment of any site related to specific signs and symptoms reported by the patient.

8.1.4 Vital Sign Measurements

Vital sign measurements will include the participant's heart rate (beats/minute taken for

one minute), blood pressure (mm Hg), respiratory rate (breaths/minute taken for one minute), and temperature (ºC) as per the Schedule of Events and Procedures (Table 3 through Table 5). On the day of dosing measurements will be taken within 15 minutes before the study drug administrations and every 15 minutes for at least 1 hour and up to 5 hours after the study drug is administered as per Sections 6.3 and 7.3 and 7.4. Blood pressure and heart rate measurements will be obtained after the participant has been seated or reclining for at least five minutes. Ideally, each participant's blood pressure should be measured using the same arm and the same size cuff at each visit.

8.2 Blood and Urine Samples

8.2.1 Clinical Laboratory Parameters

Collection of blood and urine samples for clinical laboratory assessments will be part of a normal safety profile assessment for the study participant. Samples will be processed using standard procedures as described in the laboratory procedures manual, and will be analyzed by a central laboratory unless otherwise noted.

The samples will be analyzed for the following:

Hematology: Complete white blood cell count with differential, hemoglobin, hematocrit, and platelets.

Serum Chemistry Profile: ALT, AST, chloride, creatinine, potassium, sodium, total and direct bilirubin, albumin, alkaline phosphatase, blood urea nitrogen, magnesium and creatine phosphokinase, amylase, lipase, and phosphorus.

Fasting Lipid Profile: Includes total cholesterol, HDL, LDL, and triglycerides at designated visits indicated in Schedule of Event and Procedures (Table 3 to Table 5).

Urinalysis: Visual inspection for appearance and dipstick assessment for color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and leukocyte esterase. If dipstick assessment is abnormal then urine should be sent to the Central laboratory for a complete urinalysis. Urinalysis should be done at designated visits indicated in Schedule of Event and Procedures (Table 3 to Table 5)

Screening for Chronic Hepatitis: HBV and HCV screening will be performed for all potential participants at the study Screening visit (Table 3 to Table 5).

Tests with Grade 2 or greater abnormal results according to the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events Version 2.1 must be reported as AEs **if deemed clinically significant** by the investigator or his/her designee. Tests with Grade 2 or greater abnormal results may be repeated within two days of the site becoming aware of the abnormal value(s). See Appendix A for abnormality grading scales. Grade 3 and Grade 4 abnormal test results should be repeated for confirmation within 2 days of the site becoming aware of the abnormal value, independent of assessment of relation to investigational products.

8.2.2 Pregnancy Testing

A serum pregnancy test will be performed at Screening Visit to confirm that a female is not pregnant prior to enrolling the study. A urine pregnancy test will be performed at defined study visits to confirm that a female has not become pregnant during the study. These tests are performed for the protection and safety of the fetus, as the risk to the fetus is unknown. See Section 9.8 for a description of procedures to be followed in case of pregnancy.

8.2.3 HIV EIA and Confirmatory Testing

Blood samples will be obtained at the screening visit for HIV-1/HIV-2 EIA (enzyme immunoassay) and subsequent confirmatory testing to ensure that the participant is eligible for study participation as per Section 5.1.

8.2.4 HIV RNA (Viral Load)

Blood samples for viral load will be used to determine whether the combination of antibodies as a stand-alone maintenance regimen can maintain virologic suppression in cART treated individuals. Results will be expressed as copies/mL plasma as well as log copies/mL plasma.

8.2.5 $CD4^+/CD8^+$ Cell Count

Blood samples for CD4+/CD8+ T-cell levels will be taken over the course of the study to monitor for any effect of TMB-365 and TMB-380 on levels of CD4+/CD8+ T-cells in study participants. Results will be expressed as the number of cells per mm^3 of blood and relative %.

8.2.6 CD4 Receptor Density and Occupancy

Blood samples for CD4 receptor density will be taken to determine if the binding of TMB-365 induces any changes in surface expression of CD4. It is unknown if the number of CD4 molecules on the cell surface, or receptor density, could be altered during TMB-365 therapy.

CD4 receptor occupancy is the proportion of total CD4 molecules on participant blood cells that are occupied by bound TMB-365. Blood samples used to measure receptor density will also be used to measure receptor occupancy as a PD effect of TMB-365 administration. Results are expressed as % receptor occupancy and/or CD4 receptor density.

8.2.7 TMB-365 and TMB-380 Concentrations

Measurements of concentrations of TMB-365 and TMB-380 in serum will be used to determine the concentration-time profile of TMB-365 and TMB-380 in all participants. TMB-365 and TMB-380 serum concentrations will be measured using validated enzyme-linked immunosorbent assays (ELISAs). Results will be expressed as ng/mL serum.

8.2.8 Immunogenicity

Serum samples will be collected to test for the development of antibodies against TMB-365 and TMB-380 throughout the study. The incidence of anti-TMB-365 and anti-TMB-380 antibody production will be determined by ELISA that has been validated for the detection of anti-TMB-365 and anti-TMB-380 antibodies in human serum.

8.2.9 Resistance Analysis in Core Group Subjects

Plasma samples will be drawn as per the Schedule of Events and Procedures for resistance analyses. Phenotypic susceptibility determinations and genotypic analyses in participants with documented virologic rebound will be performed at the discretion of the Study Virologist.

Virologic rebound will be defined as:

- Two consecutive viral load determinations above 50 copies/mL plasma at least 2 weeks apart.

In the event of virologic rebound then resistance studies will be performed to assess susceptibility to TMB-365 and/or TMB-380 at virologic rebound. Additionally genotypic analyses will be performed in an attempt to identify genotypic signatures within the env coding region that may be associated with the observed phenotypic change or changes, reduced susceptibility or cross resistance. Core subjects meeting criteria for virologic failure will be immediate restarted on oral cART.

8.2.10 Archive Sample

A separate serum sample will be taken as the backup sample for assays in the study.

9 ADVERSE EVENTS

9.1 Definitions

The investigator is responsible for reporting to the Sponsor or designee all SAEs that are observed or reported by the participant during the study, regardless of their relationship to study drug or their clinical significance. Participants will be instructed to contact study site personnel at any time after informed consent is obtained if any symptoms develop.

Adverse Events

An AE is defined as any untoward medical occurrence in a participant regardless of its causal relationship to study drug. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a medicinal product), whether or not considered related to the study drug.

Treatment-Emergent Adverse Events

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency following exposure to study drug.

Serious Adverse Event

An SAE is defined as any event that results in death, is immediately life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is deemed by the investigator to be an important medical event based upon appropriate medical judgement.

An important medical event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. It may expose the participant to danger, even though the event is not immediately life-threatening or fatal, or does not result in hospitalization.

The term “immediately life-threatening” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

9.2 Eliciting Adverse Event Information

At every study visit, participants will be asked a standard, non-directive question, such as

"How have you been feeling since your last visit?" to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to participant observations, AEs will be documented from any clinically significant diagnosis resulting from abnormal laboratory test values, physical examination findings, or from other documents that are relevant to participant safety.

9.3 Reporting Adverse Events

Recording of AEs will begin after the participant signs the informed consent form. However, any AE that occurs after the informed consent is signed but before the first administration of the study drug *will be recorded as medical history*, unless it is related to a study procedure. Any AE that occurs after the first dose of study drug and until seven days after the last study-required sample collection at the end of the follow-up period, regardless of its relationship to study drug, will be recorded in the AE section of the CRF.

All AEs reported or observed during the study must be reported in detail in the AE section of the CRF and followed to a satisfactory resolution or until the principal investigator deems the event to be chronic/stable.

Information to be collected includes type of event, date of onset, date of resolution, investigator-specified assessment of severity and relationship to study drug, whether or not it qualifies as an SAE, as well as any required treatment or evaluations and outcome.

Preexisting conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the pre-existing condition worsens in severity, the investigator must report is as an AE. Each AE should be recorded to represent a single diagnosis. Accompanying signs or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as AE(s). Changes in laboratory values are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required). If abnormal laboratory values are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported as an AE.

Pre-planned procedures (surgeries or therapies) that were scheduled prior to the start of AE collection are not considered AEs. However, if a pre-planned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured as an AE. Elective procedures performed where there is no change in the participant's medical condition should not be recorded as AEs, but should be documented in the participant's source documents.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used by the sites to code all AEs.

All AEs, whether serious or not, should be followed to a satisfactory resolution or until the principal investigator deems the event to be chronic/stable, and the AE is determined to be not clinically significant.

9.4 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process. If there is any doubt as to whether or not a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized by the investigator using the following classifications and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgement based on the investigator's clinical experience, the association of the event with study drug administration seems likely.

Definite: This relationship suggests that a definite causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

9.5 Assessment of Severity

The intensity of the AE will be rated by the investigator as mild, moderate, severe, or potentially life-threatening using the following criteria:

Mild: Symptoms causing no or minimal interference with usual social and functional activities.

Moderate: Symptoms causing greater than minimal interference with usual social and functional activities.

Severe: Symptoms causing inability to perform usual social and functional activities.

Potentially Life-Threatening: Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.

Details for grading severity are given in Appendix A. Increases in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed.

9.6 Infusion Reactions

The Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0 scale will be used for assessment of any infusion reactions, or anaphylactic events. All other adverse events will be graded as per the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events Version 2.1 (see Appendix A).

For infusion reaction, the following assessment of severity per the CTCAE toxicity table should be used:

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion Related Reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					

9.7 Serious Adverse Event Reporting

Any AE considered serious by the principal investigator according to the previously described criteria must be reported by either email, phone, or fax within 24 hours from the time when site personnel first learn about the event.

SAE Email: WestatPVG@Westat.com

The site should notify the Sponsor or designee within 24 hours of the site becoming aware of the event. Sites will submit information using the appropriate reporting form and mechanism, as required by the safety management provider/Sponsor or designee. This report should include the following information regarding the study participant and the event: demographics, medical history, complete information on the SAE, and concomitant medications information. If the participant is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge summary and any pertinent laboratory or diagnostic reports should be faxed or mailed to the Sponsor or designee as soon as it becomes available.

The investigator should forward to the safety management provider/Sponsor or designee any additional written documentation on the event that becomes available after the first report. The information should be sent as instructed by the safety management provider/Sponsor or designee immediately or within one working day of receipt.

The Sponsor or designee will notify the appropriate regulatory agencies of any fatal or life-threatening unexpected SAEs associated with the use of the study drug as soon as possible but no later than seven calendar days after the initial receipt of the information. Initial notification will be followed by a written report within 15 calendar days. For other SAEs that do not meet the life-threatening or fatal criteria, but are reported to be unexpected and associated with the use of the study drug, the Sponsor or designee will notify the proper regulatory agency in writing as soon as possible but no later than 15 calendar days from the initial receipt of information. Copies of any reports to regulatory agencies regarding serious and unexpected SAEs will be provided to the investigators by the Sponsor or designee for review and submission to the institutional review board (IRB) or ethics review committee (ERC).

The principal investigator is responsible for informing his/her IRB/ERC of any SAEs at that site. Copies of SAE correspondence with the principal investigator, regulatory authorities, ethics committees, and Sponsor must be submitted to the Sponsor or designee for filing.

A participant experiencing one or more SAEs will receive treatment and follow-up evaluations by the principal investigator, or he/she will be referred to another appropriate physician for treatment and follow-up. Withdrawal from the study and all therapeutic measures will be at the discretion of the principal investigator at the site.

All AEs, whether serious or not, should be followed to a satisfactory resolution or until the principal investigator deems the event to be chronic/stable and the AE is determined to be not clinically significant.

9.8 Pregnancy

Childbearing Potential

Females of childbearing potential are female participants who are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy), are not postmenopausal (at least one year without menses), and are not otherwise sterile by medical

evaluation. These participants must use one adequate form of birth control.

Suspected Pregnancy

During the study, all females of childbearing potential will be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., late or missed menstrual period). Male participants will be instructed to contact the investigator if a sexual partner suspects she may be pregnant.

If a participant or investigator suspects that the participant may be pregnant before study drug administration, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the participant must not receive the study drug and must be withdrawn from the study. If a participant already on the study is confirmed to be pregnant, the investigator must immediately notify the Medical Monitor of a pregnancy associated with study drug exposure and record the event on the Pregnancy Surveillance Form that will be provided to each site. Other appropriate follow-up procedures should be considered if indicated.

Women who are found to be pregnant and participants in the Core Group should be taken off study and restart cART as per the DHHS Perinatal Guidelines with the guidance of her primary care physician.

The investigator must follow up with a pregnant participant or the pregnant partner of any sexually active male participant every 4 weeks while the woman is pregnant and every 4 weeks thereafter for at least 12 weeks, to follow perinatal and neonatal outcome. The investigator must report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome on the appropriate Pregnancy Surveillance Form.

9.9 Data Monitoring Committee

An independent DMC will review the progress of the trial and the accumulating data to detect evidence of safety issues for participants while the trial is ongoing.

The DMC will make recommendations regarding the continuation, modification, or termination of the trial to the Sponsor or designee following each meeting. The DMC will consist of three independent clinicians and a statistician. The DMC will consist of independent individuals who have no relationship to the principal investigator and sub-investigators involved in the trial or financial interest in the Sponsor. No member of the DMC will have any direct responsibility for the clinical care of trial participants. The DMC may invite the principal investigator or designee and Sponsor representative to an open session of a DMC meeting to provide information on study conduct, present data, or to respond to the DMC members' questions.

The name, university affiliation and title, area of expertise, and contact information of each of the DMC members will be provided to the IRB/ERC. All updated versions of the protocol and Investigator’s Brochure (IB) will be provided to the DMC members.

The DMC will review the trial data after the first 7 sentinel participants have completed infusions and 2 weeks follow-up to consider dose escalation to a higher dose of either antibody to meet both safety and PK criteria for initiation of a Core group.

Should there be Grade 3 or higher adverse events in the first 3 subjects in any Sentinel group then dosing should cease and the DMC should meet ad hoc with the Medical Monitor to discuss possible changes to the administration of TMB-365 and TMB-380.

The DMC will be responsible for adhering to study stopping guidelines outlined in Section

5.3.2.

In the event of a Grade 3 or Grade 4 infusion reaction as per the Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0 (Section 9.6) in any dosing group, further dosing will be immediately stopped. The DMC will be immediately notified and will determine whether additional dosing may occur.

During dosing of Core Subjects the DMC will be notified of all SAEs, Grade 3 and 4 adverse events deemed possibly or probably due to study drug as well as all cases of virologic failure to determine whether continued enrollment and treatment of Core Subjects is safe and potentially effective. Stopping rules for individuals in Core as well as dosing of Core subjects is stated in Sections 5.3.2 and 7.8.

10 STATISTICAL CONSIDERATIONS

10.1 Determination of Sample Size

The sample size is not statistically driven and will be primarily descriptive with emphasis placed on tabular and graphical displays. Summary statistics will be calculated along with interval estimates of solicited and unsolicited adverse events and measurement of antiviral activity.

10.2 Analysis Populations

The full analysis set (FAS) includes all participants who are administered any fraction of study drug. The efficacy population consists of all participants who receive at least one infusion of TMB-365 and TMB-380 (FAS). Similarly the PK population consists of all participants in the FAS. The analysis of study data will be primarily descriptive, with emphasis on tabular and graphical displays. Summary descriptive statistics will be calculated, along with point and interval estimates of solicited and unsolicited AEs. This study is exploratory, and any statistical inferences will be hypothesis generating, and not confirming.

10.3 Study Endpoints

The primary objectives of this study are to:

- Evaluate the safety and tolerability of various doses and dosing regimens of IV infusions of TMB-365 and TMB-380 given q8wks in suppressed, cART treated HIV-1 infected participants.
- Define the pharmacokinetic (PK) profile of TMB-365 and TMB-380 when given q8wks in suppressed, cART treated HIV-1 infected participants
- Evaluate the antiviral activity of the combination of TMB-365 in combination with TMB-380 as maintenance therapy in suppressed HIV infected individuals (Core only)

Exploratory objectives of this study are to:

- Characterize the emergence of viral resistance to TMB-365 and TMB-380 in HIV-1 infected participants who fail to maintain suppression on the combination of TMB-365/TMB-380

- Determine the immunogenicity of TMB-365 and TMB-380 in HIV-1 infected suppressed participants

10.3.1 Efficacy Analysis

Efficacy will be assessed by longitudinal measurements of plasma HIV-1 RNA levels. The efficacy of the combination of TMB-365 and TMB-380 as maintenance therapy in suppressed HIV-1 infected participants will be expressed as the percent of participants who remain suppressed that is a plasma HIV-1 RNA below detection, at Day 168 / Week 24.

10.3.2 Safety Analysis

Safety will be assessed by both clinical and laboratory examinations. Laboratory results that are Grade 2 or greater according to the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events Version 2.1 must be reported as AEs **if the investigator deems the abnormal result as clinically significant.** Standard panels of hematology, chemistry, lipids, and urinary analyses will be performed at regular intervals as per the schedule of events and procedures. Additionally, TMB-365- and TMB-380-specific laboratory assessments will be obtained and include serum TMB-365 and TMB-380 levels, immunogenicity, CD4+ T-cell counts, and CD4 receptor density/occupancy assessments. Complete and focused physical examinations will be performed throughout the study.

In addition to general safety parameters assessed by physical exam and review of clinical laboratory data, all participants will be closely monitored for infusion-related AEs during and after administration of TMB-365.

10.3.3 Pharmacokinetic and Pharmacodynamic Analyses

PK and PD profiles will be assessed. The serum concentration-time profile of TMB-365 and TMB-380 will be measured in all participants at time points chosen to determine minimum and maximum concentrations.

PD end points will include CD4+ T-cell counts, CD4 receptor density (on CD4+ T-cells), CD4 receptor occupancy (by TMB-365, on CD4+ T-cells), and plasma HIV-1 RNA.

The PK data will be used to determine levels of monoclonal antibodies that may be associated with maintenance of suppression of antiviral response.

The PD data will be evaluated to determine the relationship among TMB-365 and TMB-380 serum concentrations, CD4 receptor number, and CD4 receptor occupancy and maintenance of virologic suppression. TMB-365 binds to CD4 receptors where clearance is mediated, in part, by receptor turnover. The overall number of CD4 receptors in the body has not been accurately determined and the rate of receptor turnover is unknown, but is thought to be highly variable. TMB-380 does not bind to cellular receptors and is directed against the CD4 receptor binding domain of the viral envelope.

10.3.4 Safety Endpoints

Safety endpoints include the following:

- Incidence of TEAEs;
- Incidence of TEAEs by severity;

- Incidence of TEAEs by relationship to study drug;
- Incidence of SAEs;
- Incidence of SAEs by severity;
- Incidence of SAEs by relationship to study drug;
- Discontinuation of participants from the study due to AEs;
- Discontinuation of participants from the study due to deaths;
- Clinical laboratory results;
- Vital sign measurements; and
- Physical examination results.

10.4 Statistical Analyses

All data collected at each visit will be summarized. Continuous variables (e.g., age, weight) will be summarized using descriptive statistics consisting of number of participants, mean, standard deviation, minimum, median, and maximum values. Categorical variables (e.g., gender) will be summarized using the number and percentage of participants in each category. If there are unscheduled assessments between visits or repeat assessments at a visit, the one closest to the scheduled time of the visit will be used in the summaries. The association of data collected with a visit (i.e., whether it is scheduled, unscheduled, or a repeat) will be unambiguous in the CRF. All data collected will be included in the data listings.

All statistical analyses and data summaries will be performed using SAS® Version 9.1 or higher. A Statistical Analysis Plan (SAP) detailing the analyses described below, which may include mock table and listing shells.

10.4.1 Participant Accountability

Participants who are screened but not eligible will not be included in the statistical analyses. These participants will be summarized in the participant accountability table only.

Participants who are screened, eligible, but do not receive TMB-365 and TMB-380 will not be included in the statistical analysis but will be summarized in the participant accountability table only.

Participants who receive at least one dose of TMB-365 and TMB-380 will be included in the safety analysis.

Sentinel group subjects who complete the required clinic visits will be included in the PK analysis. Subjects failing to complete the required visits within prescribed windows may be replaced as the determination PK targets required to signal the enrollment of the Core participants must be met.

Efficacy analysis will include an “intent to treat” which includes all participants who receive one dose of TMB-365 and TMB-380 as well as an “as treated” analysis which includes all participants who complete through Day 168 / Week 24.

The number of participants discontinuing and the reasons for discontinuing will also be summarized. The number of participants included in the FAS and PK analysis sets will be presented. A list of participants excluded from any analysis set and the reason for exclusion

will be prepared.

10.4.2 Demographic and Background Characteristics

Demographic and background characteristics will be summarized.

10.4.3 Concomitant Medications

All concomitant medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the trial and different from the study drug must be documented in the Concomitant Therapy section of the CRF. Reported information will include a description of the type of the drug, treatment period, dosage group, route of administration, and its indication. Any change in dosage of any non-investigational medication must also be reported in the Concomitant Therapy section.

Female participants of childbearing potential and sexually active male participants with partners of childbearing potential must use birth control methods as outlined previously and must be willing to continue practicing these birth control methods throughout the trial and for at least 30 days after the last administered dose. The use of oral, injectable, and implantable hormonal contraceptives is to be recorded in the CRF.

10.4.4 Treatment Emergent Adverse Events

The incidence (n and %) of TEAEs, SAEs, and early termination of study medication or study participation due to an AE will be presented. Additionally, TEAEs will be tabulated according to severity and relatedness categories as reported by the investigator. TEAEs will be presented in tables organized alphabetically by Preferred Term within System Organ Class. Each patient will be counted only once for each TEAE reporting level.

10.4.5 Vital Signs

Actual values and change from Baseline values for vital signs and weight will be summarized descriptively by dose group at all scheduled study visits. Potentially clinically significant (PCS) criteria may be applied to vital signs as clinically indicated. If applied, the overall incidence of participants having met any of the PCS criteria will be presented. The number and percentage of participants with each individual PCS criteria will also be presented. Listings of participants with PCS vital signs will be provided.

10.4.6 Laboratory Determinations

Actual values and change from Baseline values for continuous data from laboratory determinations will be summarized descriptively at relevant study visits including HIV-1 RNA and CD4+ T cell determinations. Categorical data from clinical laboratory tests will be similarly summarized for the actual values. Clinical laboratory tests categorized as in or out of normal range will be summarized using worst-case shift tables. Worst-case shift tables will be the cross tabulation of the Baseline result category (high, normal, low) with the worst-case result during the treatment period.

PCS criteria may also be applied to laboratory determinations as clinically indicated, and if applied, will be summarized as described above.

10.4.7 Physical Examinations

Physical examination findings will be summarized by dose group at each visit collected according to the number (%) of participants with abnormal findings.

10.4.8 Immunogenicity Testing

Anti-TMB-365 and anti-TMB-380 antibody levels will be summarized in a separate report issued by the study virologist.

10.4.9 Pharmacokinetic Variables

All blood samples collected for TMB-365 and TMB-380 serum concentration analysis in Sentinel group will be used to assess the PK profile (total drug exposure and drug elimination profile). PK parameters, such as half-life, AUC, and clearance, will be estimated for all participants by non-compartmental analysis. Missing plasma concentration data will not be imputed. Exploratory data analysis will include graphical and descriptive statistical evaluations.

Blood samples collected from all participants in Core group will be used to summarize peak (maximum) and trough (minimum) TMB-365 and TMB-380 concentrations.

10.4.10 Other Information

All other information recorded in the CRF (e.g., inclusion and exclusion criteria, results of serum pregnancy tests, screens for drugs of abuse) will be listed by dose group/investigator/participant. No summaries will be presented.

11 DATA HANDLING AND QUALITY ASSURANCE

11.1 Case Report Forms

All data must be entered in English. The CRF should always reflect the latest observations on the participants in the trial. Therefore, the data are to be entered into the CRF as soon as possible during, or within seven days of the participant's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial Day 0 determinations completes all safety evaluations. The study monitor will verify that all data entries in the CRF are accurate and correct. If some assessments have not been done, or if certain information is not available, or not applicable, or is unknown, the investigator should indicate this in the CRF. The investigator will be required to sign off on the clinical data.

The Sponsor or designee will review the CRF and evaluate the entries for completeness and consistency. The data captured in the CRF will be compared with the source documents to ensure no discrepancies between critical data recorded in the CRF and the source documents. All entries, corrections, and alterations are to be made by the responsible investigator or his/her designee.

The study monitor cannot enter data in the CRF. Corrections to the data fields in the CRF should be tracked by an audit trail, meaning that the reason for the change and the name of the person who performed the change, together with the time and date the change was made

should be logged. Roles and rights of the site personnel responsible for entering the clinical data into the CRF will be determined in advance and documented on the appropriate form.

If additional corrections are needed, the responsible study monitor or project manager will issue a query. The appropriate investigational staff will answer queries sent to the investigator.

11.2 Monitoring of the Study

The clinical monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the principal investigator and study facility periodically, or, remotely monitor if travel is restricted due to the COVID-19 pandemic or other unforeseen circumstances, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the principal investigator and staff.

All aspects of the study will be carefully monitored by the Sponsor or designee for compliance with applicable government regulations with respect to the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E6(R2): Guideline for Good Clinical Practice and current standard operating procedures.

Each investigator is expected to make a reasonable effort to accommodate the clinical monitor when site visits are necessary.

11.3 Inspection of Records

Principal investigators and institutions involved in the study will permit trial-related monitoring, audits, IRB/ERC review, and regulatory inspection(s), by providing direct access to all study records. In the event of an audit, the principal investigator will agree to allow the Sponsor, representatives of the Sponsor, or other relevant regulatory authorities access to all study records.

The principal investigator should promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or designee.

11.4 Study Record Retention

Essential documents including clinical records, laboratory results, and regulatory documents should be retained at least 15 years after the end of the study.

12 ADMINISTRATIVE CONSIDERATIONS

12.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant (or the participant’s guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the applicable regulatory authorities, or the IRB/ERC.

The principal investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, records, or other unpublished confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or designee must be obtained for the disclosure of any said confidential information to other parties.

12.2 Ethics Review Committee

The ICH guidelines require that approval be obtained from an IRB/ERC before participation of human participants in research studies. Before the study onset, the protocol, informed consent, advertisements to be used for participant recruitment, and any other written information regarding this study to be provided to the participant or the participant's legal guardian must be approved by the IRB/ERC. Documentation of all IRB/ERC approvals and of the IRB/ERC compliance with ICH E6(R2) will be maintained by the site and will be available for review by the Sponsor or designee.

All IRB/ERC approvals should be signed by the IRB/ERC chairperson or designee, and they must identify the IRB/ERC by name and address, the clinical protocol by title with or without the protocol number, and the date approval and/or favorable opinion was granted.

The principal investigator is responsible for obtaining continued review of the clinical research at intervals specified by the IRB/ERC, but not exceeding one year. The principal investigator must supply the Sponsor or designee with written documentation of continued review of the clinical research.

12.3 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the participant, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol must be submitted in writing to the principal investigator's IRB/ERC for approval and the applicable regulatory authorities, as necessary, before participants can be enrolled into an amended protocol.

12.4 Informed Consent

A signed informed consent form, in compliance with applicable regulatory requirements, will be obtained from each participant before the participant enters the study or any unusual or non-routine procedure is performed that involves risk to the participant. An informed consent template may be provided by the Sponsor or designee to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent must be reviewed by the Sponsor or designee before IRB/ERC submission. Once reviewed, the consent will be submitted by the principal investigator to his/her IRB/ERC for review and approval before the start of the study. If the informed consent form is revised during the course of the study, all active participating participants must sign the revised IRB/ERC-approved consent form.

Before enrollment, each prospective participant and/or his/her legal guardian will be given a full explanation of the study and be allowed to read the approved informed consent form. Once the principal investigator is assured that the participant/legal guardian understands the implications of participating in the study, the participant/legal guardian will be asked to give consent to participate in the study by signing the approved informed consent form. The principal investigator will also sign the form at that time.

The principal investigator will provide a copy of the signed informed consent form to the participant and/or legal guardian. The original form will be maintained in the participant's medical records at the site.

12.5 Protocol Violations and Deviations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes that were approved by the Sponsor and the IRB/ERC and were agreed to by the principal investigator. Deviations usually have an impact on an individual participant or a small group of participants, and do not involve inclusion/exclusion or primary endpoint criteria. A protocol violation occurs: (a) when there is a non-adherence to the protocol that results in significant additional risk to the participant; (b) when the participant or principal investigator has failed to adhere to significant protocol requirements (e.g., inclusion/exclusion criteria); (c) when the participant was enrolled without prior Sponsor approval; or (d) when there is non-adherence to applicable regulations and/or ICH E6(R2) guidelines.

All departures from the protocol (e.g., missed visit windows, laboratory samples not collected on the required day) will be documented as protocol deviations. The principal investigator or designee must document and explain any protocol deviation or violation in the participant's source documentation. The IRB/ERC should be notified of all protocol violations in a timely manner by the investigator. Protocol deviations and violations will be documented by the responsible clinical monitor during monitoring visits, and those observations will be reviewed with the investigator.

The principal investigator may implement a change from the protocol without prior Sponsor and IRB/ERC approval only to eliminate an immediate hazard to a participant. If the investigator believes that an exception to the protocol is justified for an individual participant, the investigator may present the facts and rationale to the Medical Monitor and request a one-time exception. This request will be submitted in writing on a protocol inquiry form, which will be emailed to the Medical Monitor for review and disposition. The Medical Monitor will then email the decision to the investigator regarding approval or denial of the request. This written documentation must be filed in the investigator's study file.

This process will apply if the investigator believes that a participant should receive an excluded concomitant medication and remain in the study, or if the investigator believes that a participant should remain in the study when the protocol dictates that the participant should be discontinued. The implemented change should be submitted to the IRB/ERC for review as soon as possible. However, it is the policy of the Sponsor that there will be no exceptions granted concerning the inclusion and exclusion criteria. Laboratory support of inclusion and exclusion criteria may be repeated once during the Screening period.

12.6 Study Reporting Requirements

By participating in this study, the principal investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the principal investigator agrees to submit periodic reports to his/her IRB/ERC as appropriate.

12.7 Financial Disclosure and Obligations

Principal investigators and sub-investigators are required to provide financial disclosure information to allow the Sponsor or designee to submit the complete and accurate certification or disclosure statements under regulatory requirements. In addition, the principal investigator and sub-investigators must provide the Sponsor or designee with a

commitment to update this information promptly, if any relevant changes occur during the course of the investigation and for one year following the completion of the study.

The Sponsor or designee is not financially responsible for further testing/treatment of any medical condition that may be detected during the Screening process. In addition, in the absence of specific arrangements, the Sponsor or designee is not financially responsible for treatment of the participant's disease.

12.8 Investigator Documentation

Before beginning the study, the principal investigator will be asked to comply with ICH E6(R2) and applicable regulatory requirements by providing the essential documents to the Sponsor or designee, which include but are not limited to the following:

- An original investigator-signed investigator agreement page of the protocol.
- The IRB/ERC approval of the protocol and informed consent.
- The IRB/ERC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the participant or legal guardian.
- Curriculum vitae for the principal investigator and each sub-investigator. Current licensure must be noted on the curriculum vitae or a copy of the license provided. The curriculum vitae must be signed and dated by the principal investigator and sub-investigators within two years before study start-up to indicate the documents are accurate and current.
- Completed financial disclosure forms to allow the Sponsor or designee to submit complete and accurate certification or disclosure statements under applicable regulatory requirements. In addition, the investigators must provide to the Sponsor or designee a commitment to update this information promptly if any relevant changes occur during the course of the investigation and for one year following the completion of the study (Section 12.7).
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with applicable regulatory requirements.

12.9 Study Conduct

The principal investigator agrees that the study will be conducted according to the principles of ICH E6(R2) and the principles of the World Medical Association Declaration of Helsinki. The principal investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

12.10 Publications

Following completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor or designee will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor.

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