STUDY PROTOCOL

A Phase 3 Study of the Safety of Trogarzo® Administered as an Undiluted "IV Push" over a Reduced Interval or as an Intramuscular Injection in Clinically Stable HIV-1 Infected Trogarzo® Experienced Patients and Healthy HIV-uninfected Volunteers

PROTOCOL NUMBER: TMB-302 - Amendment 6

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Ethics Statement:

The study will be completed according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines E6(R2): Good Clinical Practice: Consolidated Guideline and E2A: Clinical Safety Data Management. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki. The study will also follow the standards set forth in the Code of Federal Regulations Title 21 Parts 11 (Electronic Records), 50 (Protection of Human Subjects), 54 (Financial Disclosure by Clinical Investigators), 56 (Institutional Review Boards), and 312 (Investigational New Drug Application).

INVESTIGATOR'S STATEMENT

I agree to conduct the study as outlined in the protocol entitled, "A Phase 3 Study of the Safety of Trogarzo® Administered as an Undiluted "IV Push" over a Reduced Interval or as an Intramuscular Injection in Clinically Stable HIV-1 Infected Trogarzo® Experienced Patients and Healthy HIV-uninfected Volunteers" 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 11).

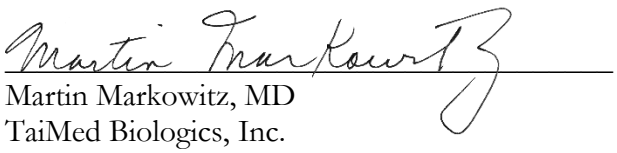
_____
Investigator's Name

_____
Investigator's Institution

_____ _____
Investigator's Signature Date

SPONSOR APPROVAL

Approved by:



Martin Markowitz, MD
TaiMed Biologics, Inc.

9 June 2022
Date

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Appendices

Appendices to this protocol are presented in a separate document entitled:

"Appendices to Protocol TMB-302: A Phase 3 Study of the Safety of Trogarzo® Administered as an Undiluted "IV Push" over a Reduced Interval or as an Intramuscular Injection in Clinically Stable HIV-1 Infected Trogarzo® Experienced Patients and Healthy HIV-uninfected Volunteers"

The Appendices include the following:

Appendix A: CDC AIDS Defining Conditions

Appendix B: Division of AIDS: Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1 (July 2017)

Appendix C: "The diagnosis and management of anaphylaxis: An updated practice parameter"

Appendix D: HIV Treatment Satisfaction Questionnaires (HIVTSQs, HIVTSQc) and Study Medication Satisfaction Questionnaires (SMSQs, SMSQc)

SYNOPSIS

Protocol Number:	TMB-302
Title:	A Phase 3 Study of the Safety of Trogarzo® Administered as an Undiluted "IV Push" over a Reduced Interval or as an Intramuscular Injection in Clinically Stable HIV-1 Infected Trogarzo® Experienced Patients and Healthy HIV-uninfected Volunteers
Sponsor:	TaiMed Biologics, USA Corp. 4790 Irvine Blvd. Suite 105-697 Irvine, CA 92620
Study Phase:	3
Subjects and Investigator Sites:	A total of approximately 40 subjects will be enrolled into this study. Approximately twenty (20) will receive Trogarzo® as an intravenous (IV) push and approximately 20 subjects will receive Trogarzo® as an intramuscular (IM) injection at approximately 7-8 sites in the United States. Subjects who receive Trogarzo® as an IV Push can also receive Trogarzo® as an IM injection once they complete the IV push portion of study. After 20 subjects enroll to complete the IV push portion of the study, subjects who enroll may participate in the IM portion exclusively.
Study Drug Dosage and Route of Administration:	The study drug, Trogarzo®, is a humanized IgG4 monoclonal antibody (MAb) approved for use in treatment-experienced subjects in combination with other antiretroviral agents for the treatment of multi-drug resistant HIV-1 infection and is administered via intravenous infusion (IV). Maintenance doses of 800 mg Trogarzo® will be administered to all study subjects every 2 weeks throughout their participation in the study. For subjects receiving Trogarzo® as an IV push, the Day1/Baseline and Day 15 doses will be administered as diluted intravenous infusions (IVI - 800 mg in 250 mL normal saline; 3.2 mg/mL) over 15 minutes in accordance with Trogarzo® prescribing information. Subsequent Trogarzo® doses on study will be administered at increased concentration over a shorter interval (<15 minutes – see Study Design for more detail). For subjects receiving Trogarzo® via IM injection, the Day 1/Baseline and Day 15 doses will be administered as diluted IVI over 15 minutes in accordance with Trogarzo® prescribing information. The subsequent four (4) Trogarzo® doses on study will be administered as an IM injection.

	All subjects will continue on all other antiretroviral (ARV) medications as prescribed by the primary care provider throughout study participation. Any changes in ARV treatment will be recorded with reasons for treatment modification. All HIV-infected subjects will return to routine Trogarzo® administration via IVI over 15 minutes in accordance with the prescribing information after completing participation in the study.
Control Drug, Dosage, and Route of Administration:	None
Objectives:	The primary objective of this study is to: ■ Evaluate the safety of Trogarzo® administered as an undiluted "IV push" over 30 seconds or as an IM injection in clinically-stable HIV-1 infected subjects with at least 3 months of stable treatment with a Trogarzo®-containing ARV regimen or healthy HIV-uninfected volunteers ■ Compare the AUC and trough serum drug concentration after IVI with the diluted drug to the AUC and trough serum concentration after IV push of undiluted Trogarzo® ■ Compare the trough serum drug concentration after IVI with the diluted drug to the trough serum concentration after IM injection of undiluted Trogarzo®. The secondary objectives of this study are to: ■ Assess HIV-1 viral load for IVI compared to IV push and IM injection in HIV-1 infected subjects only ■ Characterize noted human immunodeficiency virus type-1 (HIV-1) sensitivity/susceptibility changes in participants with an increase in plasma viral load to levels above 1,000 copies/mL on 2 consecutive measurements at least 2 weeks apart in HIV-1 infected subjects only ■ Determine the presence and significance of anti-Trogarzo® antibodies, if any (immunogenicity of Trogarzo®) ■ Compare the AUC after IVI with the diluted drug to the AUC after IM injection of undiluted Trogarzo®
Subject Population: ***Inclusion Criteria***	**HIV-1 infected individuals:** Subjects must meet all of the following criteria to be included in the study: 1. Are capable of understanding and have voluntarily signed the informed consent document 2. Currently receiving a stable Trogarzo®-containing ARV regimen for a minimum of 3 months, and no change in

	background ARVs anticipated over the period of study participation; a stable regimen is defined as having no changes in dose or frequency and no interruptions ≥2 weeks during the 3-month period Note: For subjects who receive Trogarzo® as an IV push (Core Group) and subsequently enter the study to receive Trogarzo® as an IM injection (IM Group), the time period while receiving the IV push will be considered as having received a stable Trogarzo®-containing ARV regimen. Note: HIV-infected subjects who are enrolled in the IM injection study and are unable to adhere to the study schedule for IM dosing due to factors outside the study will be discontinued. Re-enrollment of HIV-infected IM Group subjects will be allowed after a Discontinuation Visit and Screening Visit are completed provided that inclusion/exclusion criteria continue to be satisfied and dosing after discontinuation is resumed according to the Trogarzo® Prescribing Information. For re-enrolling subjects, the inclusion criteria for stable a Trogarzo®-containing ARV regimen is satisfied with a loading dose of 2000mg IVI and at least one maintenance dose of 800mg IVI given according to Trogarzo® labeling prior to Day 1 enrollment. 3. Have no acquired immunodeficiency syndrome (AIDS)-defining events in the 3 months before Screening, other than cutaneous Kaposi's sarcoma or wasting syndrome due to HIV 4. Are able and willing to comply with all protocol requirements and procedures 5. Are 18 years of age or older 6. Have a life expectancy that is >6 months. 7. Have a viral load <1,000 copies/mL at Screening 8. $CD4^+$ T-cell count >50 cells/mm^3 at Screening 9. Prothrombin time (PT) and partial thromboplastin time (PTT) <1.5 times the upper limit of normal value (for IM Group only) **HIV-uninfected individuals:** Subjects must meet all of the following criteria to be included in the study: 1. Healthy volunteers born male and female as assessed by medical history and physical examination

	2. Aged ≥18 and ≤50 years at the time of Screening 3. Ability and willingness to provide written informed consent 4. Willingness to comply with protocol schedule 5. Willingness to undergo HIV-1 testing 6. Non-reactive 4th generation point of care HIV-1 test at Screening 7. Hepatitis B Surface antigen negative 8. Hepatitis C antibody negative, or if reactive, Hepatitis C RNA undetectable in plasma 9. PT and PTT <1.5 times the upper limit of normal (for IM Group only) 10. Volunteers born female of reproductive potential who are 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. Volunteers born female with reproductive potential are defined as pre-menopausal volunteers born female who have not had a sterilization procedure (e.g., hysterectomy, bilateral oophorectomy, tubal ligation or salpingectomy). Volunteers born female are considered menopausal if they have not had a menses for at least 12 months and have a follicle-stimulating hormone (FSH) of greater than 40 IU/L or if FSH testing is not available, they have had amenorrhea for 24 consecutive months.
Subject Population: ***Exclusion Criteria***	**HIV-infected participants:** Subjects having or meeting any of the following conditions or characteristics will be excluded from the study: 1. Any active AIDS-defining illness according to the Centers for Disease Control and Prevention (CDC) Revised Surveillance Case Definitions for HIV Infection 2008 (MMWR Vol.57/No. RR-10), or history of the same during the 3 months preceding Screening, with the following exceptions: cutaneous Kaposi's sarcoma and wasting syndrome due to HIV 2. Any significant diseases (other than HIV-1 infection) or clinically significant findings, including psychiatric and behavioral problems, determined from Screening, medical history, and/or physical examination that, in the investigator's opinion, would preclude the subject from participating in this study

	3. Any significant acute illness within 1 week before the initial administration of study drug 4. Any active infection secondary to HIV requiring acute therapy; however, subjects that require maintenance therapy (i.e., secondary prophylaxis for opportunistic infections) will be eligible for the study. 5. Any immunomodulating therapy (including interferon), systemic steroids, or systemic chemotherapy within 12 weeks before Enrollment 6. Any vaccination within 7 days before Day 1 7. Any female subject who either is pregnant, intends to become pregnant, or is currently breastfeeding 8. Any current alcohol or illicit drug use that, in the investigator's opinion, will interfere with the subject's ability to comply with the study schedule and protocol evaluations 9. Any radiation therapy during the 28 days before first administration of study medication 10. Any Grade 3 or 4 laboratory abnormality according to the Division of AIDS grading scale, except for the following asymptomatic Grade 3 events: ➢ Triglyceride elevation ➢ Total cholesterol elevation ➢ Grade 3 or 4 reductions in levels of CD4+ T cells 11. History of coagulopathy that would preclude administration of IM injections (IM Group only) 12. Skin rashes or tattoos that would prevent ability to assess IM injection-site reactions (IM Group only) 13. Use of high-dose aspirin, clopidogrel, prasugrel, ticagrelor, dipyridamole or other antiplatelet medication that would interfere with the ability to receive IM injections (IM Group only) **HIV-uninfected individuals** 1. Confirmed HIV-1 infection at screening 2. At high risk of severe COVID-19 disease as defined by one of the following: ➢ History of hypertension, atherosclerotic cardiovascular disease (ASCVD), coronary artery disease, diabetes mellitus

	➢ History of asthma or chronic pulmonary disease ➢ History of renal disease and chronic renal insufficiency ➢ Body mass index (BMI) over 35 3. Any acute or chronic medical condition that in the opinion of the investigator would preclude participation 4. Chronic autoimmune disease 5. Active IV drug use 6. Excessive use of alcohol or recreational drugs that in the opinion of the investigator would preclude participation. 7. Decompensated psychiatric illness 8. Need for chronic immunotherapy including systemic corticosteroids, other monoclonal antibody (MAb) therapy, or immunosuppressive drugs 9. Volunteers born female who are pregnant, lactating, or planning on becoming pregnant over the study period 10. Any of the following laboratory parameters: ➢ Hemoglobin <10.0 g/dL ➢ Absolute neutrophil count <1,000/mm^3 ➢ Absolute lymphocyte count <500/mm^3 ➢ Platelet count <100,000/mm^3 ➢ Creatinine >1.25x upper limit of normal (ULN) ➢ Aspartate aminotransferase (AST) >1.5 x ULN ➢ Alanine aminotransferase (ALT) >1.5 x ULN ➢ Glucose (non-fasting) >160 mg/dL ➢ Proteinuria: 2+ or greater ➢ Hematuria: >10 red blood cells (RBCs) per high-power field 11. Previous receipt of an experimental mAb to HIV-1 in a research study 12. History of severe allergic reactions to drugs, vaccines, or drug infusion 13. Participation in another investigational clinical trial within the past 12 weeks or anticipated during the course of the current study 14. History of coagulopathy that would preclude administration of IM injections (IM Group only) 15. Skin rashes or tattoos that would prevent ability to assess IM injection-site reactions (IM Group only)

	16. Use of high-dose aspirin, clopidogrel, prasugrel, ticagrelor, dipyridamole or other antiplatelet medication that would interfere with the ability to receive IM injections (IM Group only)
Study Design:	This Phase 3 study will evaluate the safety and serum concentrations of Trogarzo® administered in progressively increasing concentrations over shortening intervals with the goal of administration of an undiluted IV push over an interval of 30 seconds in clinically stable subjects currently receiving treatment with a stable Trogarzo®-containing regimen for a minimum of 3 months or healthy HIV-uninfected volunteers. The study will also evaluate an IM administration of Trogarzo®. The first five (5) subjects enrolled will comprise the Sentinel Group. Subjects six (6) through twenty (20) comprising the Core Group will not be screened until the Sentinel Group has completed Day 99 (14 weeks) of the study and the DMC has reviewed accumulated data and given approval for the study to continue. The IM Group will comprise twenty (20) subjects receiving Trogarzo® as an IM injection. Subjects completing the IV push portion of the study (from the Sentinel and Core Groups) are eligible to participate in the IM Group. <u>Sentinel Group (Subjects 1 to 5)</u> Subjects in the Sentinel Group will receive an 800 mg maintenance dose of Trogarzo® in accordance with the prescribing information (diluted in 250 mL normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. Every two weeks thereafter through Day 85 (12 weeks), subsequent maintenance doses will be administered at successively increasing concentrations via IVI, IV bolus, and concluding with IV push over successively shorter intervals according to the following schedule: ■ Day 1/Baseline and Day 15: 800 mg diluted in 250 mL normal saline (at 3.2 mg/mL) via IVI over 15 minutes per approved Trogarzo® prescribing information ■ Day 29 (4 weeks): 800 mg diluted in 50 mL normal saline (at 16 mg/mL) via IVI over 10 minutes ■ Day 43 (6 weeks): 800 mg diluted in 16 mL normal saline (at 50 mg/mL) via IV bolus over 5 minutes ■ Day 57 (8 weeks): 800 mg diluted in 8 mL normal saline (at 100 mg/mL) via IV bolus over 1 minute

	■ Day 71 (10 weeks): 800 mg undiluted (at 150 mg/mL) via IV push over 30 seconds ■ Day 85 (12 weeks): 800 mg undiluted (at 150 mg/mL) via IV push over 30 seconds For the End of Study (EOS) visit at Day 99 (14 weeks), Sentinel Group subjects will revert to diluted IVI dosing over 15 minutes in accordance with the Trogarzo® prescribing information. Enrollment into the Sentinel Group will be staggered, and a DMC will review available data at scheduled intervals and upon the occurrence of identified safety events throughout the study (see Section 4.3). When five (5) subjects in the Sentinel Group have completed Day 99 (14 weeks) of the study, the DMC will review the available data to determine whether the study should proceed to enrollment of the Core Group. Core Group (Subjects 6 to 20) **HIV-1 infected individuals:** After DMC review and approval, the Core Group (subject numbers six [6] through twenty [20]) will be enrolled. Subjects in the Core Group will also receive an 800 mg maintenance dose of Trogarzo® in accordance with the prescribing information (diluted in 250 mL normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. Every 2 weeks thereafter through Day 71 (10 weeks), subsequent maintenance doses will be administered via undiluted IV push over 30 seconds. At Day 85 (12 weeks), Core Group subjects will revert to diluted IVI dosing over 15 minutes in accordance with the Trogarzo® prescribing information. **HIV-uninfected individuals:** Pre-steady State Phase: Subjects will receive a 2000 mg infusion over 60 minutes on Day -55 followed by 3 doses of 800 mg infusion over 15 minutes on Days -41, -27, and -13. On Day 1 the subjects will enter the Treatment Study Phase. Treatment Study Phase: These HIV-uninfected subjects will receive an 800 mg dose of Trogarzo® in accordance with the prescribing information (diluted in 250 mL normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. Every 2 weeks thereafter through Day 71 (10 weeks), subsequent doses will be administered via undiluted IV push over 30 seconds. After the Day 71 administration, HIV-uninfected Core Group subjects will discontinue Trogarzo® therapy.

	IM Group The IM Group will enroll either subjects who were enrolled and completed the study from the Sentinel and Core groups or other subjects new to the study who were not previously involved in the IV push portions. Subjects for inclusion in the IM Group will be recruited only once all subjects for the Core Group have been enrolled in and completed the Core study. **HIV-1 infected individuals:** Subjects will receive the first two doses of study drug in accordance with the Trogarzo® prescribing information (diluted in normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. The next four doses of Trogarzo® through Day 71 (10 weeks) will be administered as an IM injection. At Day 85 (12 weeks), IM Group subjects will revert to diluted IVI dosing over 15 minutes in accordance with the Trogarzo® prescribing information. For re-enrolling subjects, a loading dose of 2000mg IVI and at least one maintenance dose of 800mg IVI will be given according to the label to re-establish study eligibility from a Trogarzo® dosing perspective starting at least 4 weeks prior to Day 1. The day of the 2000mg loading dose may also serve as the Discontinuation or Re-screening visit, as appropriate for subject and study site scheduling needs for re-enrolling subjects. **HIV-uninfected individuals:** Pre-Steady State Phase: Subjects will receive four doses of Trogarzo® as described above for Core Group HIV-uninfected individuals prior to the Study Treatment Phase. Study Treatment Phase: HIV-uninfected subjects in the IM Group will receive the first two doses of Trogarzo® in accordance with the prescribing information (diluted in 250 mL normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. The next four doses of Trogarzo® will be administered as an IM injection. HIV-uninfected subjects will discontinue dosing after the Day 71 study drug administration. A total volume of 5.32 mL, corresponding to 800 mg Trogarzo, will be injected intramuscularly and will be split into two injections of approximately 2.66 mL each. The two IM injections should be administered in the muscle tissue of the subject's anterolateral aspect of the thighs (left, right, or both) or, alternatively, in the

	dorsogluteal site (upper outer quadrant of the buttock). In either area, injections sites should be at least 1 inch apart. All Groups: After each study drug administration, all HIV-infected study subjects in both groups will be observed for at least 15 minutes, and HIV-uninfected subjects will be observed for at least 60 minutes for acute injection-related reactions. Injection-site reactions will also be monitored during subsequent study visits. All AEs will be recorded. Vital signs will be measured and recorded at the beginning and end of this observation period. Clinical site personnel and emergency medications and equipment will be available to manage any infusion or injection reactions as medically indicated. Hypersensitivity reactions including infusion-related reactions and anaphylactic reactions have been reported following infusion of ibalizumab during post-approval use. Subjects should be monitored closely for such symptoms during observation. Injection site reactions will be assessed in subjects who receive IM injections of Trogarzo® at each visit during IM administration and follow-up. Subjects will be followed for safety through 28 days after the last administration of Trogarzo® on study (from Day 85 [12 weeks] through Day 113 [16 weeks] for the Sentinel and HIV-infected IM Groups, from Day 71 [10 weeks] through Day 99 [14 weeks] for the HIV-uninfected Core and IM Groups, and at Day 99 for the HIV-infected Core Group).
Safety Assessments:	Safety assessments will include results of the following measurements through Day 99 (14 weeks) for the Sentinel Group, Day 85 (12 weeks) for the HIV-1 infected Core Group and IM Group subjects, and Day 99 (14 weeks) for the HIV-uninfected healthy volunteers in the Core Group and IM Group: ■ Physical examinations ■ Vital sign measurements ■ Clinical laboratory parameters (hematology, serum chemistry, urinalysis and $CD4^+$ T-cell count) ■ Monitoring of AEs and concomitant medications ■ Anti-Trogarzo® antibody levels (immunogenicity of Trogarzo®)

	Laboratory samples will be collected every 2 weeks, at visits where Trogarzo® is administered. Beginning at Day 29 (4 weeks), non-laboratory safety assessments will be performed weekly through Day 99 (14 weeks) for the Sentinel Group, through Day 85 (12 weeks) for the HIV-1 infected Core Group and IM Group, and Day 99 (14 weeks) for the HIV-uninfected Core Group and IM Group.
Statistical Considerations:	**Sample Size:** A sample size of approximately 40 subjects will be enrolled including approximately 20 subjects who will receive Trogarzo® as an IV push and approximately 20 subjects who will receive Trogarzo® as an IM injection. Subjects who have previously received Trogarzo® as an IV push are permitted to screen/enroll for participation in the IM Group. The safety and PK analysis will include all subjects. Intra-subject AUC and serum trough concentrations of study drug after IV infusion will be compared with concentrations following both IV push and IM injection. 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 AEs. **Analysis Sets:** A Safety (SAF) and an Intent-to-Treat (ITT) analysis dataset will be created. The SAF will include all subjects receiving at least one partial dose of study drug and ITT is all subjects enrolled into the study. The SAF Analysis Set will be used for the primary safety analysis. The ITT Analysis Set will be used for the AUC and trough serum drug concentration and the secondary effectiveness analysis. **Safety Analyses:** The safety analyses will include descriptions of treatment-emergent AEs, Class C events per the CDC Classification System for HIV Infection, clinical laboratory test results, physical examination findings, vital sign results, and immunogenicity of Trogarzo®. Data collected at each visit will be summarized where applicable. Continuous variables (e.g., age, weight) will be summarized using descriptive statistics consisting of number of subjects, mean, standard deviation (SD), and minimum, median, and maximum values . Categorical variables will be summarized using the number and percentage of subjects in each category. **Pharmacokinetic Analysis:** The exposure-response relationship established for the review of the ibalizumab Biologics License Application (BLA) was based on C_{trough}, rather than AUC. C_{trough}

	was used as an indicator of exposure and a clear trend between exposure and the efficacy endpoint was observed. Therefore, C_{trough} is more representative of efficacy for this pharmacokinetic bridging study than AUC. A PK bridge between the IV push and IVI and between the IM injection and IVI is demonstrated if the proportions of subjects with average C_{trough} equal to or exceeding the threshold of 300 ng/mL are comparable using a Fisher's Exact test. A PK bridge is also demonstrated for AUC if the 90% confidence interval of log transform of the ratio of the geometric means for IV push or IM injection (test product) to IVI (reference product) for the 40 subjects in the study is within an 80%-125% criteria. **Secondary Endpoint Analysis:** Assessment of the HIV-1 viral load measurements will be made as a secondary endpoint in HIV infected subjects by comparing the mean viral load at visits when subjects received an IV infusion to the visits when receiving an IV push over 30 seconds or receiving IM injections. HIV-infected study subjects will be considered virologic failures if: 1. Viremic subjects experience a sustained >0.5 log increase in plasma HIV-1 RNA from baseline or 2. A sustained VL>200 copies/mL if subject VL was <50 copies/mL at baseline that cannot be explained by intercurrent illness, a change in adherence to the background regimen, or unanticipated changes to the background regimen will meet the definition of virologic failure. Sustained is defined as 2 consecutive viral load determinations at least 2 weeks apart. Exploratory statistical analyses will examine any noted changes in HIV-1 drug sensitivity/susceptibility in participants with an increase in plasma viral load to levels above 1,000 copies/mL on 2 consecutive measurements at least 2 weeks apart.
Pharmacokinetics (PK)	**PK Analysis:** PK samples will be collected during the study as shown in the Schedule of Events. These samples will be collected from subjects at selected times to evaluate PK parameters.

ABBREVIATIONS

ABBREVIATION	TERM
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	Antiretroviral
ASCVD	Atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the curve
BLA	Biologics License Application
BMI	body mass index
CD4	cluster of differentiation 4 (glycoprotein expressed on the surface of T-helper cells)
$CD4^+$	cluster of differentiation 4 positive (type of white blood cell, also called T-lymphocytes, T-cells, or T-helper cells)
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CL	Clearance
C_{peak}	Peak concentration
CRF	Case Report Form
CSR	clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
DAIDS	Division of AIDS
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
EC	Ethics Committee
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
EOS	end of study
FDA	U.S. Food and Drug Administration
FSH	follicle-stimulating hormone
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type-1
HIVTSQ	HIV Treatment Satisfaction Questionnaire
HTE	heavily treatment experienced
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IgG4	immunoglobulin 4
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	intent-to-treat
IV	Intravenous
IVI	intravenous infusion

ABBREVIATION	TERM
IVP	intravenous push
LLOQ	lower limit of quantitation
MAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MEF	missing equals failure
MMWR	Morbidity and Mortality Weekly Report
Mu5A8	murine progenitor of Trogarzo®
NAAT	Nucleic acid amplification
OBR	optimized background regimen
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
POC	Point of Care
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
q2wk	every 2 weeks
q4wk	every 4 weeks
QoL	Quality of Life
qwk	once a week
RA	regulatory affairs
RBC	Red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAF	safety dataset for analysis
SC	Subcutaneous
SD	Standard Deviation
SMSQc	Study Medication Satisfaction Questionnaire change version
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TFDA	Taiwan Food and Drug Administration
T_{max}	time to maximum concentration
ULN	upper limit of normal
U.S.	United States
USP	United States Pharmacopoeia
VF	virologic failure
VL	Viral load
WHODD	World Health Organization Drug Dictionary

1. Introduction

1.1 Background

TaiMed Biologics, Inc. has developed a monoclonal antibody (MAb), ibalizumab-uiyk (Trogarzo®, formerly TNX-355, TMB-355 and Hu5A8), to be used in combination with an optimized background regimen (OBR) to treat human immunodeficiency virus type 1 (HIV-1) infected treatment-experienced subjects who are multi-drug resistant. The approved drug Trogarzo® is administered intravenously over 15 minutes after dilution in physiological saline at an initial loading dose of 2000 mg with maintenance doses of 800 mg administered once every 2 weeks (q2wk). The current study evaluates the safety and pharmacokinetics of the undiluted drug administered during the maintenance phase at 800 mg q2wk as an intravenous (IV) push over 30 seconds or as an intramuscular (IM) injection. The possibility of administering the undiluted drug as an IV push or as an IM injection would avoid occasional saline shortages, simplify drug administration for the pharmacy and health practitioner and improve subject adherence. If deemed comparable to administration by IV infusion (IVI), administration by IV push or IM injection would be desirable to improve the logistics of administration by eliminating the need for saline bags and infusion apparatus as well as improving convenience for subjects and physicians.

In 2012, over 35 million people worldwide were living with human immunodeficiency virus (HIV) infection and 1.6 million people died from HIV/acquired immunodeficiency syndrome (AIDS).[1] Currently available treatment regimens (referred to as antiretroviral therapy [ART]) are composed of medications to inhibit HIV-1 replication and viral entry. In regions of the world like the United States with access to antiretroviral medications, combination ART successfully controls HIV replication in a majority of subjects that take the medications. However, approximately 20% of subjects in the United States (U.S.) still fail to achieve the goal of HIV treatment, suppression of viral replication to undetectable levels. Even in subjects who initially benefit from ART, development of drug resistance and severe side effects are major concerns.[2] Additional treatment modalities are urgently needed.

Other therapies designed to prevent infection of host cells (i.e., entry inhibitors) are currently approved for treatment of HIV infection in treatment-experienced subjects. Fuzeon® (enfuvirtide, T-20), a fusion inhibitor and Selzentry™ (maraviroc), a coreceptor antagonist have both been shown

to be efficacious when combined with an OBR in treatment-experienced subjects.[3,4,5] Trogarzo®, a MAb, is a cluster of differentiation 4 (CD4)-directed post-attachment inhibitor that also blocks HIV entry and is approved for use in combination with other approved antiretroviral (ARV) medications in treatment-experienced subjects with multi-class resistant HIV-1.

Clinical trials conducted with IV Trogarzo® to assess safety and efficacy are described in the sections that follow. The safety data from two small studies with subcutaneous (SC) and IM administration are also discussed.

1.2 Clinical Studies

Prior studies with Trogarzo® administered via IVI have been conducted in HIV-positive individuals and are summarized below. In addition, a study of Trogarzo® administered subcutaneously (Study TMB-108) to HIV-negative at-risk volunteers has been completed as has a study (Study TMB-121) exploring both SC and IM administration routes in both HIV-negative and HIV-positive participants.

Results from the Phase 1a clinical trial (Hu5A8.01) demonstrated that IV administration of a single dose of Trogarzo® to HIV-infected subjects was associated with dose-dependent mean viral load reductions of approximately 1 $\log_{10}$ in those receiving doses of 10 mg/kg or greater. Mean viral load reductions persisted for 2-3 weeks. In a subsequent Phase 1b study (Study TNX-355.02) Trogarzo® was given to HIV-infected subjects as a single agent (monotherapy) or added to failing ART. Multiple doses of Trogarzo® again demonstrated clinically significant viral load reductions (median reductions approximately 1 $\log_{10}$) with viral load nadirs at 1-2 weeks. A 24-week, double-blind, placebo-controlled, randomized, three-arm Phase 2a study (Study TNX-355.03) evaluated the safety, efficacy, and pharmacokinetic (PK) activity of 2 Trogarzo® dose regimens (10 mg/kg and 15 mg/kg) in combination with an OBR versus placebo with an OBR in treatment-experienced subjects. As in the Phase 1 program, the Phase 2a study clearly demonstrated the antiviral activity of Trogarzo®. Viral load reductions in the treatment arms were statistically significantly different from placebo, with approximately 1 $\log_{10}$ reductions seen in the Trogarzo®-containing arms at 24 weeks (primary endpoint) and at 48 weeks. Also at 48 weeks, increases in $CD4^+$ T-cell counts of approximately +50 cells/μL were observed for both of the active treatment arms versus virtually no change from baseline for the placebo arm (+1 cell/μL).

All single-dose and multiple-dose administrations of Trogarzo® were generally well tolerated with no serious adverse events (SAEs) related to study drug, no dose-limiting toxicities related to study drug, and no evidence of adverse effects on the $CD4^+$ T-cells of treated subjects. When compared with placebo (Phase 2a) the incidences, spectrum, and intensity of adverse events (AEs) were similar between the active treatment arms and the placebo arm. Although no statistically significant difference in incidence was observed between either of the active treatment arms and the placebo arm, rash (mostly mild to moderate severity) did occur more often in active treatment arms than in the placebo arm. This observation appears to be consistent with the known association of rash with administration of humanized MAb medications.[6] The administration of Trogarzo® was not associated with immunosuppression, as evidenced by the lack of any increase in infections or malignancies in the study population treated with Trogarzo®. Intradermal skin tests performed on a subset of subjects were also similar between active treatment arms and placebo. Anti-Trogarzo® antibodies have been detected transiently and at low titers in a small number of subjects (2.4%). The observation of anti-Trogarzo® antibody activity was not associated with any AEs and appeared to have no impact on antiviral efficacy. The significance of anti-Trogarzo® antibodies is not known.

A Phase 2b clinical trial (Study TMB-202) in 113 HIV-infected subjects was also completed. Heavily treatment-experienced (HTE) subjects enrolled in this study received IV doses of 800 mg of Trogarzo® q2wk or 2000 mg every 4 weeks (q4wk) in combination with an OBR. The key primary efficacy endpoint was the proportion of subjects with HIV-1 ribonucleic acid (RNA) levels below the assay limit (<50 copies/mL) at Week 24. The percent of subjects with <50 copies/mL at Week 24 were 44% and 28% for the 800 mg q2wk arm and the 2000 mg q4wk arm respectively in the most stringent intent-to-treat (ITT) missing equals failure (MEF) analysis. Other noteworthy efficacy endpoints included mean change from Baseline in HIV-1 ribonucleic acid (RNA) at Week 24 and mean change in $CD4^+$ T-cell counts. The mean change from Baseline at Week 24 was -1.6 $\log_{10}$ for the 800 mg q2wk arm and -1.5 $\log_{10}$ for the 2000 mg q4wk arm. The mean change from Baseline in $CD4^+$ T-cells at Week 24 was + 37 cells/µL for the 800 mg q2wk group and +40 cells/µL for the 2000 mg q4wk group. These results are consistent with quantitative measures of immune system recovery in a treatment-experienced population over 24 weeks in studies of other drugs. There was no statistically significant difference between the 800 mg q2wk and 2000 mg q4wk arms in viral load outcomes at 24 weeks.

Similar to previous studies, Trogarzo® in combination with OBR was well tolerated in the Phase 2b investigation. The incidences, spectrum, and intensity of AEs were similar across the two treatment

arms. A total of 15 SAEs were reported in 14 randomized subjects, and all SAEs were assessed as not related to study drug. The most frequent non-laboratory AEs were rash (13%), diarrhea (12%), and headache (9%); most did not result in discontinuation. Other clinical treatment-emergent adverse events (TEAEs) that were reported in ≥5% of subjects were nausea, nasopharyngitis, upper respiratory tract infection, cough, oral candidiasis, vomiting, and fatigue. Only rash and headache were considered treatment-related TEAEs in ≥5% of subjects on study. One treatment-related TEAE (moderate rash) resulted in study discontinuation. Based on the overall study results, the 800 mg q2wk dose and the 2000 mg q4wk dose demonstrated safety and efficacy in this treatment-experienced HIV positive subject population.

Study TMB-301 was a Phase 3, single-arm, 24-week, multicenter study of Trogarzo® plus an OBR in treatment-experienced subjects infected with multi-drug resistant HIV-1. The primary objective was to demonstrate the antiviral activity of Trogarzo® at Day 14 and at Week 25 (end of study [EOS]). The secondary objectives were to assess the safety and tolerability of Trogarzo® through Week 25 (EOS), assess the mean change from Day 7 (Baseline) in CD4+ cell count at Week 25 (EOS), HIV-1 sensitivity/susceptibility changes associated with protocol-defined virologic failure (VF) after Trogarzo® administration in combination with OBR, determine the presence and significance of anti-Trogarzo® antibodies, if any (immunogenicity of Trogarzo®), assess the CD4 receptor density and occupancy, and determine the impact of Trogarzo® on quality of life (QoL) as assessed by subject-reported outcomes .

A total of 63 HTE HIV-positive subjects were screened and 40 were enrolled into the study and received at least one dose of study drug. At Day 14, using the ITT–MEF analysis, 33 subjects (82.5%) achieved a protocol-defined virologic endpoint (virologic response), with 1 subject (2.5%) achieving a complete virologic response (viral load <50 HIV-1 RNA copies/mL). At Week 25 (EOS), viral load <50 HIV-1 RNA copies/mL (complete virologic response) was reached in 43% of subjects. Virologic failure was reported in 17.5% of subjects at EOS. Overall, 32 subjects (80%) received all scheduled doses of study drug, and 31 subjects (77.5%) completed all scheduled visits in the study. Of the 9 subjects not completing the study (did not complete all scheduled study visits), 4 subjects were discontinued because of death (Kaposi's sarcoma, lymphoma, hepatic failure, and asthenia) and 1 additional subject was discontinued because of an SAE (progressive multifocal leukoencephalopathy [PML]). None of the deaths was considered to be related to Trogarzo®. All other reasons for discontinuation were reported in a single subject each (physician's decision, withdrawal by subject, subject noncompliance, and lost to follow-up). One of the subjects who died

completed the study treatment but did not complete the study (thus 8 subjects discontinued study treatment).

Examination of all resistance test results for subjects enrolled in the study revealed extensive ARV resistance and medical history findings were consistent with a population of HTE HIV-positive subjects.

In this study of Trogarzo® with OBR in treatment-experienced subjects infected with multi-drug resistant HIV-1, 80% of subjects reported at least 1 TEAE and 17.5% of subjects reported at least 1 treatment-related TEAE. Severe TEAEs (Grade 3 or 4) were reported in 27.5% of subjects and Class C TEAEs were reported in 10% of subjects. The most common TEAE was diarrhea (reported by 20% of the subjects) and was considered related to Trogarzo® in approximately 7.5% of subjects.

On the basis of results from Study TMB-301, and also Study TMB-202, Trogarzo® was approved by the U.S. Food and Drug Administration (FDA) for treatment of multi-class resistant HIV. Trogarzo® is the first approved agent in a new class of HIV entry inhibitors, known as CD4-directed post-attachment HIV-1 inhibitors.

Study TMB-121 was a study conducted in Taiwan with Trogarzo® administered via SC or IM injection. The study was a Phase 1/2, randomized, placebo-controlled, safety, tolerability, PK, and pharmacodynamic (PD) study of SC and IM Trogarzo® administered to HIV-1-infected and healthy HIV-negative volunteers at-risk of acquiring HIV-1 infection.

The study investigated two cohorts – HIV-1-infected volunteers (Cohort 1), and healthy HIV-negative volunteers at-risk of acquiring HIV-1 infection (Cohort 2). Cohort 1 consisted of HIV-1 seropositive subjects who had not received ART for 1 year prior to entry, with HIV-1 RNA ≥5000 copies/mL Cohort 1, consisting of 35 volunteers, enrolled into six study dosage arms. Eight volunteers were enrolled into Arm 1A (600 mg q4wk SC, total of 2 administrations), 7 volunteers into Arm 1B (450 mg followed by 180 mg once a week [qwk] SC, total of 4 administrations), 6 volunteers into Arm 1C (1200 mg q4wk IM, total of 2 administrations). Analysis of data from Cohort 1C were used to make the decision to not enroll Arm 1D. Eight volunteers were enrolled into Arm 1E (800 mg q2wk IM, total of 3 administrations). After the completion of Arm E enrollment, 6 volunteers were enrolled into Arm 1F (2000 mg q4wk IM, total of 2 administrations).

Cohort 2 enrolled six HIV-negative at-risk volunteers into Arm A. Participants in Arm 2A (900 mg IM weekly for 2 administrations followed by q4wk, total of 4 administrations). Cohort 2 subjects were also evaluated on the basis of their ability to mount an immune response against novel antigen challenge with Hepatitis A vaccine, and novel/recall antigen challenge with tetanus toxoid.

Volunteers in Arms 1C, and 1F were followed through Day 70 of the study; Volunteers in Arm 1E were followed through Day 56.

Of the 41 subjects completing the study, 18 subjects (43.9%) experienced TEAEs, including 2 of 2 subjects (100.0%) in the placebo group and 16 of 39 subjects (41.0%) in the Trogarzo® group.

Although most reported events were considered not related to study drug, 6 of 39 subjects (15.4%) experienced treatment-related AEs. The most frequently reported treatment-related AEs were in the System Organ Class (SOC) of skin and subcutaneous tissue disorders (reported in 4 of 39 subjects, 10.3%) including 1 subject in Arm 1C . The second most frequently reported treatment-related AEs were in the SOC of in general disorders and administration site conditions (reported in 2 of 39 subjects, 5.1%) and occurred in Arm 1C. There were no treatment-related AEs reported in Cohort 2 Arm A. All of the AEs were mild to moderate in severity.

No subjects had any changes from baseline laboratory values that raised any clinical concerns. Likewise, there were no physical examination findings or vital signs that raised any clinical concerns.

No injection-site reactions or evidence of reactogenicity were reported in Arms 1E, 1F, and 2A. All (100.0%) subjects in Arm 1B (7 of 7 subjects) reported an injection-site reaction at one or more injection sites on Day 0, and 3 of 6 subjects (50%) in Arm 1C reported injection-site reactions on Day 0. Injection-site reactions were still observed in subsequent visits, but the incidences were equal or lower when compared with Day 0. There were neither SAEs nor discontinuations due to AEs reported during the study.

Anti-Trogarzo® antibodies were detected in 1 subject (1 of 41 subjects, 2.4%). The nonresponse to the Hepatitis A vaccine in a qualitative assay reported in half (3 of 6, 50.0%) of HIV-negative subjects at Week 7 was temporary and was restored in all subjects at Week 27 and Week 31. No

negative effect on mounting tetanus antibody response was seen in HIV-negative subjects receiving Trogarzo®.

In conclusion, Trogarzo® delivered by IM injection to HIV-negative at-risk volunteers at doses of 900 mg (Days 0, 7, 35, and 63) was safe and well tolerated. Trogarzo® delivered by IM injection to HIV-1 infected subjects (Arms 1C, 1E, and 1F) was safe and well tolerated.

Taken together, the reported results of completed clinical studies suggest that Trogarzo® is safe and has potent activity against HIV in humans when administered by IV infusion, SC injection, and IM injection.

1.3 Pharmacokinetic and Pharmacodynamic Profile

Intravenous administration of escalating single doses of Trogarzo® (Study Hu5A8.01) demonstrated that serum concentrations of Trogarzo® generally peaked at the end of the infusion period. Trogarzo® pharmacokinetics were dose-dependent, as both systemic exposure and elimination half-life increased disproportionately with increasing dose. This indicated that the elimination of Trogarzo® is capacity limited and saturable at higher doses. A similar conclusion was reached after a multiple-dose study of IV Trogarzo® (Study TNX-355.02), which demonstrated that the steady-state half-life following multiple doses of 10 and 25 mg/kg was 75 and 79 hours, respectively. The capacity-limited elimination is likely due to CD4 receptor turnover, given the short half-life for Trogarzo® relative to endogenous immunoglobulin 4 (IgG4) molecules. In the IV Trogarzo® studies conducted to date, there was a correlation between Trogarzo® trough serum concentrations of 0.3 μg/mL or higher and saturated binding of CD4 (receptor occupancy) on $CD4^+$ T-cells, and between CD4 receptor occupancy and reductions in HIV viral load.

The Phase 2b trial (Study TMB-202) investigated the correlation between Trogarzo® serum concentration, using an assay with 100 ng/mL sensitivity, and CD4 receptor occupancy. Paired measurements for individual subject samples were evaluated. Data were available for pre-dose samples collected at Baseline through Week 24, along with Baseline post-dose samples. The data evaluated were confined to those samples for which both serum Trogarzo® and receptor occupancy measurements were reported. Pharmacokinetic data were censored (as described in the clinical study report [CSR] Appendix 16.5) and receptor occupancy data were censored accordingly (mainly to eliminate outliers resulting from improper sample collection and/or labeling).

Eighty-four percent of pre-dose samples collected at Baseline had Trogarzo® levels below the limit of detection (<100 ng/mL). The remaining samples (16%) had detectable levels of serum Trogarzo®, generally in the range of 100 to 200 ng/mL, despite no prior treatment with Trogarzo®. As expected for pre-dose samples, all were reported to have had low receptor occupancy (<32%), as indicated previously. Although low but detectable levels of Trogarzo® may result from faulty sample collection or sample handling, it may also be due to interference with measurements of low serum Trogarzo® concentrations for specific subjects. This could confound attempts to correlate PD parameters with serum Trogarzo® concentrations in the range of 100 to 200 ng/mL, at least for certain subjects.

Serum Trogarzo® concentrations ranged from <100 to >100,000 ng/mL, collectively, for Baseline samples (pre-dose and post-dose) and pre-dose samples from Weeks 2 through 24. Comparison with receptor occupancy measurements indicated a direct relationship between serum Trogarzo® levels and CD4 receptor occupancy. A greater proportion of samples having intermediate or high receptor occupancy was evident with serum Trogarzo® concentrations ≥150 ng/mL. At serum Trogarzo® concentrations >300 ng/mL, over 90% of all samples were reported to have high receptor occupancy (median = 100% receptor occupancy).

In the Phase 3 study (Study TMB-301), 40 HIV-positive subjects received a 2000 mg Trogarzo® loading dose followed by 800 mg q2wk by IVI. The assay sensitivity for serum Trogarzo® concentration was 10 ng/mL. The maximum serum concentrations were observed immediately after the end of the 2000 mg Trogarzo® infusion. Steady state was reached at Week 4 after the first dose. The mean Trogarzo® concentrations were >30 μg/mL and the CD4 receptor occupancy was >85% throughout the dosing period, suggesting that the regimen was sufficient to maintain the drug concentration above the therapeutic level. The loading dose effect was substantial. With the loading dose, the percentage of subjects below effective concentration and receptor occupancy decreased from ~50% to ~20% at Week 2 after the first dose by comparison between the TMB-202 and TMB-301 studies. At Week 24 after the first dose, Trogarzo® serum concentration and receptor occupancy were comparable between these two regimens.

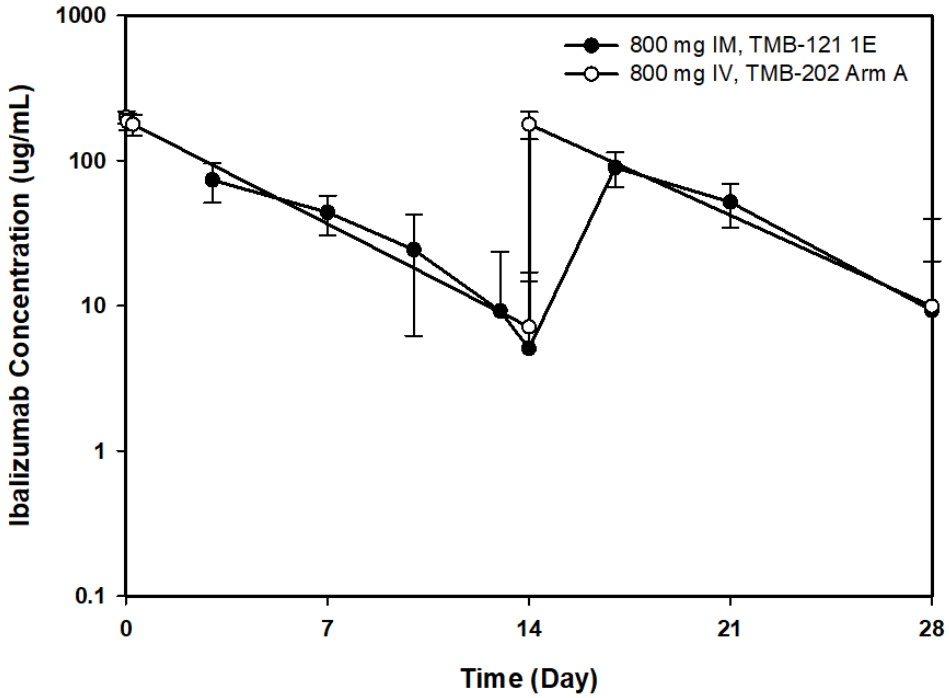
Both Day 7 concentration (peak concentration, C_{peak}) and Week25 trough concentration (C_{trough}) were decreased with increased body weight. The median C_{trough} in the high body weight group

(>85 kg) was 0.23 µg/mL, which was close to the concentration necessary to support 85% receptor occupancy.

The elevations in CD4 receptor occupancy were generally associated with increased Trogarzo® serum concentrations. Trogarzo® serum concentrations greater than 0.13 µg/mL supported 85% CD4 receptor occupancy. Following Trogarzo® administration, transient down-modulation of surface CD4 receptors by up to 20% was observed. The maximum HIV viral load reduction was -2.35 $\log_{10}$ occurring at Week 8 after the first dose and were maintained throughout the dosing period. There were no apparent associations between Trogarzo® serum concentrations and receptor density and viral load reduction, respectively.

Trogarzo® serum concentrations following IM administrations were determined in Study TMB-121. Subjects in Arm 1E received 800 mg IM q2wk for three doses. The mean Trogarzo® serum concentration in these subjects reached a maximum after 2 to 3 days (time to maximum concentration [T_{max}] = 2.13) and declined to 5.1 µg/mL at Day 14. The mean trough concentrations at 14 days post-dose (Days 14, 28, and 42) were all greater than the effective concentration (0.3 µg/mL), and 63% of subjects' trough concentrations were greater than 0.3 µg/mL. These preliminary results indicate that 800 mg was sufficient for a q2wk dosing schedule for the majority of subjects. As shown in Figure 1, the mean ibalizumab concentrations after 800 mg IM ibalizumab injections were comparable with IV ibalizumab injections (TMB-202 results).

Figure 1 Mean (± SD) Ibalizumab Serum Concentrations after 800 mg IM and IV Administration



In addition, a population PK model was developed using the PK data from six clinical studies conducted in HIV-infected patients (Studies Hu5A8.01, TNX355.02, TNX355.03, TMB-202, TMB-301, and TMB-121). One-hundred subjects with body weight ranging from 50-140 kg were simulated to receive a 2000 mg loading dose via IVI followed by 800 mg IM q2wk dosing. Trogarzo® serum concentrations remained above the effective concentration (0.3 µg/mL) throughout the dosing period, consistent with clinical data.

2. Study Objectives

2.1 Primary Objectives

The primary objectives of this study are to:

- Evaluate the safety of Trogarzo® administered as an undiluted "IV push" over 30 seconds and by IM injection in clinically-stable HIV-1 infected subjects with at least 3 months of

stable treatment with a Trogarzo®-containing ARV regimen or in healthy HIV-uninfected volunteers

- Compare the area under the curve (AUC) and trough serum drug concentration after IVI with the diluted drug to the AUC and trough serum concentration after IV push of undiluted Trogarzo®

- Compare the trough serum drug concentration after IVI with the diluted drug to the trough serum concentration after IM injection of undiluted Trogarzo®

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Assess HIV-1 viral load for IVI compared to IV Push and to IM injection in HIV-1 infected subjects only

- Characterize noted HIV-1 sensitivity/susceptibility changes in participants with an increase in plasma viral load to levels above 1,000 copies/mL on 2 consecutive measurements at least 2 weeks apart in HIV-1 infected subjects only

- Determine the presence and significance of anti-Trogarzo® antibodies, if any (immunogenicity of Trogarzo®)

- Compare the AUC after IVI with the diluted drug to the AUC after IM injection of undiluted Trogarzo®

3. Study Plan

3.1 Overall Design

The goal of this Phase 3 study is to evaluate the safety of administering Trogarzo® 800 mg q2wk as an undiluted IV push over 30 seconds or as IM injection in clinically stable HIV-1 infected subjects currently receiving treatment with a stable Trogarzo®-containing regimen and in HIV-uninfected healthy volunteers who receive Trogarzo® as either an IV push or as an IM injection after achieving a steady-state level of Trogarzo® after a 2000 mg loading dose followed by 3 IVI of 800 mg Trogarzo® q2wk. A stable regimen is defined as having no changes in dose or frequency and no interruptions ≥2 weeks during the 3-month period preceding Screening. For subjects who receive Trogarzo® as an IV push (Core Group) and then continue in the study and receive Trogarzo® as an

IM injection (IM Group), the time period while receiving the IV push will be considered as having received a stable Trogarzo®-containing ARV regimen.

Note: HIV-infected subjects who are enrolled in the IM injection study and are unable to adhere to the study schedule for IM dosing due to factors outside the study will be discontinued. Re-enrollment of HIV-infected IM Group subjects will be allowed after a Discontinuation Visit and rescreening visit are completed provided that inclusion/exclusion criteria continue to be satisfied and dosing after discontinuation is resumed according to the Trogarzo® Prescribing Information. For re-enrolling subjects, the inclusion criteria for stable a Trogarzo®-containing ARV regimen is satisfied with a loading dose of 2000mg IVI and at least one maintenance dose of 800mg IVI given according to Trogarzo® labeling prior to Day 1 enrollment.

The first five (5) subjects enrolled will comprise the Sentinel Group. Subjects six (6) through twenty (20) (the Core Group) will not be screened until the Sentinel Group has completed Day 99 (14 weeks) of the study and the Data Monitoring Committee (DMC) has reviewed the data accumulated and given approval for enrollment of the Core Group to proceed.

An additional group of approximately 20 subjects (the IM Group), which will include subjects receiving Trogarzo® as an IM injection, will also be evaluated. Subjects who have previously received Trogarzo® as an IV push are permitted to screen/enroll for participation in the IM Group. Subjects for inclusion in the IM Group who were part of Sentinel or Core Groups will enter the IM Group only once they have completed the Sentinel or Core study. New subjects enrolled in the IM Group who were not part of the Sentinel or Core Groups will be recruited only once all Core Group subjects have been enrolled and completed the Core study. These subjects may be HIV-infected or -uninfected.

Sentinel Group

Subjects in the Sentinel Group will receive an 800 mg maintenance dose of Trogarzo® in accordance with the prescribing information (diluted in normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. Every 2 weeks thereafter through Day 85 (12 weeks), subsequent maintenance doses will be administered at increasing concentrations and over decreasing intervals according to the following schedule:

- Day 1/Baseline: 800 mg diluted in 250 mL normal saline (at 3.2 mg/mL) via IVI over 15 minutes per approved Trogarzo® prescribing information

- Day 15: 800 mg diluted in 250 mL normal saline (at 3.2 mg/mL) via IVI over 15 minutes per approved Trogarzo® prescribing information
- Day 29 (4 weeks): 800 mg diluted in 50 mL normal saline (at 16 mg/mL) via IVI over 10 minutes
- Day 43 (6 weeks): 800 mg diluted in 16 mL normal saline (at 50 mg/mL) via IV bolus over 5 minutes
- Day 57 (8 weeks): 800 mg diluted in 8 mL normal saline (at 100 mg/mL) via IV bolus over 1 minute
- Day 71 (10 weeks): 800 mg undiluted (at 150 mg/mL) via IV push over 30 seconds
- Day 85 (12 weeks): 800 mg undiluted (at 150 mg/mL) via IV push over 30 seconds

For the EOS visit at Day 99 (14 weeks), Sentinel Group subjects will revert to diluted IVI dosing over 15 minutes in accordance with the Trogarzo® prescribing information. When five (5) subjects in the Sentinel Group have completed Day 99 (14 weeks) of the study, the DMC will review the available data to determine whether the enrollment of the Core Group should proceed.

Core Group

HIV-infected individuals: After DMC review and approval, the Core Group (subject numbers six [6] through twenty [20]) will be enrolled. Subjects in the Core Group will also receive an 800 mg maintenance dose of Trogarzo® in accordance with the prescribing information (diluted in normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. Every 2 weeks thereafter through Day 71 (10 weeks), maintenance doses will be administered via undiluted IV push over 30 seconds. At Day 85 (12 weeks), Core Group subjects will revert to diluted IVI dosing over 15 minutes in accordance with the Trogarzo® prescribing information.

HIV-uninfected individuals:

Pre–Steady-State Phase: Subjects will receive a 2000 mg infusion of Trogarzo® over 60 minutes on Day -55 followed by 3 doses of 800 mg infusion over 15 minutes on Days -41, -27, and -13. On Day 1 the subjects will enter the Study Treatment Phase.

Study Treatment Phase: These HIV-uninfected subjects will receive an 800 mg dose of Trogarzo® in accordance with the prescribing information (diluted in 250 mL normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. Every 2 weeks thereafter through Day 71 (10 weeks), subsequent doses will be administered via undiluted IV push over 30 seconds. After the Day 71 IV push dose, HIV-uninfected Core Group subjects discontinue Trogarzo® therapy.

Pharmacokinetic samples will be collected in the study to evaluate serum concentrations and the PK profile of Trogarzo®. In particular, data will be collected to compare serum drug concentrations (AUC and trough) after IVI of the 800 mg diluted drug over 15 minutes to IV push of the undiluted drug over 30 seconds. Pre-dose samples will be collected at selected timepoints, along with samples at 1, 24, and 72 hours post-dose, and 7 and 14 days post-dose for the first two doses of study drug (via IVI) for HIV-infected participants and after steady state is achieved in HIV-uninfected healthy volunteers, and for all 30-second IV push doses for all subjects in the Sentinel and Core Groups (see Table 1, Table 2, and Table 3 for sample collection timepoints). Samples collected at the 24- and 72-hour post-dose timepoints, and those collected at the 7-day post-dose timepoints when a study visit is not otherwise already scheduled will require additional visits for PK sample collection only.

IM Group

The IM Group will enroll either subjects who were enrolled and completed the study from the Sentinel and Core groups or other subjects new to the study who were not previously involved in the IV push portions. Subjects for inclusion in the IM Group will be recruited only once all subjects for the Core Group have been enrolled in and completed the Core study.

HIV-infected individuals: Subjects will receive the first two doses of study drug in accordance with the Trogarzo® prescribing information (diluted in normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. The next four doses of Trogarzo® through Day 71 (10 weeks) will be administered as an IM injection. At Day 85 (12 weeks), IM Group subjects will revert to diluted IVI dosing over 15 minutes in accordance with the Trogarzo® prescribing information. For re-enrolling subjects, a loading dose of 2000mg IVI and at least one maintenance dose of 800mg IVI will be given according to the label to re-establish study eligibility from a Trogarzo® dosing perspective starting at least 4 weeks prior to Day 1. The day of the 2000mg loading dose may also serve as the Discontinuation or Screening Visit, as appropriate for subject and study site scheduling needs for re-enrolling subjects.

HIV-uninfected individuals:

Pre–Steady-State Phase: Subjects will receive four doses of Trogarzo® as described above for Core Group **HIV-uninfected individuals** prior to the Study Treatment Phase.

Study Treatment Phase: HIV-uninfected subjects in the IM Group will receive the first two doses of study drug in accordance with the Trogarzo® prescribing information (diluted in normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. The next four

doses of Trogarzo® will be administered as an IM injection. HIV-uninfected subjects will discontinue dosing after the Day 71 study drug administration.

A total volume of 5.32 mL, corresponding to 800 mg Trogarzo®, will be injected intramuscularly and will be split into two injections of approximately 2.66 mL each. The two IM injections should be administered in the muscle tissue of the subject's anterolateral aspect of the thighs (left, right, or both) or alternatively in the dorsogluteal site (upper outer quadrant of the buttock). In either area, injections sites should be at least 1 inch apart.

For the PK profile of Trogarzo® following IM administrations, pre-dose samples will be collected at selected timepoints, along with samples at 2, 7, 10, and 14 days post-dose for the last two doses of study drug (via IVI), and for the last two IM injection doses for all subjects (see Table 4 for sample collection timepoints). Samples collected at the 2-, 7-, 10- and 14-day post-dose timepoints when a study visit is not otherwise already scheduled will require additional visits for PK sample collection and injection site assessment only.

All Groups

After each study drug administration, all HIV-infected study subjects in both groups will be observed for at least 15 minutes, and HIV-uninfected subjects will be observed for at least 60 minutes. All AEs will be recorded. Vital signs will be measured and recorded at the beginning and end of this observation period.

Clinical site personnel and emergency medications and equipment will be available to manage any infusion or injection reactions as medically indicated. Hypersensitivity reactions including infusion-related reactions and anaphylactic reactions have been reported following infusion of Trogarzo® during post-approval use. Subjects should be monitored closely for such symptoms during observation (see Appendix C for information on management of anaphylactic symptoms).

Injection site reactions will be assessed in subjects who receive IM injections of Trogarzo® at each visit during IM administration and follow-up.

Subjects will be monitored through 28 days after the last administration of Trogarzo® on study: from Day 85 (12 weeks) through Day 113 (16 weeks) for the Sentinel Group and for HIV-infected subjects in the Core and IM Groups and from Day 71 (10 weeks) through Day 99 (14 weeks) for the HIV-uninfected Core and IM Group participants. Refer to Section 4.3 for the study Safety Monitoring and Toxicity Management Plan, and to Section 4.4 for the Study Stopping Rules.

3.2 Discussion of Trial Design

This study is designed to assess the safety and PK profile (serum AUC and C_{trough}) and of 800 mg Trogarzo® q2wk administered via IV push (undiluted drug administered over 30 seconds) or as IM injection compared with the approved Trogarzo® administration (diluted in 250 mL normal saline administered intravenously over 15 minutes). The study will also assess the maintenance of established virologic control, characterize changes in the viral susceptibility/resistance in HIV-infected subjects, and the development of anti-drug antibodies in all subjects as secondary endpoints. If deemed comparable to administration by IVI, administration by IV push or as IM injection would be desirable to improve the logistics of administration by eliminating the need for saline bags and infusion apparatus as well as improving convenience for subjects and physicians.

3.3 Dose Selection

The efficacy and safety of Trogarzo® in Study TMB-301, a Phase 3 trial, where a single 2000 mg loading dose was followed by 800 mg q2wk maintenance, was the basis for the U.S. approval of the commercial drug, Trogarzo®, for the treatment of HIV-1 infected subjects with multi-class resistance in combination with an optimized background ARV regimen. The approved regimen administers diluted drug over 15-minute infusions. The current study uses the same doses. This study assesses the administration of the undiluted 800 mg maintenance drug dose IV over 30 seconds or as IM injection.

3.4 Schedule of Events

Table 1 provides the Schedule of Events for the Sentinel Group in this study, from Screening through the follow-up visit at Day 113 (16 weeks). Table 2 provides the Schedule of Events for HIV-uninfected individuals (Core and IM Groups) from the Screening visit through the end of the Pre-Steady State Phase. Table 3 provides the Schedule of Events for the HIV-infected Core Group subjects from Screening through the follow-up visit at Day 99 (14 weeks) and for the HIV-uninfected subjects from Day 1 through Day 99 (EOS). Table 4 provides the Schedule of Events for the HIV-infected IM Group from Screening through the follow-up visit at Day 113 (16 weeks) and for the HIV-uninfected IM Group subjects from Day 1 through the follow-up visit at Day 99. Throughout the study, subjects are *not* required to fast before collection of blood

samples. However, subjects should adhere to dietary recommendations as suggested for the components of their antiretroviral treatment or other concomitant medications.

Table 1 Schedule of Events – Sentinel Group (Subjects 1-5)

	Study Visit														
	Screening	Day 1 Baseline	Day 2	Day 4	Day 8 (1 wk)	Day 15 (2 wks)	Day 16	Day 18	Day 22 (3 wks)	Day 29 (4 wks)	Day 36 (5 wks)	Day 43 (6 wks)	Day 50 (7 wks)	Day 57 (8 wks)	Day 64 (9 wks)
Visit window (days)	(-28 days)	N/A	±3 hr	±3 hr	±1	±1	±3 hr	±3 hr	±1	±1	±1	±1	±1	±1	±1
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION															
Review and discuss the Inclusion/Exclusion criteria	X														
Obtain a signed Informed Consent Form	X														
Record demographics, medical history (general and HIV); height	X														
Record agents in ART history at Screening, changes in ART on-study [1]	X	X				X				X		X		X	
Record results of a complete physical examination	X														
Record results of a targeted physical examination [2]		X				X				X	X	X	X	X	X
Record vital sign measurements	X	X				X				X	X	X	X	X	X
Record the subject's weight	X														
Record AEs [3]	X	X				X				X	X	X	X	X	X
Record concomitant medications	X	X				X				X	X	X	X	X	X
BLOOD and/or URINE [4] SAMPLES TO BE COLLECTED															
Hematology and serum chemistry (see Section 7.2.1 for list)	X	X				X				X		X		X	
Urinalysis	X	X				X				X		X		X	
HIV-1 RNA (viral load)	X	X				X				X		X		X	
$CD4^+$ cell count	X	X								X					

	Study Visit														
	Screening	**Day 1 Baseline**	**Day 2**	**Day 4**	**Day 8 (1 wk)**	**Day 15 (2 wks)**	**Day 16**	**Day 18**	**Day 22 (3 wks)**	**Day 29 (4 wks)**	**Day 36 (5 wks)**	**Day 43 (6 wks)**	**Day 50 (7 wks)**	**Day 57 (8 wks)**	**Day 64 (9 wks)**
Visit window (days)	(-28 days)	N/A	±3 hr	±3 hr	±1	±1	±3 hr	±3 hr	±1	±1	±1	±1	±1	±1	±1
Serum for pregnancy test for females of childbearing potential [5]	X														
Urine for pregnancy test for females of childbearing potential										X				X	
Antiretroviral resistance sample		X				X				X		X		X	
Archive serum sample		X				X				X		X		X	
Trogarzo® serum concentration (pre-dose if drug administered on this day) [6]		X	X	X	X	X	X	X	X	X		X		X	
Trogarzo® serum concentration post-dose – 1 hour (±10 min)		X				X									
Immunogenicity of Trogarzo® (2 tubes x 3 mL each)		X													
STUDY DRUG ADMINISTRATION AND AFTER															
Administer study drug via IVI – study drug diluted in 250mL normal saline and administered IV over 15 minutes per Trogarzo® prescribing information		X				X									
Administer study drug – reducing administration time and increasing study drug concentration in step-wise fashion at each visit per schedule [7]										X		X		X	

	Study Visit														
	Screening	**Day 1 Baseline**	**Day 2**	**Day 4**	**Day 8 (1 wk)**	**Day 15 (2 wks)**	**Day 16**	**Day 18**	**Day 22 (3 wks)**	**Day 29 (4 wks)**	**Day 36 (5 wks)**	**Day 43 (6 wks)**	**Day 50 (7 wks)**	**Day 57 (8 wks)**	**Day 64 (9 wks)**
Visit window (days)	(-28 days)	N/A	±3 hr	±3 hr	±1	±1	±3 hr	±3 hr	±1	±1	±1	±1	±1	±1	±1
Observe subject for 15 minutes post-administration; record vital sign measurements after completion of infusion and again at end of observation period[8]		X				X				X		X		X	

[1] All ART for the 3 months preceding Screening will be recorded at Screening visit; subsequent visits will only record changes to ART.

[2] Abbreviated physical examination includes examination of lymph nodes, respiratory and cardiovascular systems, abdomen, extremities, and nervous system.

[3] Only record AEs that are related to study procedures before administration of the first dose.

[4] Subjects do not need to fast before blood sampling.

[5] Serum FSH test to be conducted on postmenopausal females at Screening only.

[6] Pre-dose samples to be collected within 1 hour before the start of the infusion; 24 hr, 72, hr, and 7 Day post dose samples to be collected within 3 hours of the time the infusion ended.

[7] At Baseline and at Day 15 all subjects in the Sentinel Group (the first 5 subjects enrolled) will receive study drug diluted into 250 mL normal saline as a standard 800 mg IV infusion over 15 minutes, per Trogarzo® prescribing information. At Day 29, Sentinel Group subjects will begin receiving Trogarzo® 800 mg at increasing concentrations over decreasing intervals as follows: Day 29 (4 weeks) – 16 mg/mL delivered over 10 minutes (800 mg study drug diluted into 50 mL normal saline); Day 43 (6 weeks) – 50 mg/mL delivered over 5 minutes (800 mg study drug diluted into 16 mL normal saline); Day 57 (8 weeks) – 100 mg/mL delivered over 1 minute (800 mg study drug diluted into 8 mL normal saline). All subjects must be observed for 15 minutes after the completion of each study drug administration. Vital signs should be monitored and recorded at the beginning and end of the observation period.

[8] Any abnormalities observed need to be recorded on the AE CRF.

Schedule of Events – Sentinel Group (Subjects 1-5) (CONTINUED)

	Study Visit									
	Day 71 (10 wks)	Day 72	Day 74	Day 78 (11 wks)	Day 85 (12 wks)	Day 86	Day 88	Day 92 (13 wks)	Day 99/EOS (14 wks)	Day 113 Follow-Up (16 wks)
Visit window (days)	±1	±3 hr	±3 hr	±1	±1	±3 hr	±3 hr	±3 hr	±1	±1
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION										
Record agents in ART history at Screening, changes in ART on-study [1]	X				X				X	
Record results of a complete physical examination										
Record results of a targeted physical examination [2]	X			X	X			X	X	
Record vital sign measurements	X			X	X			X	X	
Record the subject's weight									X	
Record Aes [3]	X			X	X			X	X	X
Record concomitant medications	X			X	X			X	X	X
BLOOD and/or URINE [4] SAMPLES TO BE COLLECTED										
Hematology and serum chemistry (see Section 7.2.1 for list)	X				X				X	
Urinalysis	X				X				X	
HIV-1 RNA (viral load)	X				X				X	
$CD4^+$ cell count									X	
Serum for pregnancy test for females of childbearing potential [5]									X	
Urine for pregnancy test for females of childbearing potential					X					
Antiretroviral resistance sample	X				X				X	

	Study Visit									
	Day 71 (10 wks)	**Day 72**	**Day 74**	**Day 78 (11 wks)**	**Day 85 (12 wks)**	**Day 86**	**Day 88**	**Day 92 (13 wks)**	**Day 99/EOS (14 wks)**	**Day 113 Follow-Up (16 wks)**
Visit window (days)	±1	±3 hr	±3 hr	±1	±1	±3 hr	±3 hr	±3 hr	±1	±1
Archive serum sample	X				X				X	
Trogarzo® serum concentration (pre-dose if drug administered on this day) [6]	X	X	X	X	X	X	X	X	X	
Trogarzo® serum concentration post-dose – 1 hour (±10 min)	X				X					
Immunogenicity of Trogarzo® (2 tubes x 3 mL each)									X	
STUDY DRUG ADMINISTRATION AND AFTER										
Administer study drug via IVI – study drug diluted in 250mL normal saline and administered IV over 15 minutes per Trogarzo® prescribing information									X	
Administer study drug – reducing administration time and increasing study drug concentration in step-wise fashion at each visit per schedule [7]	X				X					
Observe subject for 15 minutes post-administration; record vital sign measurements after completion of infusion and again at end of observation period[8]	X				X				X	

[1] All ART for the 3 months preceding Screening will be recorded at Screening visit; subsequent visits will only record changes to ART.

[2] Abbreviated physical examination includes examination of lymph nodes, respiratory and cardiovascular systems, abdomen, extremities, and nervous system.

[3] Only record Aes that are related to study procedures before administration of the first dose; after administration of first dose.

[4] Subjects do not need to fast before blood sampling.

[5] Serum FSH test to be conducted on postmenopausal females at Screening only.

[6] Pre-dose samples to be collected within 1 hour before the start of the infusion; 24 hr, 72, hr, and 7 Day post dose samples to be collected within 3 hours of the time the infusion ended.

[7] At Day 71, Sentinel Group subjects receive Trogarzo® 800 mg at increased concentration over intervals reduced from the 15 minutes required for IV infusion as follows: Day 71 (10 weeks) – 150 mg/mL delivered over 30 seconds (800 mg study drug administered undiluted); Day 85 (12 weeks) – 150 mg/mL delivered over 30 seconds (800 mg study drug administered undiluted). At Day 99/EOS (14 weeks) subjects in the Sentinel Group will revert to receiving 800 mg Trogarzo® diluted into 250 mL normal saline as an IV infusion over 15 minutes, per Trogarzo® prescribing information. All subjects must be observed for 15 minutes after the completion of each study drug administration. Vital signs should be monitored and recorded at the beginning and end of the observation period.

[8] Any abnormalities observed need to be recorded on the AE CRF.

Table 2 Schedule of Events – HIV-uninfected Core and IM Groups Only (Subjects 6-40): Screening and Pre-Steady State Phase: Day -83 to Day -13

	Screening	Day – 55	Day -41	Day -27	Day -13
Visit window (days)	(-83 to -62 days)	N/A	±1	±1	±1
Review and discuss the Inclusion/Exclusion criteria	X	X			
Obtain a signed Informed Consent Form	X				
Record demographics, medical history (general and HIV); height	X				
Record results of a complete physical examination	X				
Record results of a targeted physical examination [2]		X	X	X	X
Record vital sign measurements	X	X	X	X	X
Record the subject's weight	X				
Record AEs [3]	X	X	X	X	X
Record concomitant medications	X	X	X	X	X
Hematology and serum chemistry (see Section 7.2.1 for list)	X	X	X	X	X
Urinalysis	X	X	X	X	X
$CD4^+$ cell count	X	X		X	
Hepatitis B surface antigen and hepatitis C antibody testing	X				
4th Generation POC HIV test[1]	X	X		X	
Serum for pregnancy test for females of childbearing potential [5]	X				
Urine for pregnancy test for females of childbearing potential		X	X	X	X
Archive serum sample		X	X	X	X
Trogarzo® serum concentration (pre-dose if drug administered on this day) [6]		X	X	X	X
Trogarzo® serum concentration post-dose – 1 hour (±10 min)		X			
Immunogenicity of Trogarzo® (2 tubes x 3 mL each)		X			
Administer 2000 mg study drug via IVI – study drug diluted in 250mL normal saline and administered IV over 60 minutes per Trogarzo® prescribing information[7]		X			
Administer 800 mg study drug via IVI – study drug diluted in 250mL normal saline and administered IV over 15 minutes per Trogarzo® prescribing information[7]			X	X	X
Observe subject for 60 minutes post-administration; record vital sign measurements after completion of infusion and again at end of observation period[8]		X	X	X	X

[1] 4th Generation Point of Care (POC) test should be done at the site and results recorded in the source document and CRF.

[2] Abbreviated physical examination includes examination of lymph nodes, respiratory and cardiovascular systems, abdomen, extremities, and nervous system.

[3] Only record Aes that are related to study procedures before administration of the first dose; after administration of first dose.

[4] Subjects need not fast before blood sampling.

[5] Serum FSH test to be conducted on postmenopausal females at Screening only.

[6] Pre-dose samples to be collected within 1 hour before the start of the infusion.

[7] HIV-1 uninfected Core Group will receive study drug diluted into 250 mL normal saline as a 2000 mg loading dose followed by three 800 mg IV infusions over 15 minutes, per Trogarzo® prescribing information.

[8] Any abnormalities observed need to be recorded on the AE CRF.

Table 3 Schedule of Events – HIV-infected Core Group (Subjects 6-20) and HIV-uninfected Core Group (Subjects 6-20; Days 1-99)

	Study Visit														
	Screening*	**Day 1 Baseline**	**Day 2**	**Day 4**	**Day 8 (1 wk)**	**Day 15 (2 wks)**	**Day 16**	**Day 18**	**Day 22 (3 wks)**	**Day 29 (4 wks)**	**Day 36 (5 wks)**	**Day 43 (6 wks)**	**Day 44**	**Day 46**	**Day 50 (7 wks)**
Visit window (days)	(-28 days)	N/A	±3 hr	±3 hr	±1	±1	±3 hr	±3 hr	±1	±1	±1	±1	±3 hr	±3 hr	±1
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION															
Review and discuss the Inclusion/Exclusion criteria	X														
Obtain a signed Informed Consent Form	X														
Record demographics, medical history (general and HIV); height	X														
Record agents in ART history at Screening, changes in ART on-study [1]	X	X				X				X		X			
Record results of a complete physical examination	X														
Record results of a targeted physical examination [2]		X				X				X	X	X			X
Record vital sign measurements	X	X				X				X	X	X			X
Record the subject's weight	X														
Record AEs [3]	X	X				X				X	X	X			X
Record concomitant medications	X	X				X				X	X	X			X
BLOOD and/or URINE [4] SAMPLES TO BE COLLECTED															
Hematology and serum chemistry (see Section 7.2.1 for list)	X	X				X				X		X			

	Study Visit														
	Screening*	**Day 1 Baseline**	**Day 2**	**Day 4**	**Day 8 (1 wk)**	**Day 15 (2 wks)**	**Day 16**	**Day 18**	**Day 22 (3 wks)**	**Day 29 (4 wks)**	**Day 36 (5 wks)**	**Day 43 (6 wks)**	**Day 44**	**Day 46**	**Day 50 (7 wks)**
Visit window (days)	(-28 days)	N/A	±3 hr	±3 hr	±1	±1	±3 hr	±3 hr	±1	±1	±1	±1	±3 hr	±3 hr	±1
Urinalysis	X	X				X				X		X			
HIV-1 RNA (viral load)[9]	X	X				X				X		X			
4th Generation POC HIV test[10]		X								X					
$CD4^+$ cell count	X	X								X					
Serum for pregnancy test for females of childbearing potential [5]	X														
Urine for pregnancy test for females of childbearing potential										X					
Antiretroviral resistance sample[9]		X				X				X		X			
Archive serum sample		X				X				X		X			
Trogarzo® serum concentration (pre-dose if drug administered on this day) [6]		X	X	X	X	X	X	X	X	X		X	X	X	X
Trogarzo® serum concentration post-dose – 1 hour (±10 min)		X				X						X			
Immunogenicity of Trogarzo® (2 tubes x 3 mL each)		X													
STUDY DRUG ADMINISTRATION AND AFTER															
Administer study drug via IVI – study drug diluted in 250mL normal saline and administered IV over 15 minutes per Trogarzo® prescribing information		X				X									

	Study Visit														
	Screening*	**Day 1 Baseline**	**Day 2**	**Day 4**	**Day 8 (1 wk)**	**Day 15 (2 wks)**	**Day 16**	**Day 18**	**Day 22 (3 wks)**	**Day 29 (4 wks)**	**Day 36 (5 wks)**	**Day 43 (6 wks)**	**Day 44**	**Day 46**	**Day 50 (7 wks)**
Visit window (days)	(-28 days)	N/A	±3 hr	±3 hr	±1	±1	±3 hr	±3 hr	±1	±1	±1	±1	±3 hr	±3 hr	±1
Administer study drug via IVP – undiluted Push over 30 seconds [7]										X		X			
Observe subject post-administration – 15 minutes if HIV-infected, 60 minutes if uninfected; record vital sign measurements after completion of infusion and again at end of observation period[8]		X				X				X		X			

*** Screening visit to be conducted for HIV-infected patients ONLY. See Table 2 for Screening and Pre-Steady State Phase Schedule of Events**

[1] All ART for the 3 months preceding Screening will be recorded at Screening visit; subsequent visits will only record changes to ART.
[2] Abbreviated physical examination includes examination of lymph nodes, respiratory and cardiovascular systems, abdomen, extremities, and nervous system.
[3] Only record AEs that are related to study procedures before administration of the first dose; after administration of first dose.
[4] Subjects need not fast before blood sampling.
[5] Serum FSH test to be conducted on postmenopausal females at Screening only.
[6] Pre-dose samples to be collected within 1 hour before the start of the infusion; 24 hr, 72, hr, and 7 Day post dose samples to be collected within 3 hours of the time the infusion ended.
[7] At Baseline and at Day 15, subjects in the Core Group will receive study drug diluted into 250 mL normal saline as an 800 mg IV infusion over 15 minutes, per Trogarzo® prescribing information. At Day 29 Core Group subjects will begin receiving study drug as 800 mg undiluted Trogarzo® administered by IV Push over 30 seconds once every 2 weeks.
[8] Any abnormalities observed need to be recorded on the AE CRF.
[9] HIV-infected Core subjects only.
[10] HIV- uninfected Core subjects only.

Schedule of Events – HIV-infected Core Group (Subjects 6-20) and HIV-uninfected Core Group (Subjects 6-20; Days 1-99) (CONTINUED)

	Day 57 (8 wks)	Day 64 (9 wks)	Day 71 (10 wks)	Day 72	Day 74	Day 78 (11 wks)	Day 85/EOS (12 wks) [9]	Day 85 (12 wks)[10]	Day 99 Follow-Up (14 wks)[9]	Day 99 EOS (14 wks)[10]
Visit window (days)	±1	±1	±1	±3 hr	±3 hr	±1	±1	±1	±1	±1
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION										
Record agents in ART history at Screening, changes in ART on-study [1,9]	X		X				X			
Record results of a complete physical examination										
Record results of a targeted physical examination [2]	X	X	X			X	X	X		X
Record vital sign measurements	X	X	X			X	X	X		X
Record the subject's weight							X			X
Record AEs [3]	X	X	X			X	X	X	X	X
Record concomitant medications	X	X	X			X	X	X	X	X
BLOOD and/or URINE [4] SAMPLES TO BE COLLECTED										
Hematology and serum chemistry (see Section 7.2.1 for list)	X		X				X	X		X
Urinalysis	X		X				X	X		X
HIV-1 RNA (viral load)[9]	X		X				X			
$CD4^+$ cell count							X			X
4th Generation POC HIV-1 test[10]	X		X							X
Serum for pregnancy test for females of childbearing potential [5]							X			X
Urine for pregnancy test for females of childbearing potential	X									

	Day 57 (8 wks)	Day 64 (9 wks)	Day 71 (10 wks)	Day 72	Day 74	Day 78 (11 wks)	Day 85/EOS (12 wks) [9]	Day 85 (12 wks)[10]	Day 99 Follow-Up (14 wks)[9]	Day 99 EOS (14 wks)[10]
Visit window (days)	±1	±1	±1	±3 hr	±3 hr	±1	±1	±1	±1	±1
Antiretroviral resistance sample[9]	X		X				X			
Archive serum sample	X		X				X	X		X
Trogarzo® serum concentration (pre-dose if drug administered on this day) [6]	X		X	X	X	X	X	X		X
Trogarzo® serum concentration post-dose – 1 hour (±10 min)			X							
Immunogenicity of Trogarzo® (2 tubes x 3 mL each)							X			X
STUDY DRUG ADMINISTRATION AND AFTER										
Administer study drug via IVI – study drug diluted in 250mL normal saline and administered IV over 15 minutes per Trogarzo® prescribing information							X[9]			
Administer study drug via IVP – undiluted Push over 30 seconds [7]	X		X							
Observe subject post-administration – 15 minutes if HIV-infected, 60 minutes if uninfected; record vital sign measurements after completion of infusion and again at end of observation period[8]	X		X				X			

[1] All ART for the 3 months preceding Screening will be recorded at Screening visit; subsequent visits will only record changes to ART.

[2] Abbreviated physical examination includes examination of lymph nodes, respiratory and cardiovascular systems, abdomen, extremities, and nervous system.

[3] Only record Aes that are related to study procedures before administration of the first dose.

[4] Subjects need not fast before blood sampling.

[5] Serum FSH test to be conducted on postmenopausal females at Screening only.

[6] Pre-dose samples to be collected within 1 hour before the start of the infusion; 24 hr, 72, hr, and 7 Day post dose samples to be collected within 3 hours of the time the infusion ended.

[7] At Days 57 and 71 Core Group subjects will receive study drug as 800 mg undiluted Trogarzo® administered by IV push over 30 seconds once every 2 weeks. At Day 85/EOS (12 weeks) HIV-infected subjects in the Core Group will revert to receiving 800 mg Trogarzo® diluted into 250 mL normal saline as an IV infusion over 15 minutes, per Trogarzo® prescribing information All subjects must be observed after the completion of each study drug administration – 15 minutes if HIV-infected, 60 minutes if uninfected. Vital signs should be monitored and recorded at the beginning and end of the observation period.

[8] Any abnormalities observed need to be recorded on the AE CRF.

[9] HIV-infected Core subjects only.

[10] HIV-uninfected Core subjects only.

Table 4 Schedule of Events for IM Group (HIV-Infected and HIV-Uninfected Subjects)

Day	Screen*	1 BL	3	8	11	15	17	22	25	29	43	57	59	64	67	71	73	78	81	85 [11]	99[12]	113 F/U[10]
Week	**NA**	**0**	**1**	**1**	**2**	**2**	**3**	**3**	**3**	**4**	**6**	**8**	**8**	**9**	**9**	**10**	**10**	**11**	**11**	**12**	**14**	**16**
Visit window (days)	(-28 days)	NA	±3 hr	±1	±1	±1	±3 hr	±1	±1	±1	±1	±1	±3 hr	±1r	±1	±1	±3 hr	±1	±1	±1	±1	±1
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION																						
Review/discuss Inclusion/Exclusion criteria	X																					
Obtain signed Informed Consent Form	X																					
Record demographics, medical history (general and HIV); height	X																					
Record agents in ART history at Screening, changes in ART on-study[1]	X	X				X				X	X	X				X				X[9]		
Record results of a complete physical examination	X																					
Record results of a targeted physical examination [2]		X				X				X	X	X				X				X	X[10]	
Record vital sign measurements	X	X				X				X	X	X				X				X	X[10]	
Record the patient's weight	X																			X[9]	X[10]	
Record AEs [3]	X	X				X				X	X	X				X				X	X	X
Assess injection site										X	X	X	X	X	X	X	X	X	X	X		
Record concomitant medications	X	X				X				X	X	X				X				X		
HIV Treatment Satisfaction Questionnaire (HIVTSQs)										X[9]										X[9]		
HIV Treatment Satisfaction Questionnaire (HIVTSQc)																				X[9]		
Study Medication Satisfaction Questionnaire (SMSQs)										X[10]										X[10]		
Study Medication Satisfaction Questionnaire (SMSQc)																				X[10]		
BLOOD and/or URINE SAMPLES TO BE COLLECTED																						
Hematology and serum chemistry (see Section 7.2.1 for list)	X	X				X				X	X	X				X				X	X[10]	
Urinalysis	X	X				X				X	X	X				X				X	X[10]	
HIV-1 RNA (viral load)[9]	X	X				X				X	X	X				X				X		
4th Generation POC HIV test[10]		X								X		X				X					X	
CD4+ cell count	X	X								X		X								X[9]	X[10]	
Serum for pregnancy test for females of childbearing potential[5]	X																			X[9]	X[10]	
Urine for pregnancy test for females of childbearing potential		X				X[10]				X	X[10]	X				X[10]						
Antiretroviral resistance sample[9]		X				X				X	X	X				X				X		
Archive serum sample		X				X				X	X	X				X				X	X[10]	
Trogarzo® serum concentration (pre-dose if drug administered on this day)[6,13]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]	

Day	Screen*	1 BL	3	8	11	15	17	22	25	29	43	57	59	64	67	71	73	78	81	85 [11]	99[12]	113 F/U[10]
Week	**NA**	**0**	**1**	**1**	**2**	**2**	**3**	**3**	**3**	**4**	**6**	**8**	**8**	**9**	**9**	**10**	**10**	**11**	**11**	**12**	**14**	**16**
Visit window (days)	(-28 days)	NA	±3 hr	±1	±1	±1	±3 hr	±1	±1	±1	±1	±1	±3 hr	±1r	±1	±1	±3 hr	±1	±1	±1	±1	±1
Immunogenicity of Trogarzo® (2 tubes x 3 mL each)		X																		X[9]	X[10]	
STUDY DRUG ADMINISTRATION AND AFTER																						
Administer study drug via IVI – study drug diluted in 250 mL normal saline and administered IV over 15 minutes per Trogarzo® prescribing information		X				X														X[9]		
Administer study drug via IM injection[7]										X	X	X				X						
Observe subject for 15 minutes if HIV infected and 60 minutes if HIV uninfected after administration; record vital sign measurements after dose administration and again at end of observation period[8]		X				X				X	X	X				X				X[9]		

*** Screening visit to be conducted for HIV-infected patients ONLY. See Table 2 for Screening and Pre-Steady State Phase Schedule of Events**

[1] All prior ART will be recorded at Screening; subsequent visits will only record changes to ART.

[2] Abbreviated physical examination includes examination of lymph nodes, respiratory and cardiovascular systems, abdomen, extremities, and nervous system.

[3] Only record AEs that are related to study procedures before administration of the first dose; after administration of first dose, assessments will include evaluation of injection site for reaction.

[4] Subjects need not fast before blood sampling.

[5] Serum FSH test to be conducted on postmenopausal females at Screening only.

[6] Pre-dose samples to be collected within 1 hour before the start of the infusion.

[7] At Baseline and at Day 15, subjects in the IM Group will receive study drug diluted into 250 mL normal saline as an 800 mg IV infusion over 15 minutes, per Trogarzo® prescribing information. At Day 29 IM Group subjects will begin receiving study drug as 800 mg undiluted Trogarzo® administered by IM injection once every 2 weeks.

[8] Any abnormalities observed need to be recorded on the AE case report form.

[9] HIV-infected IM group subjects only.

[10] HIV-uninfected IM subjects only.

[11] Day 85 is end of study for HIV-infected subjects.

[12] Day 99 is follow-up for HIV-infected subjects and is end of study for HIV-uninfected subjects.

[13] PK visits between Baseline and Day 29 will not be required for HIV-infected subjects participating in the IM portion of TMB-302 who have re-enrolled after receiving a 2000mg loading dose and one 800 mg dose of Trogarzo® by IVI prior to study re-enrollment since these PK samples will already have been collected during initial study participation.

3.5 Safety Assessments

Safety assessments will include the results of the following measurements through Day 99 (14 weeks) for the Sentinel Group and the HIV-uninfected Core and IM Groups Subjects, whose participation is 2 weeks longer in duration, Day 85 (12 weeks) for the HIV-1 infected Core and IM Group subjects:

- Physical examinations;
- Vital sign measurements;
- Clinical laboratory parameters (hematology, $CD4^+$ T-cell counts, serum chemistry, and urinalysis);
- Monitoring of Aes and concomitant medications;
- Anti-Trogarzo® antibody levels (immunogenicity of Trogarzo®).
- Injection site reactions in subjects receiving Trogarzo® IM

3.6 Pharmacokinetic Assessments

Pharmacokinetic samples will be collected in the study to evaluate serum concentrations of Trogarzo®. These data will be used to allow evaluation of the PK profile of Trogarzo®. In particular, data will be collected to compare serum drug concentrations (AUC and trough) after IVI of the 800 mg diluted drug over 15 minutes to IV push of the undiluted drug over 30 seconds and IM injection. Study TMB-121 results showed that following 800 mg Trogarzo® via IM injection, the T_{max} was 2.13 days. Therefore, for better estimation of AUC following IM injection, the timepoints of 2, 7, 10, and 14 days following dosing were selected. For comparison between IV infusion of the 800 mg diluted drug over 15 minutes and IM, blood will be collected at the same timepoints for both routes. See Table 1, Table 2, Table 3, and Table 4 for PK sample collection timepoints. HIV-1 infected participants who re-enroll after receiving a loading dose of 2000mg IVI and at least one maintenance dose of 800mg IVI given according to the label a minimum of 4 weeks prior to Day 1 enrollment will not undergo PK assessments between the Baseline and Day 29 visits since these PK samples will already have been collected during the subject's initial study participation. The PK assessments of the re-enrolled participants will be compared between the IVI from their first enrollment and IM from their second enrollment.

4. Study Treatment

4.1 Study Drug Dosage and Administration

The first five (5) subjects enrolled will comprise the Sentinel Group. After all subjects in the Sentinel Group have successfully completed Day 99 (14 weeks) of the study, and the DMC has reviewed the accumulated data and given approval for enrollment of the Core Group to proceed, subjects six (6) through twenty (20) will be enrolled.

For the IV administrations (IVI and IV push), study drug will be administered intravenously via a 23-gauge IV butterfly. Study drug should be administered in the cephalic vein of the subject's right or left arm. If this vein is not accessible, an appropriate vein located elsewhere can be used. The administration site will be recorded in the source documents and CRF. Once placed, the IV line should be flushed with 2-5 mL of saline to insure proper placement. Study drug administration by IV infusion, bolus, or push should be done as per the protocol. Once drug administration is completed the line should be flushed with 2-5 mL of normal saline prior to removal of the device. An infusion pump (like Baxter Flo Gard 6201, Bodyguard 323 CME, or similar – not supplied by the Sponsor) should be employed as needed to achieve study drug administration times indicated in the protocol for IVI and IV bolus. IV push dosing over 30 seconds should not be performed with a pump.

For the IM injections, a volume of 5.32 mL, corresponding to 800 mg Trogarzo®, will be administered over two injections of about 2.66 mL each. The two IM injections should be administered in the muscle tissue of the subject's anterolateral aspect of the thighs (left, right, or both). The two IM injections are to be administered in one body area and injection sites should be at least 1 inch apart. If an alternative body area is necessary for subject comfort/convenience, IM injections can be administered in the dorsogluteal site (upper outer quadrant of the buttock). Every effort should be made to limit injection sites to one body area for each dose, if possible. The injection site must be examined at baseline and described in detail for subsequent exam. This information will be recorded.

After sterilization of the injection site with an alcohol swab, the study drug will be injected using a syringe with a needle of appropriate gauge and length into the IM tissue. Injection site, body mass

index (BMI), needle gauge and length used will be collected in the eCRF. In brief, skin at the injection site will be stretched firmly and the study drug will be injected slowly into muscle tissue at a 90-degree angle.

All Subjects at Day 1/Baseline and Day 15

At the Day 1/Baseline and Day 15 visits, all subjects in the study will receive a maintenance dose of 800 mg Trogarzo® diluted in 250 mL normal saline (at 3.2 mg/mL) and administered as an IVI over 15 minutes in accordance with the approved Trogarzo® prescribing information.

Sentinel Group (Subjects 1 to 5) at Day 29 (4 weeks) through Day 85 (12 weeks)

Beginning at Day 29 and continuing through Day 85 (12 weeks), the 800 mg maintenance doses of Trogarzo® will be administered in the Sentinel Group at sequentially increasing concentrations and over sequentially reduced time periods in accordance with the study schedule (see Section 3.1 and Table 1). The sequential changes in the dilution and dosing rate in the Sentinel Group is as follows:

- Day 29 (4 weeks): 800 mg diluted in 50 mL normal saline (at 16 mg/mL) via IVI over 10 minutes
- Day 43 (6 weeks): 800 mg diluted in 16 mL normal saline (at 50 mg/mL) via IV bolus over 5 minutes
- Day 57 (8 weeks): 800 mg diluted in 8 mL normal saline (at 100 mg/mL) via IV bolus over 1 minute
- Day 71 (10 weeks): 800 mg undiluted (at 150 mg/mL) via IV push over 30 seconds
- Day 85 (12 weeks): 800 mg undiluted (at 150 mg/mL) via IV push over 30 seconds

When five (5) subjects in the Sentinel Group have completed Day 99 (14 weeks) of the study, the DMC will review the available data to determine whether the enrollment of the Core Group should proceed.

Core Group (Subjects 6 to 20) at Day 29 (4 weeks) through Day 71 (10 weeks)

After DMC review of data from the Sentinel Group and approval obtained for the study to proceed, the Core Group (subject numbers six (6) through twenty [20]) will be enrolled. Beginning at Day 29 and continuing through Day 71 (10 weeks), subjects in the Core Group will receive an 800 mg maintenance dose q2wk as undiluted drug over 30 seconds.

In HIV-infected individuals, at Day 99 (14 weeks) for the Sentinel Group, and at Day 85 (12 weeks) for the Core Group, subjects will revert to receiving Trogarzo® as a diluted IVI over 15 minutes in accordance with the prescribing information.

In HIV-uninfected individuals Trogarzo® will be discontinued after the Day 71 IV push.

At Day 113 (16 weeks) for the Sentinel Group, and Day 99 (14 weeks) for the Core Group, only safety follow-up is performed. These visits may be performed via telephone if evaluation does not require a clinic visit, and subjects should return to routine administration of Trogarzo® through their primary care provider at this time point.

IM Group (Subjects 21-40) at Day 29 (4 weeks) through Day 71 (10 weeks)

Subjects in the IM Group will receive the first two doses of study drug in accordance with the Trogarzo® prescribing information (diluted in normal saline and administered over 15 minutes via IVI). The next four doses will be administered as an IM injection. At Day 85 (12 weeks), IM Group HIV-infected subjects will revert to diluted IVI dosing over 15 minutes in accordance with the Trogarzo® prescribing information.

In HIV-uninfected individuals Trogarzo® will be discontinued after the Day 71 injection.

Subjects will be followed for safety through 28 days after the last Trogarzo® administration on study (from Day 85 [12 weeks] through Day 113 [16 weeks] for the Sentinel and HIV-infected IM Groups, from Day 71 [10 weeks] through Day 99 [14 weeks] for HIV-uninfected Core and IM Groups , and at Day 99 for the HIV-infected Core Group). Safety follow-up visits may be performed via telephone if evaluation does not require a clinic visit, and subjects should return to routine administration of Trogarzo® through their primary care provider at this time point.

All subjects will be observed after completion of each study drug administration – 15 minutes if HIV-infected, 60 minutes if HIV-uninfected. In addition to noting any general acute reactions, the site of injection will be inspected, and any unusual signs noted. Vital signs will be recorded immediately after completion of study drug administration and again at the end of the observation period. All AEs occurring during observation will be recorded.

4.2 Prohibited Medications and Restrictions

Use of and changes in concomitant medications will be recorded in the subject's source documents and the electronic data capture (EDC) system. 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 subject in the EDC system. Complete information is expected for any medication prescribed during the trial.

The prescribing information for all medications, including Trogarzo® should be reviewed carefully. The guidance provided in the respective contraindications, warning, and precautions section for any medication must be followed to prevent any potentially serious or life-threatening drug interactions. Refer to the current Trogarzo® Package Insert and/or Investigator Brochure and/or Product Monograph for relevant information.

The following medications are <u>not</u> to be administered concomitantly in HIV-infected individuals:

- Any vaccines other than influenza or COVID vaccine during the 7 days before Day 1/Baseline through EOS;
- All investigational drugs from 30 days before Day 1/Baseline through EOS, with the exception of investigational components of a qualifying stable ART regimen

In HIV-uninfected subjects vaccines may be administered during the course of the study with approval by the study staff; however, no investigational drugs may be administered.

4.3 Safety Monitoring and Toxicity Management Plan

<u>Sentinel Group</u>

This trial will employ a sentinel group of 5 subjects to determine the safety of progressively shortening the administration time while increasing the drug concentration of Trogarzo® with the goal of delivering an 800 mg dose (5.32 mL at 150 mg/mL) via IV push over 30 seconds.

A dose-limiting toxicity (DLT) will be defined as:

- Any Grade 3 or greater toxicity that the study investigators recognize as probably or definitely attributable to Trogarzo® administration. Grade 3 and 4 laboratory abnormalities must be confirmed by a repeat test obtained as soon as possible following the initial result

OR

- Any subject with Grade 2 infusion-related reaction and/or cytokine release syndrome (see Appendix B – DAIDS Grading Table V2.1 for cytokine release syndrome).

The first 2 subjects in the Sentinel Group will be enrolled and treated at least 2 weeks prior to the enrollment and treatment of the remaining 3 subjects.

If no DLT occurs within 7 days of Trogarzo® shortened IV infusion, bolus, or push administration then dosing of additional subjects may continue with approval of the DMC.

If 1 DLT occurs within 7 days of Trogarzo® dosing at a shortened IV infusion, bolus, or push administration then the DMC should be notified; however, dosing may continue. The individual experiencing the DLT should resume dosing as per current FDA-approved administration instructions and the subject will discontinue from the study.

If 2 DLTs occur within 7 days of Trogarzo® dosing at a shortened IV infusion, bolus, or push administration then such administration should be suspended and further dosing of Trogarzo® should resume as per current FDA-approved administration instructions.

Any SAE deemed related to the change in administration time and concentration of Trogarzo® in any participant in the Sentinel Group will result in cessation of dosing at increased concentration and over intervals <15 minutes. The DMC should review the event and all scheduled Trogarzo® dosing should resume as per current FDA-approved administration instructions to avoid loss of virologic control. The DMC may recommend resumption of the Sentinel Group dosing schedule after review of the SAE.

Core Group

Once the Sentinel group has completed Day 99 and the DMC has reviewed the safety data and approved additional enrolment and treatment with Trogarzo® given as an IV push over 30 seconds, the Core Group may begin enrolment and dosing as per the study design.

The Core Group will consist of 15 subjects who will receive an 800 mg maintenance dose of Trogarzo® in accordance with the prescribing information (diluted in normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. Every 2 weeks thereafter through

Day 71 (10 weeks), maintenance doses will be administered via undiluted IV push over 30 seconds. At Day 85 (12 weeks), HIV-infected Core Group subjects will revert to diluted IVI dosing over 15 minutes in accordance with the Trogarzo® prescribing information. HIV-uninfected Core Group subjects will discontinue dosing after the Day 71 study drug administration.

As above, a DLT will be defined as any Grade 3 or greater toxicity that the study investigators recognize as probably or definitely attributable to Trogarzo® administration. Grade 3 and 4 laboratory abnormalities must be confirmed by a repeat test obtained as soon as possible following the initial result.

In the absence of the occurrence of DLTs, the DMC should formally review all safety data at the following timepoints:

1. After 5 subjects in the Core Group receive 2 doses of Trogarzo® IV push (IVP) over 30 seconds.
2. After the first 5 subjects in the Core Group receive 4 doses of Trogarzo® IV push over 30 seconds and the second 5 subjects receive 2 doses of Trogarzo® IVP over 30 seconds.
3. At the conclusion of the study of all 15 Core Group subjects.

For HIV-uninfected healthy volunteers:

If 1 DLT occurs within 7 days of a subject receiving Trogarzo® by IVI or IV push over 30 seconds, then the DMC should be notified, and dosing of additional Core Group subjects may continue. However, the individual experiencing the DLT should discontinue dosing and be observed for 28 days prior to study discontinuation.

If 2 DLTs occur within 7 days of a subject receiving Trogarzo® by IVI or by IV push over 30 seconds, then the DMC should be notified; however, dosing of additional HIV-1 infected Core Group subjects may continue. The individuals experiencing the DLT should discontinue dosing and be observed for 28 days prior to study discontinuation. The DMC should at this point review.

If 3 DLTs occur within 7 days of a subject receiving Trogarzo® by IVI or IV push over 30 seconds, then the DMC should be notified, and further dosing of Core Group subjects should be suspended. All Core Group subjects should resume dosing as per current FDA-approved administration instructions.

For HIV-1 infected individuals:

If 1 DLT occurs within 7 days of a subject receiving Trogarzo® IV push over 30 seconds, then the DMC should be notified, and dosing of additional Core Group subjects may continue. However,

the individual experiencing the DLT should resume dosing as per current FDA-approved administration instructions and the subject will discontinue from the study.

If 2 DLTs occur within 7 days of a subject receiving Trogarzo® IV push over 30 seconds, then the DMC should be notified; however, dosing of additional Core Group subjects may continue. The individuals experiencing the DLT should resume dosing as per current FDA-approved administration instructions and the subjects will discontinue from the study.

If 3 DLTs occur within 7 days of a subject receiving Trogarzo® IV push over 30 seconds, then the DMC should be notified, and further dosing of Core Group subjects should be suspended. All Core Group subjects should resume dosing as per current FDA-approved administration instructions.

Any SAE deemed related to study drug administration will result in cessation of dosing by IV push over 30 seconds. The DMC should review the event and all Trogarzo® dosing should resume as per current FDA-approved administration instructions to avoid loss of virologic control. The DMC will determine whether dosing by IV push over 30 seconds may resume in additional participants.

IM Group

The IM Group will consist of approximately 20 subjects who will receive the first four doses of study drug in accordance with the Trogarzo® prescribing information (diluted in normal saline and administered over 15 minutes via IVI). The next four doses will be administered as an IM injection. HIV-infected IM Group subjects will revert to diluted IVI dosing over 15 minutes in accordance with the Trogarzo® prescribing information at Day 85 (Week 12).

As above, a DLT will be defined as any Grade 3 or greater toxicity that the study investigators recognize as probably or definitely attributable to Trogarzo® administration. Grade 3 and 4 laboratory abnormalities must be confirmed by a repeat test obtained as soon as possible following the initial result.

In the absence of the occurrence of DLTs, the DMC should formally review all safety data at the following time-points:

1. After 5 subjects in the IM Group receive 2 doses of Trogarzo® via IM injections
2. After the first 5 subjects (subjects 1-5) in the IM Group receive 4 doses of Trogarzo® via IM injections and the second 5 subjects (subjects 6-10) receive 2 doses of Trogarzo® via IM injections
3. At the conclusion of the study of all 20 IM Group subjects

For HIV-uninfected healthy volunteers:

If 1 DLT occurs within 7 days of a subject receiving Trogarzo® by IVI or IM injection, then the DMC should be notified, and dosing of additional IM Group subjects may continue. However, the individual experiencing the DLT should discontinue dosing and be observed for 28 days prior to study discontinuation.

If 2 DLTs occur within 7 days of a subject receiving Trogarzo® by IVI or by IM injection then the DMC should be notified; however, dosing of additional HIV-1 uninfected IM Group subjects may continue. The individuals experiencing the DLT should discontinue dosing and be observed for 28 days prior to study discontinuation. The DMC should at this point review.

If 3 DLTs occur within 7 days of a subject receiving Trogarzo® by IVI or by IM injection, then the DMC should be notified, and further dosing of IM Group subjects should be suspended. All IM Group subjects should resume dosing as per current FDA-approved administration instructions.

For HIV-infected individuals:

If 1 DLT occurs within 7 days of a subject receiving Trogarzo® via IM injection, then the DMC should be notified, and dosing of additional IM Group subjects may continue. However, the individual experiencing the DLT should resume dosing as per current FDA-approved administration instructions and the subject will discontinue from the study.

If 2 DLTs occur within 14 days of a subject receiving Trogarzo® via IM injection, then the DMC should be notified; however, dosing of additional IM Group subjects may continue. The individuals experiencing the DLT should resume dosing as per current FDA-approved administration instructions and the subjects will discontinue from the study.

If 3 DLTs occur within 14 days of a subject receiving Trogarzo® via IM injection, then the DMC should be notified, and further dosing of IM Group subjects should be suspended. All IM Group subjects should resume dosing as per current FDA-approved administration instructions.

Any SAE deemed related to study drug administration will result in cessation of dosing via IM injection. The DMC should review the event and all Trogarzo® dosing should resume as per current FDA-approved administration instructions to avoid loss of virologic control. The DMC will determine whether dosing by IM injection may resume in additional participants.

Refer to Appendix C for further information on the management of suspected anaphylactoid reactions. Study drug should only be administered in a setting that allows for rapid access to emergency cardiopulmonary support services in the event of a life-threatening infusion-related AE (e.g., anaphylaxis).

4.4 Study Stopping Rules

In consultation with the DMC:

- Any 2 DLTs in the Sentinel Group that the DMC confirms to be probably or definitely due to the administration of Trogarzo® at a faster rate or increased concentration or both
- Any 2 DLTs in the HIV-uninfected volunteers in the Core Group occurring within 7 days of treatment that the DMC confirms to be probably or definitely due to the administration of Trogarzo® by IVI, IV push, or IM will result in the discontinuation of enrollment of HIV-uninfected healthy volunteers. HIV-uninfected volunteers already enrolled in the study may complete the trial if they do not meet these DLT criteria.
- Any 3 DLTs in the Core IVP or IM Groups that the DMC confirms to be probably or definitely due to the administration of Trogarzo® at a faster rate or increased concentration or both
- Any SAE in any Group that the DMC confirms to be probably or definitely due to the administration of Trogarzo® at a faster rate or increased concentration or both

4.5 Study Drug Description

HIV-infected study participants will be treated with commercially packaged Trogarzo® according to the instructions for infusion in the approved prescribing information both prior to and after completion of this study. HIV-uninfected healthy volunteers will be treated with drug packaged and labeled for clinical research use provided to study sites by the study sponsor.

To prevent potential loss of benefits and disruption of drug availability to the HIV-infected participants, study drug will be obtained at the clinical sites using the same means for obtaining the commercial drug employed for that subject prior to study entry and after study completion. Thus, investigators will be asked to apply labels to the TMB-302 study drug as required for an Investigational New Drug Application (IND) study utilizing labels and procedures provided by the Sponsor or Designee.

Trogarzo® is a single-use parenteral formulation contained in a 2 mL, clear-glass vial, and packaged into cartons containing 2 vials each. The drug product contains ibalizumab-uiyk at a concentration of 150 mg/mL, histidine United States Pharmacopoeia (USP), sucrose, sodium chloride, polysorbate 80, and water for injection USP at pH 6.0. Each vial contains at least 1.33~ mL of fluid delivering a

total of 200 mg study drug per vial. Each 800 mg dose of study drug will thus require 4 vials (2 cartons for HIV-infected and 4 cartons for HIV-uninfected due to differences in packaging) of Trogarzo®. The stability of Trogarzo® at 2ºC to 8ºC is evaluated in ongoing studies. For any period of storage, Trogarzo® must be under refrigerated conditions with a temperature-monitoring device. Trogarzo® should be maintained at 2°C to 8°C (but NOT FROZEN) and protected from light in accordance with Trogarzo® packaging information.

Any spent vials or remaining contents of used vials should be destroyed according to the site's procedures for spent vial destruction and disposal only after complete drug accountability records have been reviewed and accepted during routine monitoring, and written permission has been given for spent vial destruction. The destruction should be documented.

4.6 Study Drug Accountability

The investigator will maintain accurate records of all study drug, including when, how much, and condition under which the study drug is received, dispensed, and destroyed by site personnel. In addition, the administration of study drug to each subject should be documented to the vial level for each infusion (i.e., lot number of every vial for that infusion, expiration date, time of infusion preparation, time and duration of administration, and documentation of full infusion received). Reasons for deviation from the expected dispensing regimen must also be recorded. Drug accountability will be reviewed and documented at each study monitoring visit. Reconciliation and accountability of study drug will be done throughout the study during the monitoring visits. The Sponsor or designee shall maintain written records of all drug dispositions, which will include the name of the investigator, the date, quantity, batch or code of each such shipment, and method of disposal. Disposal may only occur after complete drug accountability records have been reviewed and accepted during routine monitoring, and written permission has been given for used vial destruction.

5. Subject Enrollment

Approximately 40 subjects will be enrolled into the study at approximately 7-8 sites in the United States. Approximately twenty subjects will receive Trogarzo® via an IV push and approximately 20 subjects will receive Trogarzo® via IM injection. Subjects will be enrolled only if they meet all of the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

HIV-infected participants:

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

1. Are capable of understanding and have voluntarily signed the informed consent document
2. Currently receiving a stable Trogarzo®-containing ARV regimen for a minimum of 3 months, and no change in background ARVs anticipated over the period of study participation; a stable regimen is defined as having no changes in dose or frequency and no interruptions ≥2 weeks during the 3-month period
    - Note: For subjects who receive Trogarzo® as an IV push (Core Group) and then enter the study to receive Trogarzo® as an IM injection (IM Group), the period while receiving the IV push will be considered as having received a stable Trogarzo®-containing ARV regimen.
    - Note: HIV-infected subjects who are enrolled in the IM injection study and are unable to adhere to the study schedule for IM dosing due to factors outside the study will be discontinued. Re-enrollment of HIV-infected IM Group subjects will be allowed after a Discontinuation Visit and Screening Visit are completed provided that inclusion/exclusion criteria continue to be satisfied and dosing after discontinuation is resumed according to the Trogarzo® Prescribing Information. For re-enrolling subjects, the inclusion criteria for stable a Trogarzo®-containing ARV regimen is satisfied with a loading dose of 2000mg IVI and at least one maintenance dose of 800mg IVI given according to Trogarzo® labeling prior to Day 1 enrollment.
3. Have no AIDS-defining events in the 3 months before Screening, other than cutaneous Kaposi's sarcoma or wasting syndrome due to HIV.
4. Are able and willing to comply with all protocol requirements and procedures
5. Are 18 years of age or older
6. Have a life expectancy that is >6 months
7. Have a viral load <1,000 copies/mL at Screening
8. $CD4^+$ T-cell count >50 cells/mm^3 at Screening

9. Prothrombin time (PT) and partial thromboplastin time (PTT) <1.5 times the upper limit of normal (IM Group only)

HIV-uninfected individuals:

1. Healthy volunteers born male and female as assessed by medical history and physical examination
2. Aged ≥18 and ≤50 years at the time of Screening
3. Ability and willingness to provide written informed consent
4. Willingness to comply with protocol schedule
5. Willingness to undergo HIV-1 testing
6. Non-reactive 4th generation point of care HIV-1 test at Screening
7. Hepatitis B Surface antigen negative
8. Hepatitis C antibody negative, or if reactive, Hepatitis C RNA undetectable in plasma
9. PT and PTT <1.5 times the upper limit of normal (IM Group only)
10. Volunteers born female of reproductive potential who are 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.

    Volunteers born female with reproductive potential are defined as pre-menopausal volunteers born female who have not had a sterilization procedure (e.g., hysterectomy, bilateral oophorectomy, tubal ligation or salpingectomy). Volunteers born female are considered menopausal if they have not had a menses for at least 12 months and have a follicle-stimulating hormone (FSH) of greater than 40 IU/L or if FSH testing is not available, they have had amenorrhea for 24 consecutive months.

5.2 Exclusion Criteria

HIV-infected participants:

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

1. Any active AIDS-defining illness according to the Centers for Disease Control and Prevention (CDC) Revised Surveillance Case Definitions for HIV Infection 2008 (Morbidity and Mortality Weekly Report (MMWR) Vol.57/No. RR-10, Appendix A), or history of the same during the 3 months preceding Screening, with the following exceptions: cutaneous Kaposi's sarcoma and wasting syndrome due to HIV
2. Any significant diseases (other than HIV-1 infection) or clinically significant findings, including psychiatric and behavioral problems, determined from Screening, medical history, and/or physical examination that, in the investigator's opinion, would preclude the subject from participating in this study
3. Any significant acute illness within 1 week before the initial administration of study drug
4. Any active infection secondary to HIV requiring acute therapy; however, subjects that require maintenance therapy (i.e., secondary prophylaxis for opportunistic infections) will be eligible for the study
5. Any immunomodulating therapy (including interferon), systemic steroids, or systemic chemotherapy within 12 weeks before Enrollment
6. Any vaccination within 7 days before Day 1
7. Any female subject who either is pregnant, intends to become pregnant, or is currently breastfeeding
8. Any current alcohol or illicit drug use that, in the investigator's opinion, will interfere with the subject's ability to comply with the study schedule and protocol evaluations
9. Any radiation therapy during the 28 days before first administration of study medication
10. Any Grade 3 or 4 laboratory abnormality according to the Division of AIDS (DAIDS) grading scale, except for the following asymptomatic Grade 3 events:
    - triglyceride elevation
    - total cholesterol elevation
    - or Grade 3 or 4 reductions in levels of CD4+ T cells
11. History of coagulopathy that would preclude administration of IM injections (IM Group only)
12. Skin rashes or tattoos that would prevent ability to assess IM injection for injection-site reactions (IM Group only)
13. Use of high-dose aspirin, clopidogrel, prasugrel, ticagrelor, dipyridamole or other antiplatelet medication that would interfere with the ability to receive IM injections (IM Group only).

HIV-uninfected individuals

1. Confirmed HIV-1 infection

2. At high risk of severe COVID-19 disease as defined by one of the following:
   - History of hypertension, atherosclerotic cardiovascular disease (ASCVD), coronary artery disease, diabetes mellitus
   - History of asthma or chronic pulmonary disease
   - History of renal disease and chronic renal insufficiency
   - BMI over 35

3. Any acute or chronic medical condition that in the opinion of the investigator would preclude participation

4. Chronic autoimmune disease

5. Active IV drug use

6. Excessive use of alcohol or recreational drugs that in the opinion of the investigator would preclude participation

7. Decompensated psychiatric illness

8. Need for chronic immunotherapy including systemic corticosteroids, other MAb therapy, or immunosuppressive drugs

9. Volunteers born female who are pregnant, lactating, or planning on becoming pregnant over the study period

10. Any of the following laboratory parameters:
    - Hemoglobin <10.0 g/dL
    - Absolute neutrophil count <1,000/mm^3
    - Absolute lymphocyte count <500/mm^3
    - Platelet count <100,000/mm^3
    - Creatinine >1.25x upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) >1.5x ULN
    - Alanine aminotransferase (ALT) >1.5x ULN
    - Glucose (non-fasting) >160 mg/dL
    - Proteinuria: 2+ or greater
    - Hematuria: >10 red blood cells (RBCs) per high-power field

11. Previous receipt of an experimental MAb for HIV-1treatment or prevention in a research study

12. History of severe allergic reactions to drugs, vaccines, or drug infusion

13. Participation in another investigational clinical trial within the past 12 weeks or anticipated during the course of the current study

14. History of coagulopathy that would preclude administration of IM injections (IM Group only)

15. Skin rashes or tattoos that would prevent ability to assess IM injection for injection-site reactions (IM Group only)

16. Use of high-dose aspirin, clopidogrel, prasugrel, ticagrelor, dipyridamoleor any other antiplatelet medication that would interfere with the ability to receive IM injections (IM Group only).

5.3 Subject Withdrawal and Discontinuation

5.3.1 Reasons for Withdrawal or Discontinuation

A subject may be withdrawn or discontinued from the study if:

- The subject withdraws consent to participate or requests an early discontinuation at any time during the study
- The subject is in violation of the protocol
- The subject becomes pregnant during the study (Section 8.7 for a description of procedures to be followed in case of pregnancy)
- The subject experiences a severe drug-related AE during study drug administration or during the post-administration observation period
- Upon determination by the investigator that withdrawal from the study is in the best interests of the subject
- Any HIV-uninfected subject in the Core Group who tests positive for HIV-1 during the course of the study will be withdrawn.
- Refer to Sections 6.1, 6.2, and 6.3 for additional reasons for study discontinuation

Refer to Sections 4.3 and 4.4 for detailed information on the Safety Monitoring and Toxicity Management Plan and the Study Stopping Rules.

A subject experiencing one or more treatment-emergent SAEs will receive treatment and follow-up evaluations by the investigator, or they will be referred to another appropriate physician for treatment and follow-up. Withdrawal from the study will be at the discretion of the investigator/Sponsor.

The investigator will also withdraw a subject upon the request of the DMC (Section 8.8) or if the Sponsor or local regulatory agency (e.g., FDA) terminates the study. Upon occurrence of an SAE, the Investigator will notify the Sponsor or designee via the SAE hotline of these events (Section 8.6). If a subject is discontinued because of an AE, the event will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the subject to be stable.

5.3.2 Handling of Withdrawals and Discontinuations

Subjects are free to withdraw from the study at any time upon request. Subject participation in the trial may be stopped at any time at the discretion of the investigator or at the request of the Sponsor or designee. At the time of withdrawal or discontinuation, the investigator will assess the best options for treatment and discuss these options with the subject.

If a subject in the study is discontinued due to any reason other than safety as detailed in Section 4.3 (Safety Monitoring and Toxicity Management), another subject may be enrolled.

HIV-infected subjects who are enrolled in the IM injection study and are unable to adhere to the study schedule for IM dosing due to factors outside the study will be discontinued. Re-enrollment of HIV-infected IM Group subjects will be allowed after a Discontinuation Visit and Screening Visit are completed provided that inclusion/exclusion criteria continue to be satisfied and dosing after discontinuation is resumed according to the Trogarzo® Prescribing Information. For re-enrolling subjects, the inclusion criteria for stable a Trogarzo®-containing ARV regimen is satisfied with a loading dose of 2000mg IVI and at least one maintenance dose of 800mg IVI given according to Trogarzo® labeling prior to Day 1 enrollment.

When a subject withdraws or is discontinued from the study, the reason(s) for withdrawal or discontinuation will be recorded by the investigator. Whenever possible, all subjects who withdraw,

or are discontinued from the study prematurely will undergo all safety assessments and follow-up procedures as described for Day 99 (14 weeks) and Day 113 (16 weeks) for the Sentinel and HIV-infected IM Groups, and for Day 85 (12 weeks) and Day 99 (14 weeks) for the HIV-1 infected Core Group and the HIV-uninfected IM Group, respectively, and Day 99 for the HIV-uninfected Core Group subjects, with the exception of re-enrolled HIV-infected subjects participating in the IM study. Subjects who fail to return for final assessments will be contacted by the site personnel in an attempt to have the subjects comply with the protocol. A minimum of two documented phone calls should be made over the course of at least 2 weeks. If the site personnel receive no response, they should send a certified letter requesting that the subject contact the site regarding his or her status in the study. If the subject 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 subject 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 subject withdrawn because of an AE or SAE. In such cases, the subject will be followed to satisfactory resolution or until the investigator deems the event to be chronic or the subject to be stable. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures.

5.3.3 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 (e.g., FDA). If the Sponsor discontinues the study, FDA will be notified promptly.

6. Study Visits

Subjects will complete all Screening procedures as detailed in the Schedule of Events (see Table 1, Table 2, Table 3, and Table 4). Successful Screening results will allow the subjects to proceed to the Day 1/Baseline visit.

6.1 Sentinel Group

Study drug administration visits will take place once every 2 weeks beginning at Day 1/Baseline and continuing through Day 99 (14 weeks). After the study drug administration at Day 85 (12 weeks) by IV push, Sentinel Group subjects will revert to routine administration of Trogarzo® diluted in 250 mL normal saline via IVI over 15 minutes in accordance with Trogarzo® prescribing information. The scheduled visit at Day 113 (16 weeks) is for safety follow-up only, and this visit may be conducted by telephone if no clinic visit is needed for this purpose. Trogarzo® administration at Day 113/follow-up should be conducted in the routine manner as employed prior to the study, through the primary care provider.

Safety assessments, including collection of blood and urine specimens for safety laboratory testing, as well as HIV-1 viral load and archive and viral resistance samples, will be conducted every 2 weeks beginning at Day 1/Baseline and continuing through Day 99 (14 weeks). Additionally, beginning at Day 29 (4 weeks), Sentinel Group subjects will also have non-laboratory safety assessments (vital signs, AEs, recording of concomitant medications) during visits on intervening weeks between the study drug administrations that are less than 15 minutes in duration (e.g., at Day 36 [5 weeks], Day 50 [7 weeks], Day 64 [9 weeks], etc.), through Day 92 (13 weeks).

Pharmacokinetic samples will be collected after the study drug doses at Day 1/Baseline, Day 15 (2 weeks), Day 71 (10 weeks), and Day 85 (12 weeks) at the following timepoints: 1 hour, 24 hours, 72 hours, 7 days, and 14 days after study drug administration. This schedule will require additional visits solely for sample collection on Study Days 2, 4, 8, 16, 18, 22, 72, 74, 86, 88, and 92. Pharmacokinetic samples will also be collected on Days 1, 15, 29, 43, 57, 71, 78, 85, and 99 when visits are otherwise scheduled, and extra visits are not needed on these days for collection of these samples. The 1-hour, 24-hour, and 14-day post-dose serum concentration data are required for estimation of the PK AUC.

Study participants who

1. miss 2 consecutive visits or
2. have more than one treatment visit out of window or
3. have 3 non-treatment visits over 4 weeks that are out of window

will be discontinued from the study and may be replaced. For this reason, it is important to enroll only participants who in the judgement of the investigator are likely to be compliant with the study visit and sample collection schedule.

A complete physical examination will be conducted at Screening. Targeted physical exams will be conducted at designated visit from Day 1 through Day 99 (14 weeks). Weight will be recorded at Screening and again at Day 99 (14 weeks). Immunogenicity samples will be collected at Day 1/Baseline and again at Day 99 (14 weeks). Sentinel Group subjects will be asked to return for the final study assessments indicated for the EOS and Follow-up visits at Days 99 (14 weeks) and 113 (16 weeks), respectively. Subjects who are discontinued or who withdraw from the study prematurely are also requested to complete the assessments for these 2 study visits. Refer to the Schedule of Events tables for details on procedures for each scheduled study visit and for PK sampling timepoints (for the Sentinel Group, see Table 1).

6.2 Core Group

Study drug administration visits will take place once every 2 weeks beginning at Day 1/Baseline and continuing through Day 85 (12 weeks). After the study drug administration at Day 71 (10 weeks), HIV-infected Core Group subjects will revert to routine administration of Trogarzo® diluted in 250 mL normal saline via IVI over 15 minutes in accordance with the Trogarzo® prescribing information. HIV-uninfected subjects will discontinue dosing after the Day 71 study drug administration. The scheduled visit at Day 99 (14 weeks) for the HIV-infected Core Group subjects is for safety follow-up only, and this visit may be conducted by telephone if no clinic visit is needed for this purpose. Trogarzo® administration at Day 99/follow-up should be conducted in the routine manner as employed prior to the study, through the primary care provider. The Day 99 EOS visit in the HIV-uninfected Core group subjects that is 28 days after the last dose of Trogarzo® must be completed in the clinic.

HIV-uninfected participants will have additional visits as per Table 2 and Table 3. HIV-uninfected subjects will receive a 2000 mg infusion over 60 minutes on Day -55 followed by 3 doses of 800 mg infusion over 15 minutes on Days - 41, -27, and Day -13. Safety assessments including collection of blood and urine specimens for safety laboratory testing will be conducted every 4 weeks beginning on Day -55 and will continue through Day 1 at which time the Schedule of Events will be identical to that of the HIV-infected Core subjects.

On Day 1 HIV-1 uninfected subjects will enter the Treatment Study Phase. These HIV-uninfected subjects will receive an 800 mg dose of Trogarzo® in accordance with the prescribing information (diluted in 250 mL normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and

again at Day 15. Every 2 weeks thereafter through Day 71 (10 weeks), subsequent doses will be administered via undiluted IV push over 30 seconds. After the Day 71 infusion (10 weeks), HIV-uninfected Core Group subjects will discontinue Trogarzo® infusion therapy.

Safety assessments, including collection of blood and urine specimens for safety laboratory testing, as well as HIV-1 viral load and archive and viral resistance samples (HIV-infected subjects only), will be conducted every 2 weeks beginning at Day 1/Baseline and continuing through Day 85 (12 weeks) for HIV-infected subjects, and through Day 99 for HIV-uninfected healthy volunteers. In addition, beginning at Day 29 (4 weeks), Core Group subjects will also have non-laboratory safety assessments (vital signs, AEs, recording of concomitant medications) conducted during visits on intervening weeks between the IV push study drug administrations (e.g., at Days 36 [5 weeks], 50 [7 weeks], 64 [9 weeks], etc.), through Day 78 (11 weeks) for HIV-infected subjects, and through Day 85 (12 weeks) for HIV-uninfected healthy volunteers.

Pharmacokinetic samples will be collected after study drug doses at Day1/Baseline, Day 15 (2 weeks), Day 43 (6 weeks), and Day 85 (12 weeks) at the following timepoints: 1 hour, 24 hours, 72 hours, 7 days, and 14 days after study drug administration. This schedule will require additional visits solely for sample collection on Study Days 2, 4, 8, 16, 18, 22, 44, 46, 72, and 74. Pharmacokinetic samples will also be collected on Days 1, 15, 29, 43, 50, 57, 71, 78, and 85 when visit are otherwise scheduled and extra visits are not needed on these days for collection of these samples. The 1-hour, 24-hour, and 14-day post-dose serum concentration data are required for estimation of the PK AUC. In HIV-1 uninfected subjects PK samples will also be drawn on Days -55, -41, -27, and -13.

Study participants who:

1. miss 2 consecutive visits or
2. have more than one treatment visit out of window or
3. have 3 non-treatment visits over 4 weeks that are out of window

will be discontinued from the study and may be replaced. For this reason, it is important to enroll only participants who in the judgement of the investigator are likely to be compliant with the study visit and sample collection schedule.

A complete physical examination will be conducted at Screening. Targeted physical exams will be conducted at designated visits from Day 1 through Day 85 (12 weeks) for HIV-infected and through Day 99/EOS (14 weeks) for HIV-uninfected healthy volunteers. In addition, HIV-1 uninfected

individuals will undergo targeted physical exams on study Days -55, -41, -27, and -13. Weight will be recorded at Screening and again at Day 85 (12 weeks) for HIV-infected subjects, and at Day 99/EOS (14 weeks) for HIV-uninfected healthy volunteers. Immunogenicity samples will be collected at Day 1/Baseline and again at Day 85 (12 weeks) for HIV-infected subjects or Day 99/EOS (14 weeks) for HIV-uninfected healthy volunteers.

Core Group subjects will be asked to return for the final study assessments indicated for the EOS and Follow-up visits at Days 85 (12 weeks) for HIV-infected subjects and 99 (14 weeks) for HIV-uninfected healthy volunteers. Subjects who are discontinued or who withdraw from the study prematurely are also requested to complete the assessments for these 2 study visits. Refer to the Schedule of Events tables for details on procedures for each scheduled study visit and for PK sampling timepoints (for the Core Group, see Table 3).

6.3 IM Group

HIV-infected subjects in the IM Group will receive the first two doses of study drug in accordance with the Trogarzo® prescribing information (diluted in normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. The next four doses of Trogarzo® will be administered as an IM injection. At Day 85 (12 weeks), IM Group HIV-infected subjects will revert to diluted IVI dosing over 15 minutes in accordance with the Trogarzo® prescribing information.

HIV-uninfected individuals will receive four doses of Trogarzo® (pre-Steady State Phase) as described above for Core Group HIV-uninfected individuals prior to the Study Treatment Phase. In the Study Treatment Phase, HIV-uninfected subjects will receive the first two doses of Trogarzo® in accordance with the prescribing information (diluted in 250 mL normal saline and administered over 15 minutes via IVI) at Day 1/Baseline and again at Day 15. The next four doses of Trogarzo® will be administered as an IM injection.

HIV-uninfected subjects will discontinue dosing after the Day 71 study drug administration. The scheduled visit at Day 113 (16 weeks) for the HIV-uninfected IM Group subjects is for safety follow-up only, and this visit may be conducted by telephone if no clinic visit is needed for this purpose. Trogarzo® administration at Day 99/follow-up should be conducted in the routine manner as employed prior to the study, through the primary care provider. The Day 99 EOS visit in the

HIV-uninfected IM group subjects that is 28 days after the last dose of Trogarzo® must be completed in the clinic.

Safety assessments, including collection of blood and urine specimens for safety laboratory testing, as well as HIV-1 viral load and archive and viral resistance samples (HIV-infected individuals only), will be conducted every 2 weeks beginning at Day 1/Baseline and continuing through Day 85 [12 weeks]) for HIV-infected subjects, and through Day 99 for HIV-uninfected healthy volunteers. In addition, subjects will also have non-laboratory safety assessments (vital signs, recording of concomitant medications, assessment of IM injection site) conducted during visits on intervening weeks between the study IM drug administrations through the EOS. AEs are collected at all timepoints from time of consent.

Targeted physical examinations will be conducted at various visits from Day 1 through Day 85 (12 weeks) for HIV-infected subjects, and through Day 99 for HIV-uninfected healthy volunteers. Weight will be recorded at Screening and again at EOS. Immunogenicity samples will be collected at Day 1/Baseline and again at EOS (Day 85 [12 weeks] for HIV-infected subjects or Day 99 [14 weeks] for HIV-uninfected healthy volunteers). IM Group subjects will be asked to return for the final study assessments indicated for the EOS and Follow-up visits (Day 99 [14 weeks] for HIV-infected and Day 113 [16 weeks] for HIV-uninfected see Table 4). Subjects who are discontinued or who withdraw from the study prematurely are also requested to complete the assessments for these two study visits, unless they are re-enrolled HIV-infected individuals participating in the IM study.

Pharmacokinetic samples will be collected after study drug doses at Day 1/Baseline and Days 15, 57, and 71 at the following timepoints: 48 hours, and 7, 10, and 14 days after study drug administration). This schedule will require additional visits solely for sample collection on Study Days 3, 8, 11, 17, 22, 25, 59, 64, 67, 73, 78, and 81. For IM dosing, the 2- and 14-day post-dose serum concentration data are required for the estimation of PK AUC.

Discontinued HIV-1 infected participants who re-enroll after receiving a loading dose of 2000mg IVI and at least one maintenance dose of 800mg IVI given according to the label prior to Day 1 enrollment will not undergo PK assessments between Baseline and the Day 29 visits since these PK samples will already have been collected during the subject's initial study participation. The PK assessments of the re-enrolled participants will be compared between the IVI from their first enrollment and IM from their second enrollment.

In HIV-1 uninfected subjects PK samples will also be drawn on Days -55, -41, -27, and -13.

Study participants who:

1. miss 2 consecutive visits or
2. have more than one treatment visit out of window or
3. have 3 non-treatment visits over 4 weeks that are out of window

will be discontinued from the study and may be replaced. For this reason, it is important to enroll only participants who in the judgement of the investigator are likely to be compliant with the study visit and sample collection schedule. However, discontinued HIV-1 subjects in the IM portion of the study may rescreen and re-enroll in the event of the need for a loading dose with 2000mg IVI of Trogarzo® followed by at least one maintenance dose of 800 mg IVI and with agreement to adhere to the subsequent study schedule.

Refer to Table 4 for details on procedures for each scheduled study visit and for PK sampling timepoints.

6.4 Follow-up Visits: Day 113 (Sentinel Group and HIV-Uninfected IM Group) / Day 99 (Core and HIV-infected IM Groups)

All subjects are to have a Follow-up Visit - at Day 113 (16 weeks) for the Sentinel and HIV-uninfected IM Groups, and at Day 99 (14 weeks) for the Core and HIV-infected IM Groups for collection of safety information. The medications taken during the follow-up period (the period from the previous scheduled study visit – Day 99 [14 weeks] for the Sentinel and HIV-uninfected IM Groups, Day 85 [12 weeks] for the Core and HIV-infected IM Groups through to this Follow-Up Visit) should be captured as concomitant medications in the EDC system. Any changes to background ARV medications should also be recorded, along with a reason for the change. AEs will be collected at this visit. If it is not necessary for the subject to present at the clinic for these procedures, this visit may be conducted via telephone. Administration of Trogarzo® for this visit should be conducted in the routine manner as employed prior to the study, through the primary care provider.

Subjects that withdraw or are discontinued from either study group should be followed for 28 days after receiving administration of study drug either by IV infusion, bolus, push, or IM, except for discontinued HIV-infected IM subjects that are re-enrolling into the study.

6.5 Early Withdrawal Procedures

Subjects who withdraw or are discontinued from the study at any time before EOS (Day 85 (12 weeks) for HIV-infected Core or IM Groups, or Day 99 for Sentinel and HIV-uninfected Core or IM Groups) will be asked to complete all EOS procedures to ensure safety and to collect as much study data as possible, except for discontinued HIV-infected IM subjects that are re-enrolling into the study. These individuals should be followed for 28 days after receiving study drug administration.

6.6 Unscheduled Visits

Unscheduled visits are allowed for the following reasons:

- To perform confirmatory laboratory testing for clinically abnormal values; and
- Any time the investigator feels that it is clinically required for safety reasons related to the subject's participation in this trial.

Findings during these unscheduled visits must be reported in the EDC system under the unscheduled visit section.

7. Study Assessments

A central laboratory will analyze all blood and urine samples with the exception of the HIV-1 resistance testing, immunogenicity testing, and PK assessments, which will be undertaken by appropriate specialty contract laboratories. Urine samples will be analyzed at the site; if abnormal results are obtained for a subject, a urine sample will be sent to the central laboratory for microscopic evaluation.

The following assessments will be conducted at the times indicated in the Schedules of Events (Table 1, Table 2, Table 3, and Table 4).

7.1 Activities to be Completed

7.1.1 Demographic Data, Medical History, and Concomitant Medications

Demographic data, a complete medical history (per subject report), and documentation of prior medications will be collected at Screening; information about recent or concomitant medications will be obtained at each visit.

7.1.2 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. Height and weight will be measured at Screening and weight only at other times specified.

7.1.3 Targeted Physical Examination

A targeted 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 subject.

7.1.4 Vital Sign Measurements

Vital sign measurements will include the subject's heart rate (beats/minute), blood pressure (mm Hg), respiratory rate (breaths/minute), and oral temperature (ºC). Measurements will be taken within 1 hour before the start of the study drug administration and again at both the beginning and end of the 15 minute (HIV-infected) or 60 minute (HIV-uninfected) post-administration observation period. Blood pressure and heart rate measurements will be obtained after the subject has been seated for at least 5 minutes. Ideally, each subject's blood pressure should be measured using the same arm and the same size cuff at each visit.

7.1.5 Patient Reported Outcomes

Participants in the IM Group will be asked to complete questionnaires to assess their satisfaction with the different modes of Trogarzo® administration. The questionnaires will be administered at various visits (see Table 4). The Study Medication Satisfaction Questionnaire change version (SMSQc) is a self-reported assessment tool to assess the amount of change in treatment satisfaction

over time. The questionnaire was adapted from the HIV Treatment Satisfaction Questionnaire (HIVTSQ) to remove mentions of HIV and allow satisfaction evaluation in participants who do not have HIV (see Appendix D).[7,8,9,10,11,12] HIV-infected participants in the IM Group will complete the HIVTSQ status version (HIVTSQs12) at Day 29 regarding IVI administration and at Day 85 regarding IM administration. In addition, they will also complete the change version of the questionnaire (HIVTSQc12) following completion of the IM portion of the study (Day 85). HIV-uninfected participants will complete the SMSQ status version (SMSQs) at Day 29 regarding IVI administration and at Day 85 regarding IM administration. In addition, they will also complete the change version of the questionnaire (SMSQc) following completion of the IM portion of the study (Day 85). Instructions and questionnaires are provided in Appendix D.

- HIV-infected IM Group Participants:
  - HIVTSQs12: questionnaire to be completed on D29 and D85
  - HIVTSQc12: questionnaire to be completed on D85
- HIV-Uninfected IM Group Participants:
  - SMSQs: questionnaire to be completed on D29 and D85
  - SMSQc: questionnaire to be completed on D85
- Preference assessment (Day 85): "For the past 8 weeks you have received IM injections every 2 weeks. Today we would like you to compare your experience on the IM injections with the IV infusion you received previously during this study. Which type of administration do you prefer?".

7.2 Blood and Urine Samples

7.2.1 Clinical Laboratory Parameters

Collection of blood and urine samples for clinical laboratory assessments will be part of the safety profile assessment for the study subjects. Subjects do not need to fast before blood sampling. 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. Prothrombin time and partial thromboplastin time will also be collected at Screening only for the IM group.

- **Serum chemistry profile:** albumin, alkaline phosphatase, ALT, amylase, AST, blood urea nitrogen, calcium, chloride, creatine phosphokinase, creatinine, direct bilirubin, gamma glutamyl transferase, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.
- **Urinalysis:** visual inspection for appearance and dipstick assessment for color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and leukocyte esterase.

The urinalysis will be performed at the site by qualified personnel. If the results of the urinalysis are abnormal, a urine sample will be sent to the central laboratory for microscopic evaluation. Samples will be processed as described in the laboratory procedures manual before being sent to the central laboratory for evaluation.

Tests with Grade 3 or Grade 4 abnormal results should be repeated within 72 hours of the site becoming aware of the abnormal value(s) with the exception of CD4+ T cell levels. See Appendix B for details and definitions of toxicities. The investigator should discuss any Grade 3 or 4 abnormal laboratory results with the medical monitor/Sponsor for appropriate subject disposition, including potential withdrawal from the study. Refer to Section 4.3 (Safety Monitoring and Toxicity Management Plan) for information on DMC reporting and subject discontinuation in the event of study drug–related AEs.

7.2.2 Archive Sample

A separate blood sample will be taken and stored for possible research use.

7.2.3 HIV-1 Viral Resistance Testing

Blood samples for HIV-1 viral resistance testing should be collected before the start of drug administration at the indicated visits in HIV-infected subjects only. Viral resistance testing will be conducted if a subject experiences an increase in plasma viral load to levels above 1,000 copies/mL on 2 consecutive measurements at least 2 weeks apart. Resistance testing will include assessments of reverse transcriptase, protease, integrase, and envelope genes and chemokine coreceptor utilization; the samples will be collected and stored.

7.2.4 HIV-1 RNA Level

Blood samples for viral load will be collected at Screening, Day 1, and at several additional timepoints through the study and used to determine study qualification as well as the effectiveness of the study regimens and should be drawn before drug administration in HIV-1 infected subjects only.

7.2.5 CD4+ Cell Count

Blood samples for $CD4^+$ cell count will be collected at Screening, Day 1, and at several additional time points during the study to determine study qualification as well as how well the immune system is functioning.

7.2.6 Immunogenicity of Trogarzo®

Blood samples will be collected to test for the development of antibodies against Trogarzo® during the study, including Day -55 in HIV-uninfected Core and IM subjects, Day 1/Baseline, and at EOS (Day 99 [14 weeks] for Sentinel Group, Day 85 [12 weeks]/Day 99 [14 weeks] for Core and IM Groups). Samples will be collected prior to Trogarzo® administration on those days. The incidence of anti-Trogarzo® antibody production will be determined using an enzyme-linked immunosorbent assay (ELISA) that has been validated for the detection of anti-Trogarzo® antibodies in human serum even if circulating drug is present.

7.2.7 Trogarzo® Serum Concentrations

Measurements of Trogarzo® serum concentrations will be conducted to determine the concentration-time profile of Trogarzo® in all subjects. Trogarzo® serum concentrations will be measured using a validated ELISA with a lower limit of quantitation (LLOQ) at 0.010 µg/mL.

7.2.8 Serum Follicle-Stimulating Hormone Testing

A serum FSH test will be performed on postmenopausal females at Screening (See Section 8.7). The level of FSH should exceed 40 IU/L for the subject to be considered postmenopausal. If the subject does not meet this criterion, she must agree to use proper birth control precautions as

described in Section 8.7 and must have serum and urine pregnancy tests throughout the protocol at times specified in the Schedules of Events.

7.2.9 Pregnancy Testing

A serum pregnancy test will be performed at Screening and at EOS (Day 99 [14 weeks] for the Sentinel Group, Day 85 [12 weeks]/Day 99 [14 weeks] for the Core and IM Groups) for all females of childbearing potential. A urine pregnancy test will be performed at defined subsequent 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. Any subject who becomes pregnant during the study will be withdrawn from the study. See Section 8.7 for a description of procedures to be followed in case of pregnancy.

7.2.10 4th Generation Point of Care HIV-1 Testing

All HIV-1 uninfected healthy subjects will be tested at Screening and Day -55 and during the course of the study as outlined in Table 2, Table 3, and Table 4 with a 4th generation point of care HIV test using blood collected at the visit. If a test is reactive, then blood should be sent to the Central lab for confirmatory HIV-1 testing which includes testing for HIV-1 by nucleic acid amplification (NAAT) and a serologic response to HIV-1 (Geenius HIV1/2 Biorad).

7.2.11 Hepatitis B Surface Antigen and Hepatitis C Antibody Testing

All HIV-1 uninfected healthy volunteer candidates will be tested at Screening for Hepatitis B Surface Antigen and Hepatitis C Antibody. If a sample is Hepatitis C Antibody reactive, a reflex Hepatitis C RNA quantitation will be performed.

8. Adverse Events

8.1 Definitions

Per the FDA regulations in 21 CFR (Code of Federal Regulations) 312.32, the following definitions apply to this protocol:

Adverse Events. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Adverse Reaction. Any adverse event caused by a drug or its experimental administration.

Treatment-Emergent AEs. A treatment-emergent AE is defined as any event not present before exposure to study drug or its experimental administration or any event already present that worsens in either intensity or frequency following exposure to the experimental administration of study drug.

Serious Adverse Event or Serious Suspected Adverse Reaction. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Suspected Adverse Reaction. A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug or its experimental administration caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug or its experimental administration and the AE.

Unexpected Adverse Event or Unexpected Adverse Reaction. An AE or adverse reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed.

The Common Terminology Criteria for AEs (CTCAE) v. 5.0 scale will be used for assessment of any infusion reactions, or anaphylactic events (see Section 8.5). The DAIDS: Table for Grading the Severity of Adult and Pediatric AEs Version 2.1 will be used for assessment of all other AEs (see Appendix B).

8.2 Eliciting Adverse Event Information

At every study visit, subjects will be asked a standard, nondirective 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 subject self-report, AEs will be documented from clinically significant findings resulting from abnormal laboratory test values, physical examination findings, or from other documents that are relevant to subject safety.

8.3 Reporting Adverse Events

The investigator is responsible for reporting to the Sponsor or designee all AEs that are observed or reported by the subject during the study (from the time the subject signs informed consent until 28 days after the last dose of the administration of study drug is given whether by IV infusion, bolus, or push or IM injection), regardless of their relationship to study drug or its experimental administration or their clinical significance. Subjects will be instructed to contact study site personnel at any time after informed consent if any symptoms develop. AEs will be documented in the subject's source documents and recorded in the AE section of the EDC system.

To ensure compliance with FDA regulations (21 Code of Federal Regulations [CFR] 312.64), site investigators must report immediately all AEs that meet the SAE criteria, regardless of presumed relationship to the study drug or its experimental administration, to the Sponsor. The Sponsor will carefully review the SAE information to monitor the study drug's toxicity profile and subject safety. If any event meets the FDA's reporting criteria, it will be submitted to the FDA as an IND Safety Report (21 CFR 312.32).

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

Information to be collected includes the event term, date of onset, date of resolution, investigator-specified assessment of severity and relationship to study drug or its experimental administration, and seriousness, as well as any required treatment or evaluations and outcome.

Pre-existing 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 (including abnormal laboratory values) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an 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 or if the investigator judges the change to be beyond the range of normal physiological fluctuation). If abnormal laboratory values findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be recorded 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 preexisting condition, the worsening of the condition should be captured as an AE. Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents.

Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organization Drug Dictionary (WHODD) will be used to code all AEs and classify all medicines, respectively. All coding will be performed by Westat and reviewed and approved by the medical monitor.

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

8.4 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug or its experimental administration is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug or its experimental administration in causing or contributing to the AE will be characterized by the investigator using the following classifications and criteria from 21 CFR 312.32:

Suspected Adverse Reaction. This relationship applies to any adverse event for which there is a reasonable possibility that the drug or its experimental administration caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug or its experimental administration and the adverse event. Suspected Adverse Reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unrelated. This relationship suggests that there is no association between the study drug and the reported event. To be deemed unrelated, an alternative etiology must be present.

8.5 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 (Grade 1): Symptoms causing no or minimal interference with usual social and functional activities.

Moderate (Grade 2): Symptoms causing greater than minimal interference with usual social and functional activities.

Severe (Grade 3): Symptoms causing inability to perform usual social and functional activities.

Potentially Life-Threatening (Grade 4): Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.

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.					

For Cytokine Release Syndrome and all other AEs the DAIDS toxicity table should be followed.

The DAIDS AE Grading Table v2.1 (July 2017) (Appendix B) will be used to grade AEs. Changes 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. AEs characterized as intermittent require documentation of onset and duration of each episode.

8.6 Serious Adverse Event Reporting

Any AE considered serious by the investigator according to the previously described criteria must be reported using the Westat SAE Report Form and submitted to the Westat Regulatory Affairs (RA) Department via FAX or email within 24 hours of the site becoming aware of the event. Site staff must alert Westat of incoming safety information via the Westat SAE Hotline, either prior to or immediately after faxing/emailing the SAE Form.

SAE Hotline: **888-464-5246**
SAE Fax: **888-865-1983**
Email: **Regulatory@Westat.com**

SAE reports must be supported by source documents that are maintained by the site investigator and provided to the Sponsor upon request. Key information that must be supported by source documents includes, but is not limited to the following:

- Event term
- Onset date
- Event chronology and management
- Pertinent work-up
- Investigator assessment of the relatedness of the event to the study drug
- Concomitant medications and past medical history
- Changes in study drug administration, including suspension or discontinuation of the experimental administration of Trogarzo®
- If judged not study drug-related or related to its experimental administration, an alternate etiology

- Outcome and outcome date

When reporting an SAE to Westat, a thorough summary of the event should be provided, including copies of relevant supporting documentation. Before submission of these documents to Westat, all subject identifiers must be obliterated; the documents must be labeled only with the subject's identification number to safeguard the subject's privacy.

Supplemental source documentation related to the SAE may include:

- Clinic and/or hospitalization records
- Laboratory reports
- Pathology reports
- Surgical reports
- Other test results, such as x-rays, lumbar punctures, and computed tomography (CT) scans
- Consult notes
- Hospital admission and discharge summary
- Death certificate
- Autopsy report

When an SAE results in hospitalization or prolongation of an existing hospitalization, it is recommended that a copy of the hospital admission and discharge summaries and any pertinent laboratory or diagnostic reports are faxed to Westat as soon as they become available. Documentation of the cause of death (e.g., an autopsy report or death certificate) should be submitted to Westat when a death is reported.

The investigator should report to Westat any change in the initial SAE Report information or additional information that becomes available after the initial SAE Report submission. Each follow-up SAE Report should be numbered sequentially.

All the SAE reports and supporting information received by the participating investigators will be promptly evaluated by the Sponsor's Medical Monitor who will be responsible for the safety

monitoring of the trial and for making decisions related the regulatory reporting of pertinent safety information per 21 CFR 312.32, and by the DMC as detailed in Section 4.3.

The Sponsor or designee will notify the FDA and all participating Investigators in an IND safety report about potential serious risks, from clinical trials and any other source, no later than 15 days in the following cases:

- Serious and unexpected suspected adverse reactions, only if there is evidence to suggest a causal relationship between the drug or its experimental administration and the AE.
- Findings from other studies, such as epidemiological studies, pooled analysis of multiple studies, or clinical studies, that suggest a significant risk in humans exposed to the drug.
- Findings from animal or in vitro testing. Any finding from animal or in vitro testing whether or not conducted by the Sponsor that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenesis or reports of organ toxicity.
- Increased rate of occurrence of serious suspected adverse reactions. Any clinically important increase in the rate of serious suspected adverse reactions over that listed in the protocol or IB must also be reported.

The Sponsor or designee will notify the FDA and all participating investigators of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but no later than 7 calendar days after the initial receipt of the information. The investigators will follow their institutional policies of reporting safety information to the Institutional Review Board (IRB). They will provide copies of the correspondence with the ethics committee to the Sponsor or designee for filing.

8.7 Pregnancy

Sexually active men who have partners of childbearing potential and all females of childbearing potential must use an effective method of birth control (e.g., oral contraceptives, double-barrier methods, hormonal injectable, implanted contraceptives, or vasectomy) during the study and for 28 days after the last dose of study drug is administered.

Childbearing Potential. Females of childbearing potential are female subjects who are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy), are not postmenopausal (at least 1 year without menses), and are not otherwise sterile by medical evaluation. These subjects must use an adequate form of birth control as determined by the investigator. Spermicidals are considered one component of a double-barrier

method. Complete abstinence from sexual intercourse will suffice without additional contraceptive measures. However, it is recommended that the Investigator discuss all options with these female subjects and instruct that if the subject becomes sexually active, she must use appropriate contraceptive measures.

Similarly all men who become sexually active during the study with a partner of childbearing potential must be instructed to use appropriate contraceptive measures.

Sterile or Postmenopausal. Females who are surgically sterile or postmenopausal will also be eligible for the study. Postmenopausal is defined as having had no menses for at least 12 months and having an FSH level above 40 IU/L for reproductive-age females. A surgically sterile status is defined as having a history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy.

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 subjects will be instructed to contact the investigator if a sexual partner suspects she may be pregnant.

If a subject or investigator suspects that the subject may be pregnant before experimental study drug administration, the study drug should not be administered experimentally until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive the experimental administration of Trogarzo® and must be withdrawn from the study. HIV-infected participants should discuss ongoing treatment with antiretroviral therapy including Trogarzo® with their primary care provider. The investigator must immediately notify the medical monitor of a pregnancy during experimental study drug administration and record the event on the Pregnancy Surveillance Form that will be provided to each site. Protocol-required procedures for study discontinuation must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate follow-up procedures should be considered if indicated.

The investigator must follow up with a pregnant subject or the pregnant partner of any sexually active male subject every 4 weeks while the woman is pregnant and every 4 weeks thereafter 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. Infants that result from such pregnancies should be followed for a minimum of 8 weeks for safety assurances.

Pregnancy Surveillance Forms will be submitted to Westat RA Department via the SAE FAX line. The US Department of Health and Human Services encourages the reporting of all in utero exposures to antiretroviral agents to the Antiretroviral Pregnancy Registry (telephone 800-258-4263 or fax 800-800-1052).

8.8 Data Monitoring Committee

An independent DMC will review accumulated data in accordance with the Safety Monitoring and Toxicity Management Plan (Section 4.3) and the Study Stopping Rules (Section 4.4). The DMC will make recommendations on whether or not the study may proceed with enrollment successive Sentinel Group subjects, and enrollment of the Core and IM Groups in accordance with the plan and schedule laid out in the Safety Monitoring and Toxicity Management Plan. The DMC will also conduct periodic review of data upon reaching other defined study milestones (see Section 4.3). Recommendations will be determined by the consensus of clinical opinions of the DMC members relative to AEs/SAEs/early discontinuations for any heterogeneous treatment effect in subjects in this study.

The DMC will evaluate the risk/benefit of continuation of the study and make recommendations regarding the continuation, modification, or termination of the trial to the Sponsor or designee following meetings. The DMC will consist of at least 3 clinical experts and an independent statistician. The Sponsor or designee biostatistician and the medical leader for the Trogarzo® project may be present at the DMC meeting open session to reply immediately to any questions of DMC members.

DMC meeting discussions will include AEs, abnormal laboratory test results, and a trial status update. Additionally, all Grade 3 and 4 AEs and SAEs will be forwarded to the DMC.

9. Statistical Considerations

9.1 General Methodology

The data collected are intended primarily for clinical review and interpretation. The analysis of study data will be primarily descriptive, with emphasis on tabular and graphical displays. Descriptive statistics will be used to guide decisions as to the clinical relevance of findings. Unless otherwise stated, p-values will be determined only if they appear to be warranted from the summary statistics.

For continuous data, descriptive statistics will be presented as number of subjects (n), mean, standard deviation, median, minimum, and maximum. For categorical data, the frequency and percentage of subjects in each category will be presented. Percentages will be based on non-missing data unless otherwise specified.

Data will be described and analyzed using the SAS System Version 9 (SAS Institute Inc., Cary, NC, SAS System). Individual subject data will be presented in subject data listings.

9.2 Populations for Analysis

9.2.1 Intent-to-Treat Population

The ITT population is defined as all subjects enrolled into the study. Subject disposition will be based on the ITT population.

9.2.2 Safety Population

All subjects who receive at least one partial dose of study drug will be included in the safety dataset for analysis (SAF) population. Subjects will be analyzed according to the treatment they actually received. The safety population will be used for the safety analyses.

9.3 Subject Disposition

Study completion data will be summarized for all enrolled subjects. The number and percent of subjects who complete treatment; discontinue study procedures prematurely; or discontinue the

study prematurely will be tabulated. The primary reason for premature discontinuation of the experimental administration of study drug and/or discontinuation from study participation will be tabulated. Any additional reason(s) for premature discontinuation of experimental study drug administration will also be tabulated. A listing of all enrolled subjects will be provided.

9.4 Demographics and Baseline Characteristics

Descriptive statistics will be presented for demographic and other baseline characteristics for the ITT population. Medical history and medication history findings will be listed and summarized.

9.5 Safety Analyses

The safety analyses will include descriptions of treatment-emergent AEs, Class C events per the CDC Classification System for HIV Infection, clinical laboratory test results, physical examination findings, vital sign results, and Trogarzo® antibody levels (immunogenicity of Trogarzo®).

9.5.1 Adverse Events

The incidence (n and %) of AEs, SAEs, and early termination of experimental study drug administration or study participation due to an AE will be presented. Additionally, AEs will be tabulated according to severity and relatedness categories as reported by the investigator. AEs will be presented in tables organized alphabetically by Preferred Term within SOC. Each subject will be counted only once for each AE reporting level.

9.5.2 Clinical Safety Laboratory Parameters

Clinical laboratory parameters will be presented by visit. Descriptive statistics will be used to summarize observed values by visit as well as the change from baseline at each visit. Clinical laboratory values outside the normal ranges will be flagged in subject data listings. Non-numeric data will be presented in subject data listings but will not be tabulated.

9.6 Efficacy

Assessment of the HIV-1 viral loads will be made as a secondary endpoint in HIV-1 infected subjects by comparing the mean viral load at visits when subjects received an IVI over 15 minutes to the weekly visits when receiving an IV push over 30 seconds or IM injections.

Study subjects will be considered virologic failures if:

1. Viremic subjects experience a sustained >0.5 log increase in plasma HIV-1 RNA from baseline
   or
2. A sustained viral load (VL)>200 copies/mL if subject VL was <50 copies/mL at baseline

that cannot be explained by intercurrent illness, a change in adherence to the background regimen, or unanticipated changes to the background regimen that will meet the definition of virologic failure.

Sustained is defined as 2 consecutive viral load determinations at least 2 weeks apart.

Exploratory statistical analyses will explore changes in HIV-1 drug sensitivity/susceptibility to determine relationships with Trogarzo® administration in combination with background ARVs.

9.7 Pharmacokinetic Analyses

Serum concentrations will be used to estimate PK parameters. PK parameters will be estimated for all subjects by noncompartmental analysis of the serum concentration-time data. Missing data will not be imputed. For the re-enrolled participants, the PK parameters of IVI and IM will be estimated from their first enrollment and second enrollment, respectively. The exposure-response relationship established for the review of the ibalizumab Biologics License Application (BLA) was based on C_{trough}, rather than AUC. C_{trough} was used as an indicator of exposure and a clear trend between exposure and the efficacy endpoint was observed. Therefore, C_{trough} is more representative of efficacy for this pharmacokinetic bridging study than AUC. A PK bridge between the IV push and IVI and between the IM injection and IVI is demonstrated if the proportions of subjects with average C_{trough} equal to or exceeding the threshold of 300 ng/mL are comparable using a Fisher's Exact test. A PK bridge is also demonstrated for AUC if the 90% confidence interval of log transform of the ratio of the geometric means for IV push or IM injection (test product) to IVI (reference product) for the 40 subjects in the study is within the 80%-125% criteria.

9.8 Sample Size and Power Considerations

Considering the large PK variability of Trogarzo® (~70% variability for clearance (CL) based on the population PK model developed for the review of BLA 761065), a minimum subject number of 20 for each type of administration (IVP or IM) is sufficient to achieve 80% power. In addition, the within-subject CV% of AUC with IM (Study TMB-121) and IVI (current TMB-302 preliminary data) administration, are comparable. The median within-subject CV% is 7% for IM and IVI, while the maximum within-subject CV% is 22%-23% for IM and IVI. These data also support that a minimum subject number of 20 for each type of administration is sufficient to achieve 80% power.

10. Data Handling and Quality Assurance

10.1 Electronic Case Report Forms

An EDC system will be used to capture data electronically for this trial, meaning that all data will be entered in the EDC system from source documents at the investigational site. Case report forms (CRFs) will be developed to be used as worksheets. Completion of these worksheets is optional.

A subject identification (ID) list will be maintained separately from the research records and will not be recorded or stored with the CRFs.

All data must be entered in English. The EDC system should always reflect the latest observations on the subjects participating in the trial. Therefore, the data are to be entered into the EDC as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all antiviral activity/safety evaluations. The clinical site monitor will verify that all data entries in the EDC system are accurate and correct. If some assessments have not been done, or if certain information is not available, not applicable, or is unknown, the investigator should indicate this in the EDC system. The investigator will be required to sign off on the clinical data.

The Sponsor or designee will review the EDC system and evaluate the entries for completeness and consistency. The clinical site monitor will compare the data captured in the EDC system with the source documents to ensure there are no discrepancies between critical data recorded in the EDC system and the source documents. All entries, corrections, and alterations are to be made by the

responsible investigator or his/her designee. The clinical site monitor cannot enter data in the EDC system. Once clinical data in the EDC system have been submitted corrections to the data fields will be marked by an audit trail, meaning that the reason for the change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering the clinical data into the EDC system will be determined in advance and documented on the appropriate form.

If additional corrections are needed, the responsible clinical site monitor or project data manager will raise a query in the EDC application. The appropriate investigational staff will answer queries sent to the investigator. This correspondence will be marked by an audit trail by the EDC application, meaning that the name of investigational staff, time and date stamp are captured for each interaction/revision.

10.2 Monitoring of the Study

The purpose of clinical site monitoring is to ensure that the trial is conducted in an ethically sound and scientifically rigorous manner. Specifically, sites will be carefully monitored by the Sponsor or designee to ensure that: (1) the rights and well-being of participants are protected; (2) data are complete, accurate, and verifiable; and (3) the trial is conducted in compliance with the protocol, applicable government regulations (e.g., FDA, Taiwan Food and Drug Administration [TFDA]), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R1): Guidelines for Good Clinical Practice, local IRB policies, and current standard operating procedures at the sites and Sponsor/Sponsor's representative.

The clinical site monitor, as a representative of the Sponsor, formally evaluates the accuracy and completeness of the data collected and assesses compliance with the relevant regulations and policies. In doing so, the clinical site monitor will visit the investigator and study facility periodically, in addition to maintaining necessary telephone, email, or letter contact. The clinical site 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 investigator and staff.

Each investigator is expected to make a reasonable effort to accommodate the clinical site monitor when site visits are necessary. Because this trial is utilizing an EDC system, the monitor will need to access the data entry computer and internet during the visit.

10.3 Inspection of Records

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

The investigator should immediately 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.

10.4 Study Record Retention

Essential documents should be retained for at least 2 years after the last approval of a marketing application in an ICH region (or longer if mandated by the local IRB or regulatory affairs). Moreover, they should be retained until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor or designee to inform the Investigator or institution as to when these documents no longer need to be retained.

11. Administrative Considerations

The following administrative items are meant to guide the Investigator in the conduct of the trial but may be changed based on industry and government standard operating procedures, working practice documents, or guidelines. Any changes in trial procedures will be reported to the IRB but will not necessarily result in a protocol amendment.

11.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject 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

subject (or the subject's guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA or applicable regulatory authorities, or the IRB.

The 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, record, 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.

11.2 Institutional Review Board or Independent Ethics Committee Approval

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

The Investigator is responsible for obtaining continued review of the clinical research at intervals specified by the IRB, but not exceeding 1 year. The investigator must supply the Sponsor or designee with written documentation of continued review of the clinical research.

11.3 Modification of the Protocol

This protocol will be implemented as approved by the IRB and no changes will be implemented prior to IRB approval except those necessary to remove an apparent immediate hazard to the subject. Amendments to the protocol must be approved by the IRB prior to implementation.

11.4 Informed Consent

A signed informed consent form, in compliance with Title 21 of the US CFR Part 50 and according to other regulations for non-US sites, will be obtained from each subject before any study-related procedures are performed and any personal information is collected. An informed consent template

may be provided by the Sponsor or designee to investigative sites. If any institution-specific modifications to study-related procedures, the risk language or any other significant changes that would alter the information relayed are proposed or made by the site, the consent must be reviewed by the Sponsor or designee before IRB submission. Once reviewed, the consent will be submitted by the Investigator to his or her IRB 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 subjects must sign the revised IRB-approved consent form.

Before enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved informed consent form. The information given should in a language or manner that is easily understandable to participant or legal guardian. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study and have been given the proper time to consider whether to participate or not, the subject/legal guardian will be asked to give consent to participate in the study by signing the informed consent form. The Investigator will also sign the form at that time.

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

11.5 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 and were agreed to by the investigator. Deviations usually have an impact on individual subjects or a small group of subjects 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 subject, (b) when the subject or investigator has failed to adhere to significant protocol requirements (e.g., inclusion/exclusion criteria, no changes in background ARV), or (c) when there is non-adherence to FDA regulations and/or ICH E6(R2) guidelines.

For this protocol, violations will be defined as exceptions to the inclusion or exclusion criteria, administering an incorrect dosage, making a change to the subject's background ARV, failure to collect vital signs before and after administering study drug, situations where a subject is required to withdraw but the investigator believes the subject should remain in the study, and the use of an excluded concomitant medication. All other departures from the protocol (e.g., missed visit

windows, laboratory samples not collected on the required day) will be documented as protocol deviations. The Investigator or designee must document and explain any protocol deviation or violation in the subject's source documentation. The IRB should be notified of all protocol violations and deviations per local institutional policy by the investigator. Protocol deviations and violations will be documented by the responsible clinical site monitor during monitoring visits, and those observations will be reviewed with the investigator.

The investigator may implement a change from the protocol without prior Sponsor and IRB approval only to eliminate an immediate hazard to a subject. The implemented change should be submitted to the IRB for review as soon as possible.

If the investigator believes that an exception to the protocol is justified for an individual subject, 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 via email 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 subject should receive an excluded concomitant medication and remain in the study, or if the investigator believes that a subject should remain in the study when the protocol dictates that the subject should be discontinued. The implemented change should be submitted to the IRB 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.

11.6 Study Reporting Requirements

By participating in this study, the Investigator agrees to submit reports of AEs according to the timeline and method outlined in the protocol. In addition, the Investigator agrees to submit periodic reports to his/her IRB as appropriate.

11.7 Financial Disclosure and Obligations

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 required under Title 21 CFR 54. In addition, the 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 1 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 subject's disease.

11.8 Investigator Documentation

Before beginning the study, the Investigator will be asked to comply with ICH E6(R2) 8.2, Title 21 CFR and other 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;
- Documentation of IRB approval of the protocol and informed consent;
- The IRB-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 subject or legal guardians;
- A Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572;
- Curricula vitae for the investigator and each sub-investigator listed on Form FDA 1572. A copy of the current license must be provided. The curricula vitae must be signed and dated by the Investigators and sub-investigators within 1 year 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 required under Title 21 CFR 54. 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 1 year following the completion of the study (Section 11.7); and
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with Title 42 CFR 493.

11.9 Study Conduct

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

11.10 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.

A description of this clinical trial (study) will be available on http://clinicaltrials.gov, as required by US Law.

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