STATISTICAL ANALYSIS PLAN

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

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SIGNATURE PAGE

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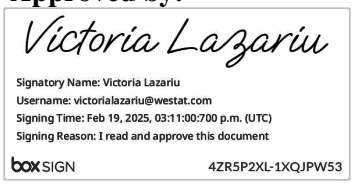

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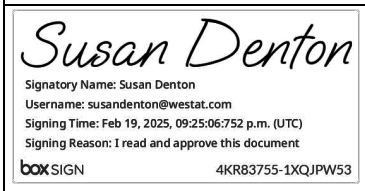

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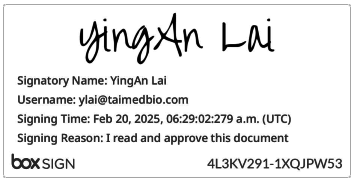

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VERSION HISTORY

Version Number	Version Date	Modified By	Summary of Changes
0.1	20MAY2022	Jennifer Fulton	Initial draft
0.2	16JUN2022	Jennifer Fulton TaiMed	Updates after initial review
1.0	28JUN2022	Jennifer Fulton	Final Version 1
2.0	07JUN2023	Jennifer Fulton	Updates to reflect protocol amendments 1 and 2, and well as the protocol administrative update dated Nov 1, 2022 which added glucose, calcium, uric acid and gamma-glutamyl transferase (GGT) to the list of planned assessments.
3.0	17MAY2024	Susan Denton Duck-Hye Yang	Added text throughout regarding grouping of subjects according to assigned treatment group. Updated to match study plan with one Core Group with 8-week dosing.
4.0	05FEB2025	Victoria Lazariu	Updated language in statistical section to correct inconsistency and improve clarity.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
SAP	Statistical Analysis Plan
cART	Combination antiretroviral therapy
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
SAE	Serious Adverse Event
PK	Pharmacokinetic
PD	Pharmacodynamic
TEAE	Treatment-emergent Adverse Event
FAS	Full Analysis Set
ITT	Intent-to-Treat
PP	Per-Protocol
SD	Standard Deviation
MIN	Minimum
MAX	Maximum
CI	Confidence Interval
PCS	Potentially Clinically Significant
CDISC	Clinical Data Interchange Standards Consortium

1 INTRODUCTION

This statistical analysis plan (SAP) describes the methods and data presentations to be used in the summary and analysis of **safety and efficacy** of **the combination of TMB-365 and TMB-380**. Background information is provided for the overall study design and objectives. For details about study conduct and data collection, refer to the study protocol and associated **data collection forms**.

The proposed methods and approaches to the data analysis should be viewed as flexible. If the data suggest and warrant it, deviations from this plan will be considered. However, any deviations from this SAP must be substantiated by sound statistical rationale and documented in the clinical study report.

2 PROJECT OVERVIEW

2.1 Study Design

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 three Sentinel Groups (N=10) and a Core Group (N=20).

Study participants must be on a continuous DHHS-recommended suppressive cART regimen for at least 6 months and have documented viral suppression as demonstrated by a plasma HIV-1 viral load below the limit of detection at Screening as well as one documented undetectable value within 3 months of 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.

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 dosing:

Single intravenous doses of 2400 mg, 3200 mg, 4800 mg of each antibody.

Sentinel group dose escalation:

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 at least 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).

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.

Should protocol defined virologic failure occur in more than 2 subjects in any Core Group then dosing within that Core Group will cease and all subjects will resume oral cART.

2.2 Study Objectives

2.2.1 Primary Study Objective(s)

- 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)

2.2.2 Exploratory Study Objective(s)

The exploratory objective(s) of the study are to report and describe the following:

- 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*.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent of subjects in the Core group who remain suppressed, that is a plasma HIV-1 RNA below detection, at Day 168 / Week 24.

2.3.2 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.

2.3.3 Pharmacokinetic (PK) and Pharmacodynamic (PD) Endpoints

PK endpoints:

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 endpoints:

- CD4+/CD8+ 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.

2.4 Number of Subjects

This adaptive study design will be comprised of 3 Sentinel Groups (N=10 each) and 1 Core Group (N=20 each), for up to 70 planned subjects.

2.5 Treatment and Study Duration

Screening period: 6 weeks

Sentinel Groups: 12 to 16 weeks (post infusion)

Core Groups: 28 weeks (4 weeks follow-up post infusion phase and cART reinstitution)

2.6 Procedures

2.6.1 Enrollment and Randomization

Dose group assignments are not randomized. Subjects will be enrolled into the dose group with an available slot at the time of enrollment.

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.

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% Sentinel Group subjects at the selected dose level having met the safety and PK criteria.

2.6.2 Masking and Unmasking

The study does not require masking and unmasking.

2.6.3 Replacement

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

2.6.4 Statistical Software

Data will be described and analyzed using the SAS System Version 9 (SAS Institute Inc., Cary, NC, SAS System).

3 STATISTICAL ANALYSIS CONSIDERATIONS

3.1 Sample Size Justification and Power Analysis

Up to 70 HIV-positive participants are planned to 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.

3.2 Analysis Populations

3.2.1 Intent-to-Treat Population

The intent-to-treat (ITT) population includes all participants enrolled in the study, regardless of whether they receive a dose of study drug.

3.2.2 Full Analysis Set Population

The full analysis set (FAS) includes all participants who are administered any fraction of study drug. This also constitutes the Safety Population.

3.2.3 Per-Protocol Population

The per-protocol (PP) population consists of all participants in the FAS population and in the Core Groups who complete through the Week 24 visit. In addition, subjects with the following major protocol deviations:

- subjects who miss one or more doses of study drug,
- subjects who receive an unplanned dose level of study drug,
- subjects who miss more than 80% of visits*

will be excluded from the PP population.

*A missing visit will be defined as a visit for which neither PK nor viral load samples are collected (lab's inability to process a collected sample does not constitute a missing visit).

3.2.4 Pharmacokinetic Analysis Population

The pharmacokinetic (PK) population will consist of all subjects in the **FAS** population. 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 PK targets required to signal the enrollment of the Core participants must be met.

3.2.5 Completed Population

The completed population will consist of all subjects for whom study completion was documented on the End of Study form. This population will not be indicated for any specific analysis but will be flagged in the submitted data package.

3.3 Data Handling

3.3.1 Handling of Multiple Observations

A subject may have multiple scheduled or unscheduled visit assessments that are associated with a protocol defined visit (nominal visit). If the scheduled visit assessment exists, it will be used for data summary and analysis. Otherwise, if no scheduled visit assessment exists but at least one unscheduled visit assessment is available within the protocol-defined time window, then the data at the latest unscheduled assessment within the protocol-defined time window will be used for data summary and analysis.

Any unscheduled visit assessments that cannot be attributed to a scheduled visit assessment will not be included in the statistical summaries or analyses but will be presented in listings.

3.3.2 Defining Study Baseline

In general, the study baseline is defined as the last non-missing observation obtained prior to dosing. The actual dose date will be compared with the date of data collection to define the study baseline.

3.3.3 Handling of Safety Results Beyond the Limit of Quantification

In general, any safety laboratory tests with results given as '< xx' or '> xx' in the database will be imputed with the absolute value of the number without the sign (e.g., < 2.5 will be imputed as 2.5) for the descriptive analysis and summary. Some specific analytes may be imputed with a more appropriate rule on a case-by-case basis as determined in consultation with the Medical Monitor and the laboratory. These rules will be documented in the data package.

3.3.4 Imputation of Incomplete Dates

No imputations will be performed in the study.

3.3.5 Handling of Missing Data

For summary descriptive statistics, missing data will be represented by counts and treated as missing at random; no adjustments will be made. No imputation of missing data will be performed.

3.4 Statistical Methods

3.4.1 Statistical Notation and Presentation

For descriptive statistical summaries, the mean, sample size (n), standard deviation (SD), median, minimum (MIN), and maximum (MAX) will be calculated for continuous variables. For categorical variables, count and percentage in each category will be provided.

MIN and MAX values will be presented to the precision of the original value. Means and medians will be rounded to one decimal place greater than the precision of the original value. SDs and 95% confidence intervals (CIs) will be rounded to two decimal places greater than the precision of the original value. Percentages for summarizing categorical data will be rounded to

one decimal place. P-values, if reported, will be presented with four decimal places and values less than 0.0001 will be presented as < 0.0001.

The by-subject listings, including data at scheduled and unscheduled visits, will be sorted by **dose group, subject number, and then by date/time of the records**.

3.4.2 Statistical Hypothesis

There will be no formal hypothesis testing. Statistical analysis will be descriptive only.

3.4.3 Interim Analysis

No pre-specified formal interim analyses are planned for the study. Interim reviews of the PK data will be provided in a separate report.

4 STATISTICAL ANALYSIS

4.1 Study Subjects

4.1.1 Subject Eligibility

A listing of subjects who violated study inclusion and exclusion criteria will be provided for the **FAS** population.

4.1.2 Subject Disposition

Subject disposition will be presented for the **FAS** population. Counts and percentages of subjects who are **enrolled,** completed, or discontinued from the study, as well as the discontinuation reasons, will be summarized by **dose group** and overall. A listing of subject dispositions will also be provided.

4.1.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by **dose group**, including but not limited to, age **(years)**, sex, race, and ethnicity. These summaries will be presented for the **FAS** population. A listing of demographic and baseline characteristics will also be provided.

4.1.4 Medical History

A listing of medical history details will be provided for the **FAS** population.

4.1.5 Investigational Product Administration

Investigational product administration **and post-administration observation** information will be presented in a listing for the **FAS** population.

4.1.6 Protocol Deviations/Violations

Protocol deviations/violations will be listed for the **FAS** population. All protocol deviations/violations will be reviewed by clinical and statistical personnel prior to database lock. The protocol deviations will be used to determine subjects' eligibility for inclusion in the per-protocol population.

4.1.7 Concomitant Medications and Procedures

All prescriptions or over-the-counter medications continued at the start of the trial or started during the trial, and different from the study drug will be recorded. All of these medications will be coded using WHO-Drug Dictionary version B3, March 2022. The use of another version will not be considered a violation of the SAP, nor require an amendment to the plan. Both the coded terms and verbatim terms will be presented in data listings for:

- Previous and Concomitant medications
- cART medications

- Concomitant procedures (procedures are not coded)

4.2 Analysis of Efficacy

An analysis of efficacy will be performed on the **FAS and PP** populations.

4.2.1 Analysis of the Primary Efficacy Endpoint(s)

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 fail to remain suppressed, that is a plasma HIV-1 RNA above detection, at Day 168 / Week 24.

The percent of subjects with HIV-1 RNA above detection will be presented by **dose group** at each scheduled visit, including the primary efficacy endpoint visit of Day 168/Week 24, in both a table and corresponding graph. The table will include the 95% Confidence Interval around each percent.

4.3 Analysis of Safety Endpoints

An analysis of endpoints will be performed on the safety population.

4.3.1 Extent of Exposure

Summary statistics will be presented for the cumulative dose **(mg)** and duration of treatment received by the subjects in the safety population. Duration of treatment will be represented both as number of days from first dose and total number of doses for each subject. A corresponding listing will also be generated for investigational product administration.

4.3.2 Adverse Events

The MedDRA Dictionary version 25.0 will be used for the coding of AEs. A treatment-emergent AE (TEAE) is defined as any event not present before exposure to the investigational product or any event already present that worsens in either intensity or frequency following exposure to the investigational product. AEs with missing start dates, but with stop dates either overlapping into the dosing period or missing, will be considered TEAEs. A TEAE with missing severity or relationship will be considered severe or related, respectively. The number and percentage of subjects having the following will be tabulated:

- TEAE
- Serious TEAE
- TEAE leading to discontinuation
- TEAE with outcome of death
- Causality (Probable or Definite)
- Severe (Grade 3 or 4) TEAE
- Class C TEAE per the Centers for Disease Control and Prevention (CDC) Classification System for HIV Infection

Additional summaries will include:

- Overall incidence of TEAEs by System Organ Class (SOC) and by SOC and Preferred Term (PT).
- Overall incidence of serious TEAEs by System Organ Class (SOC) and by SOC and PT.
- TEAEs leading to study discontinuation (if any)
- TEAEs by severity/grade (mild, moderate, severe, or potentially life threatening)
- Serious TEAEs by severity/grade (mild, moderate, severe, or potentially life threatening)
- TEAEs by relationship to the investigational product (unrelated, probable, or definite)
- Serious TEAEs by relationship to the investigational product (unrelated, probable, or definite)

If there are multiple occurrences of the same TEAE within any SOC or PT for the same subject, only the most severe will be counted. The number and percentage of subjects reporting an event as well as the number of events reported by the subjects will be tabulated.

All other AEs will be classified as non-TEAEs and identified in listings only. Serious TEAEs, TEAEs leading to study discontinuation, and TEAEs with an outcome of death will be presented in separate listings, if needed.

4.3.3 Laboratory Evaluations

Laboratory results will be grouped as follows for analysis (scheduled visits vary based on Sentinel and Core cohorts, consult the Schedule of Events in the protocol for details):

All Groups: Screening

HEPATITIS B AND C: HBV and HCV

HIV EIA and Confirmatory Testing

Sentinel Groups: Screening, Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16

Core Group: Screening, Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28

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

CHEMISTRY: ALT, AST, chloride, creatinine, potassium, sodium, total and direct bilirubin, albumin, alkaline phosphatase, blood urea nitrogen, magnesium and creatine phosphokinase, amylase, lipase, phosphorus, glucose, calcium, uric acid and gamma-glutamyl transferase (GGT), and all pregnancy test results.

FLOW CYTOMETRY: CD4+/CD8+ T-cells, CD4 receptor density, CD4 receptor occupancy

All Groups: Baseline and (Week 12 or Week 16 or Week 24)

FASTING LIPID PROFILE: total cholesterol, HDL, LDL, and triglycerides.

All Groups: Screening, Baseline, Week 8 and [(Week 12 and Week 16) or (Week 24 and Week 28)]

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.

Sentinel Groups: Screening, Baseline and (Week 12 or Week 16)

Core Group: Screening, Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28

HIV-1 RNA (VIRAL LOAD)

Results will be presented in the units provided by the central laboratory.

All results will be listed, including scheduled and unscheduled assessments (if any). Laboratory assessments that are outside of normal ranges and/or with clinical significance will be flagged in the listings.

Baseline values, values at post-baseline visits, and changes from the baseline values will be summarized descriptively for quantitative laboratory assessments by **dose group** and visit. Count and percentage will be summarized for laboratory assessments with categorical results by **dose group** and visit. Tables that summarize the count and percentage of values outside of normal ranges will also be provided where applicable.

4.3.4 Vital Signs

For vital signs (**heart rate (beats/minute taken for one minute), blood pressure (mm Hg), respiratory rate (breaths/minute taken for one minute), and temperature (ºC)**), study baseline values, post-baseline values, and changes from study baseline values will be summarized descriptively by **dose group** and visit. A listing of vital signs at all visits, including unscheduled visits, will also be included.

Sentinel Groups: Screening, Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16

Core Group: Screening, Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28

Weight will only be recorded on Baseline and Week 12 or Week 16 for Sentinel Groups, and Baseline and Week 28 for Core Group.

4.3.5 Physical Examination

The number and percentage of subjects with abnormal physical examination findings by body system will be tabulated by **dose group** and visit. A listing of physical examination findings at all visits, including unscheduled visits, will also be included.

Sentinel Groups: Screening and (Week 12 or Week 16) + Directed Physical Examination: Baseline, Week 1, Week 2, Week 4, Week 8, Week 12

Core Group: Screening, Week 12, Week 24, Week 28 + Directed Physical Examination: Baseline, Week 2, Week 4, Week 8, Week 16, Week 20

4.4 Analysis of Pharmacokinetics and Pharmacodynamics

PK data will be included as part of the CDISC data submission, but analysis will be presented in a separate report prepared by TaiMed. Per protocol, all blood samples collected for TMB-365 and TMB-380 serum concentration analysis in Sentinel groups 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.

PD endpoints 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. Summary tables and listings of PD endpoints are described in section 4.3.3 of this document.

Scheduled visits (both pre- and post-dose at Baseline, post-dose only at other visits):

Sentinel Groups: Baseline, Week 1, Week 2, Week 4, Week 6, Week 7, Week 8, Week 9, Week 10, Week 12, Week 13, Week 14, Week 16

Core group participants receiving either antibody every 8 weeks 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:

Baseline, Week 2 (± 3d), Week 4 (± 3d), Week 8 (± 3d), Week 12 (± 3d), Week 16 (± 3d), Week 20 (± 3d), Week 24 (± 3d), Week 28 (± 3d).

4.5 Questionnaires

Patient reported outcome measures (POCM) for the Core Group will be assessed at various time points using the following validated questionnaires (see Appendix C of the protocol for details):

- HIV Treatment Satisfaction Questionnaire-status (HIVTSQs) – Baseline, Week 8, Week 12, Week 24, Week 28
- HIV Treatment Satisfaction Questionnaire-change (HIVTSQc) – Week 24

Summary statistics by visit will be presented for all subjects who answered each question.

Results will also be presented in a listing.

4.6 Exploratory Analysis

A separate report will be produced by TaiMed to summarize immunogenicity of TMB-365 and TMB-380 in HIV-1 infected suppressed participants.

A separate report will be produced by TaiMed to summarize the resistance profiles of TMB-365 and TMB-380 *in vivo*.

5 REFERENCES

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. February 5, 1998. *ICH E9: Statistical principles for clinical trials*. https://database.ich.org/sites/default/files/E9_Guideline.pdf. [Accessed May 9, 2022].

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. November 30, 1995. *ICH E3: Structure and content of clinical study reports*. https://database.ich.org/sites/default/files/E3_Guideline.pdf. [Accessed May 9, 2022].